XXXIII CONGRESO ANUAL SAN 2018 CORDOBA – ARGENTINA 24 AL 26 DE OCTUBRE

PRE-CONGRESS COURSE "NEUROBIOLOGY OF DRUG ADDICTION"

SAN IBRO LARC Course and ISN Small Conference (ISN-CC) Associated to the XXXIII SAN 2018 Meeting

October 22nd -23rd, 2018

Ciudad Universitaria, Córdoba, Argentina

ORGANIZER:

Dr. Liliana M. Cancela. *IFEC-CONICET, Full Professor, Department of Pharmacology, School of Chemical Sciences, Universidad Nacional de Córdoba.*

COORDINATOR:

Dr. Flavia Bollati. IFEC-CONICET, Assistant Professor, Department of Pharmacology, School of Chemical Sciences, Universidad Nacional de Córdoba.

COLABORATORS:

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Dr. María Estela Andrés (Chile)
Dr. Bruno Averbeck (USA)
Dr. Rudy Bernabeu (Argentina)
Dr. Martine Cador (Francia)
Dr. Peter W. Kalivas (USA)
Dr. Silvia Cruz (México)
Dr. Juan Carlos Molina (Argentina)
Dr. Gabriela Paglini (Argentina)
Dr. Mariela Pérez (Argentina)
Dr. Marcelo Rubinstein (Argentina)
Dr. Mirian Virgolini (Argentina)

LOCATIONS:

-Salón Auditorio, Edificio Integrador, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba.
-Salón de Actos Pabellón Argentina, Ciudad Universitaria, Córdoba, Argentina

Travel Awards ISN Small Conference ISN-CC on "Neurobiology of Drug Addiction"

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Llanos, Silvina Fundacion H Laborit - Cba Cordoba Capital
Luna Castro, Cristian Federico Instituto de Biotecnología UNLaR La Rioja

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McCarthy, Clara Inés IMBICE La Plata
Merlo, Santiago Abel Laboratorio de Neurobiología de la Memoria IFIBYNE (UBA - CONICET)Ciudad Autónoma de Buenos Aires
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Villa, María Agustina Instituto de Investigaciones en Ingeniería Genética y Biología Molecular CABA
Zamberlan, Federico. COCUCO - IFIBA CABA

WORKSHOP *Homage to Ricardo Miledi*
"Workshop: Past, Present and Beyond of Synaptic Transmission"

Previous and satellite activity of the XXXIII Annual Congress of the Argentine Society of Neuroscience Research – SAN

October 22th – 23th, 2018 – Instituto Martín y Mercedes Ferreyra, Córdoba

LOCATION:
Instituto de Investigaciones Médicas
Mercedes y Martín Ferreyra (INIMEC)
Ciudad de Córdoba, República Argentina

ORGANIZING COMMITTEE:
Dr. Joaquín Piriz
Dr. Juan D. Goutman
Dr. Daniel J. Calvo
Dr. Osvaldo Uchitel

SPEAKERS:
Piotr Bregestovski (France)
Ataúlfo Martínez Torres (México)
Carlos Matute (Spain)
Ian Parker (USA)
Angela Vincent (UK)
Cecilia Bouzat (Argentina)
Daniel J. Calvo (Argentina)
Juan D. Goutman (Argentina)
Antonia Marín-Burgin (Argentina)
Osvaldo Uchitel (Argentina)

Pre-Congress Activities

Monday, October 22nd
09:00 – 18:00 PRE-CONGRESS COURSE "Neurobiology of Drug Addiction" / *Auditorio Ciencias I Facultad de Ciencias Químicas – UNC*

14:00 – 18:00 WORKSHOP Ricardo Miledi / *Instituto de Investigación Médica M y M Ferreyra (INIMEC-CONICET-UNC)*
Tuesday, October 23rd
09:00 – 18:00 PRE-CONGRESS COURSE "Neurobiology of Drug Addiction" / *Auditorio Ciencias I Facultad de Ciencias Químicas – UNC*

10:00 – 18:00 WORKSHOP Ricardo Miledi / *Instituto de Investigación Médica M y M Ferreyra (INIMEC-CONICET-UNC)*

14:00 – 18:00 REGISTRATION / *Pabellón Argentina, UNC.*
16:00 – 19:00 OPEN HOUSE: Neuroscience for Community / *Salón de Actos. Pabellón Argentina*

XXXII Congress of the Argentine Society for Research in Neuroscience

October 24th – 26th, 2018
Pabellón Argentina, Ciudad Universitaria, UNC

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Vocal

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CIQUIBIC CONICET-Universidad Nacional de Córdoba

Dr. Pablo Lopez,
Instituto de Investigación Medica Mercedes y Martin Ferreyra, CONICET

PROGRAM

DAY 1 / Wednesday, October 24th

07:30 – 08:15 Registration
08:25 – 08:30 Welcome by Organizers
08:30 – 10:30 SYMPOSIUM I / *Room A*

"**Neurobiology of drug addiction**"
Chairs: *Liliana M. Cancela; Marcelo Rubinstein*

Dissecting the roles of dopamine D2 receptors in the basal ganglia and motivated behaviors
Verónica Álvarez
Laboratory on Neurobiology of Compulsive Behaviors. National Institute on Alcohol Abuse and Alcoholism, USA

Opiate withdrawal memories: Behavior and neural network
Martine Cador
Université Bordeaux, France

Neural systems underlying reinforcement learning
Bruno Averbeck
Laboratory of Neuropsychology, NIMH/NIH, USA

Using the Neurobiology of Willpower to Treat Drug Addiction
Peter W Kalivas
Medical University of South Carolina, USA.

10:30 – 11:00 Coffee Break

11:00 – 12:00 OPENING LECTURE / *Room A*
Tubulin tyrosination-detyrosination cycle : key role in neuronal functions
Annie Andrieux,
Univ. Grenoble Alpes, France

12:30 Lunch with activities:

ARG Scientific Financial Support
Fernando Stefani

14:30 - 15:30 Young Investigator Lectures
Room A: YIL 1 – 3
Room B: YIL 4 – 6

15:30 – 17:30 SYMPOSIUM II / *Room A*
"**Emerging mechanisms in neuronal signaling: from cell biology to pathogenesis**"
Chairs: *Gabriela Salvador; Mauricio Martín*

c-Fos, a moonlighting protein: what we know about its lipid activator capacity in the nervous system
Beatriz L. Caputto
CIQUIBIC (CONICET), Fac. de Cs. Químicas, UNC.

Specific Phospholipids Regulate the Acquisition of Neuronal and Astroglial Identities in Post-Mitotic Cells
Claudia Banchio
Instituto de Biología Molecular y Celular de Rosario IBR-CONICET , Argentina

Fatty acids participation in neuronal differentiation of SH-SY5Y cells
Lisandro J.Falomir Lockhart
Laboratory of Biophysics and Cell Biology of Lipid-Binding Proteins, INIBIOLP, CONICET- Universidad Nacional de La Plata, Argentina.

Role of isoprenoids in autophagy and prion-like spread of Amyloid beta pathology.
Elena Posse de Chaves,
Neuroscience and Mental Health Institute, University of Alberta, Canada

SYMPOSIUM III / Room B

"**Chronic pain: basic research and translational perspectives**"
Chair: *Susana González*

Role of 2-pore domain potassium channels in spontaneous pathological pain
Cristian Acosta
Facultad de Ciencias Médicas-IHEM-CONICET, Universidad Nacional de Cuyo, Argentina

Role of pannexin 1 in the chronic pain: a preclinical study
Luis Constandil Córdova
Universidad de Santiago de Chile, Laboratorio de Neurobiología, Chile

IMT504 for the treatment of chronic pain: Preclinical observations and translational perspective
Pablo R. Brumovsky
Instituto de Investigaciones en Medicina Traslacional, CONICET-Universidad Austral, Argentina

Neuroactive steroids and central neuropathic pain
Dr. Florencia Coronel
Instituto de Biología y Medicina Experimental – CONICET
Laboratorio de Nocicepción y Dolor Neuropático, Argentina

17:30 Coffee Break
17:30 – 19: 30 POSTER SESSION /*Pabellón Argentina Hall*

19:30 – 20:30 RANWEL CAPUTTO LECTURE /*Room A*
Visual Cortical Dynamics
Charles Gilbert
The Rockefeller University, USA

20:45 WELCOME PARTY / *Pabellón Argentina Hall*

DAY 2 / Thursday, October 25th

08:30 – 10:30 **SYMPOSIUM IV** / *Room A*

"Oligodendrocytes: its role in myelination and remyelination"
Chairs: *Juana Pasquini; Jorge Correale*

Signaling mechanisms regulating CNS myelination
Wendy B. Macklin
Department of Cell and Developmental Biology, University of Colorado, USA

NG2-glia: old friends or new strangers? Implications and roles in the adult brain
Leda Dimou
Molecular and Translational Neuroscience, Dept. of Neurology, Ulm University, Germany

The dialogue between oligodendrocytes and axons in the process of neurodegeneration and neuroprotection
Jorge Correale
Instituto de Investigaciones Neurológicas Dr Raúl Carrea, FLENI, Buenos Aires, Argentina

Experimental demyelination models: effects of apotransferrin administration
Juana Pasquini
Dept Química Biológica, IQUIFIB. Facultad de Farmacia y Bioquímica, UBA-CONICET, Argentina

10:30 – 11:00 Coffee Break

11:00 – 12:00 PLENARY LECTURE / Room A
"Retinal Degenerations: The Isoprenoid Connection"
Steven J. Fliesler
Departments of Ophthalmology and Biochemistry and Graduate Program in Neurosciences, University at Buffalo- The State University of New York, and the VA Western New York Healthcare System, Buffalo VA Medical Center, USA

12:15 Lunch with Activities
-Group Photo
-IBRO-ISN-FALAN Round Table

14:30 – 16:00 Young Investigator Lectures
Room B: YIL 7-10

Oral Communications
Room C: OC 1-6

16:00 – 18:00 SYMPOSIUM V / *Room A*

"**Move on! Neural circuits underlying sensorimotor transformations**"
Chairs: *Violeta Medan; Martín Carbo Tano*

Spinal circuits for somatosensation and movement
Martyn Goulding
Salk Institute for Biological Studies Molecular Neurobiology Laboratory, La Jolla, USA

Brainstem circuits for the control of locomotion
María Soledad Espósito
Silvia Arber Lab, Friedrich Miescher Institute for Biomedical Research, Bassel, Suiza

Neuronal networks for motor Control
Lidia Szczupak
IFIByNE-CONICET-UBA, CABA, Argentina

Neural mechanisms of leg proprioception and motor control in Drosophila
Jhon Tuthill
University of Washington, Seattle, USA

SYMPOSIUM VI / Room B

"Astroglial heterogeneity: an opportunity for neuroprotection and regeneration?"
Chair: *Elaine Del-Bel*

Cellular targets of tyrosine kinase inhibitors in Amyotrophic Lateral Sclerosis
Luis Barbeito
Instituto Pasteur de Montevideo, Uruguay

Astrocyte Transforming Growth Factor Beta 1 Protects Synapses against Aβ Oligomers in Alzheimer's Disease Model.
Flávia C A Gomes
Instituto de Ciências Biomédicas, Rio de Janeiro, Brazil

Astrocytes as active players of the innate immune system: Another layer of astroglial heterogeneity? *Alberto Javier Ramos*
Laboratorio de Neuropatología Molecular, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis", CONICET, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

Are neuroinflammation and astrocytes key elements in L-DOPA-induced dyskinesia in Parkinson's disease?
Elaine Del-Bel
Department of MFPB-Physiology, FORP, University of São Paulo, Brazil.
Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), São Paulo, Brazil.

18:00 Coffee Break

18:00 – 20:00 Poster Session / *Pabellón Argentina Hall*

19:30 – 20:00 Reunión RAN (Red Argentina en Neurociencias) / *Room A*

20:00 SAN General Assembly / *Room A*

DAY 3 / Friday, October 26th

08:30 – 10:30 SYMPOSIUM VII / *Room A*
"Synaptic drive and neuromodulatory circuits in cognitive and emotional processes"
Chairs: *Joaquin Piriz; Mariano Soiza Reilly*

"Experience-dependent synaptic plasticity in the lateral habenula"
Manuel Mameli
Department of Fundamental Neuroscience, The University of Lausanne, Switzerland

"Synaptic Tagging and Capture: From Synapses to Behavior"
Sadegh Nabavi PhD
Danish Research Institute of Translational Neuroscience (DANDRITE), Denmark.
Department of Molecular Biology and Genetics, Aarhus University, Denmark

"Cholinergic mechanisms shaping VTA dopaminergic mal-adaptations to stress and nicotine"
Sebastian P. Fernandez, PhD
Institut de Pharmacologie Moléculaire et Cellulaire, CNRS, Nice, France.
Université Côte d'Azur, Valbonne, France

"Prefrontal serotonin transporter shapes cortico- raphe circuits and long-term emotional deficits of early-life exposure to SSRIs"
Mariano Soiza-Reilly
Instituto de Fisiología, Biología Molecular y Neurociencias (IFIBYNE) – CONICET, Universidad de Buenos Aires, Argentina

10:30 – 11:00 Coffee Break

11:00 – 13:00 SYMPOSIUM VIII / *Room A*

"Cell strategies in degenerative and regenerative processes of the nervous system"
Chair: *Luis E. Politi*

Multipotent cells as mediators of peripheral nerve regeneration
Patricia Setton
IQUIFIB-CONICET-UBA, Buenos Aires, Argentina.

Restoring the connectomes of regenerated retinal bipolar neurons following a tissue-disrupting retinal lesion in adult zebrafish.
Stenkamp Deborah
Professor, Biological Sciences, University of Idaho, USA

3D Retinal Organoids: New Frontiers for Stem Cell-based Clinical Applications
M. Valeria Canto-Soler
Associate Professor - Department of Ophthalmology
University of Colorado, School of Medicine, Aurora, USA

13:00 Lunch with Activities

14:30 – 15:30 ORAL COMMUNICATIONS
Room B: OC 7-10
Room C: OC 11-14

15:30 – 17:30 SYMPOSIUM IX / *Room A*

"Cellular and molecular mechanisms in retina degeneration"
Chairs: *Nora Rotstein; Cecilia Sánchez*

Neuroprotection of photoreceptors as a therapeutic strategy in retinal degeneration.
Thomas G Cotter
School of Biochemistry and Cell Biology, University College Cork, Ireland

Vascular and non-vascular alterations in retinopathies: towards a change in the therapeutic strategy
Sánchez M.Cecilia
Centro de Investigaciones en Bioquímica Clínica e Inmunología (CIBICI), CONICET, Departamento de Bioquímica Clínica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina.

Molecular Mechanisms of PEDF Peptides in Retinal Degenerations
S Patricia Becerra
National Eye Institute, National Institutes of Health, Bethesda, USA

SYMPOSIUM X / *Room B*

"Epilepsy from bench to the patients"
Chairs: *Jerónimo Auzmendi; Alberto Lazarowski*

Progressive P-glycoprotein overexpression and its relationship with SUDEP
Alberto Lazarowski
Clinical Biochemistry Department, FFyB, University of Buenos Aires, Argentina

Epigenetic changes induced by antiepileptic drugs and their relevance in epilepsy
Luisa Rocha Arrieta
Dept. Farmacobiología, Centro de Investigación y de Estudios Avanzados, México.

Kainic acid as a preclinical experimental model for the study of new molecules for the treatment of epilepsy and neurodegenerative diseases.
Antoni Camins
Departamento de Farmacología, Toxicología i Química Terapéutica, Facultad de Farmacia i Ciencias de la Alimentación, Universidad de Barcelona,España.
Biomedical Research Networking Centre in Neurodegenerative Diseases (CIBERNED), Madrid, Spain.
Instituto de Neurociencias, Universidad de Barcelona, Barcelona, España

Identification of epileptogenicity markers from the register of individual neurons in patients candidates to epilepsy surgery
Silvia Kochen
Epilepsy Center, Ramos Mejía y El Cruce Hospital, EnyS-CONICET, Buenos Aires, IBCN-CONICET-UBA, Buenos Aires, Argentina

17:30 Coffee Break

17:30 – 19:30 POSTER SESSION / *Pabellón Argentina Hall*

19:30 – 20:30 CLOSING LECTURE / *Room A*

DE ROBERTIS LECTURE:
Unraveling a novel NGF metabolic pathway and its deregulation in Alzheimer's pathology
A. Claudio Cuello
OC, MD, DS, FRSC, FMedSci
Department of Pharmacology and Therapeutics, McGill University, USA

20:30 **CLOSING CEREMONY** / *Room A*

21:30 **CLOSING DINNER** / *Patio de las Palmeras*

LECTURE ABSTRACTS

Wednesday, 24th- 11:00 – 12:00 OPENING LECTURE / Room A

Tubulin tyrosination-detyrosination cycle : key role in neuronal functions

Annie Andrieux[1,2], C. Aillaud[1], C. Bosc[1], L. Peris[1], L. Lafanechère[3], E.Denarier[1,2], C.Boscheron[1,2], M. Bogyo[4], K. Rogowski[5], Y.Wehland[6†], D.Job[1] & M.J. Moutin[1]

[1]Univ. Grenoble Alpes, GIN, Inserm U1216; [2]CEA, BIG-GPC; [3]Inserm U1209, Grenoble, France. [4]Stanford University School of Medicine, Stanford, California, USA. [5]CNRS UMR9002, IGH, Univ. Montpellier, France. [6]HZI, Braunschweig, Germany

Microtubules are cytoskeletal polymers of α/β tubulin hetero-dimers, centrally involved in cell division, motility and morphogenesis. In the de/tyrosination cycle of tubulin, the C-terminal tyrosine of α-tubulin is removed by a carboxy peptidase (TCP), and re-added by the enzyme tubulin tyrosine ligase (TTL). This cycle, which is unique to tubulin and mostly conserved throughout evolution, has a vital role *in vivo* (Erck *et al.* 2005, PNAS). Although the detyrosination reaction was first described 40 years ago (Hallak *et al.* 1977, FEBS Lett), the molecular identity of TCP has long remained unknown. We have now successfully identified vasohibin/SVBP complexes as TCP enzymes (Aillaud *et al.* 2017, Science). Based on data obtained in yeast, neurons and mouse models, we will present results demonstrating the crucial role of the tubulin de/tyrosination cycle in neuronal physiology. The impact of abnormal tubulin tyrosination levels on neuronal functions during neurodevelopment and neurodegenerative processes will also be presented.

Wednesday, 24th- 19:30 – 20:30 RANWEL CAPUTTO LECTURE / *Room A*

Visual Cortical Dynamics

Charles Gilbert
The Rockefeller University,USA

Vision is an active and dynamic process. The strategy our brain uses to parse scenes and recognize objects depends on experience. Our interpretation of visual scenes requires an interaction between internal representations of object properties acquired through experience and the immediate information coming from the retina. These internal representations enable the brain's analysis of scenes to be subject to top-down influences of attention, expectation, perceptual tasks, perceptual learning, working memory and motor commands. At the level of brain circuitry this process involves an interaction between long range and intrinsic cortical connections and enables neurons to assume different functional states according to the task being executed. Each cortical

area represents an association field, whereby bits of information are dynamically linked via a plexus of long range horizontal connections. Although each neuron receives 10^5 inputs from other neurons, neurons are capable of selecting a small subset of task relevant inputs and suppressing the influence of task irrelevant inputs. The circuitry of the adult cortex therefore is under a continual long term process of modification as we assimilate new information, and short term dynamics as we analyze the constituents of visual scenes. These mechanisms are common to all regions of the brain, and when disrupted may account for visual and behavioral disorders.

Thursday, 25th- 11:00 – 12:00 PLENARY LECTURE / *Room A*

"Retinal Degenerations: The Isoprenoid Connection"

Steven J. Fliesler

Departments of Ophthalmology and Biochemistry and Graduate Program in Neurosciences, University at Buffalo- The State University of New York, and the VA Western New York Healthcare System, Buffalo VA Medical Center, Buffalo, NY (USA)

The mevalonate pathway generates a number of biologically important isoprenoid products, including sterols (*e.g*., cholesterol), steroid hormones, bile acids, dolichol and its derivatives, isoprenylpyrophosphates, and biogenically related compounds. Cholesterol-quantitatively the dominant product of the pathway-is a ubiquitous component of the membranes of almost all eukaryotic cells and tissues, as well as of blood-borne lipoproteins. However, although cholesterol is essential for the viability and normal function of higher eukaryotes, an over-abundance of cholesterol has been associated with human disease, including Alzheimer's disease and age-related macular degeneration. Similarly, a paucity of cholesterol also can be deleterious, even lethal. Hence, defective cholesterol biosynthesis can lead to disruption of cellular and systemic physiology, resulting in profound pathologies. Using a rat model that mimics one such human recessive disease (Smith-Lemli-Opitz Syndrome (SLOS)), it has been shown that blocking the last step in cholesterol synthesis causes a progressive and irreversible retinal degeneration. Studies in our lab indicate that the molecular mechanism underlying this degeneration is not simply due to cholesterol deficiency; rather, it is complex, involving marked lipidomic, proteomic, and genomic changes, including lipid and protein oxidation. Hence, providing exogenous cholesterol alone (the current standard of care for SLOS patients) is not an effective therapeutic strategy. We hypothesized that

combined antioxidant-cholesterol supplementation should prevent or markedly reduce the severity of the retinal degeneration in the SLOS rat model. This prediction has been validated, providing the necessary proof-of-principle to guide an evidence-based clinical trial for developing an improved therapeutic intervention for SLOS and related diseases.

Friday, 26th- 19:30 – 20:30 DE ROBERTIS LECTURE / *Room A*

Unraveling a novel NGF metabolic pathway and its deregulation in Alzheimer's pathology

A. Claudio Cuello
OC, MD, DS, FRSC, FMedSci
Department of Pharmacology and Therapeutics, McGill University

We have revealed a novel brain metabolic pathway responsible for the activity-dependent release of proNGF from cortical cells, its conversion to mature NGF (mNGF), and subsequent degradation by metalloproteases (Bruno and Cuello), a pathway validated pharmacologically (Allard et al). Both Alzheimer's disease (AD) and Down syndrome (DS) exhibit a marked atrophy of the NGF-dependent Basal Forebrain (BF) cholinergic system. Applying the NGF pathway paradigm in AD and DS human brain we demonstrated that in both conditions a marked pathway deregulation (Bruno et al, Iulita et al) indicating a trophic factor deprivation of NGF-dependent BF neurons given the failure of proNGF conversion to mNGF and aggravated mNGF degradation. In brief, that higher levels of the NGF precursor (proNGF) in AD are not "good news" but rather an indication of the trophic factor failure to sustain the BF cholinergic phenotype.

SYMPOSIUM ABSTRACTS

Neurobiology of Drug Addiction Symposium
October 24
8:30-10:30 h

Chairs: Dr. Liliana M. Cancela and Marcelo Rubinstein

A hallmark of drug addiction is the uncontrollable desire to consume drugs at the expense of severe negative consequences. Moreover, addicts that successfully refrain from drug use have a high vulnerability to relapse even after months or years of abstinence. The current understanding of drug-induced neuroplasticity within the mesocorticolimbic brain system that contributes to the development of addiction and the persistence of relapse to drug seeking is one of the most prominent challenges in neurobiology of drug addiction. The long-lived behavioral abnormalities associated with addiction are thought to arise from pathological plasticity not only in dopaminergic but also in glutamatergic neurotransmission. Identification of drug-induced neuroplasticity is crucial to understand how molecular and cellular adaptations contribute to the end stage of addiction, which from a clinical perspective, is a time-point where pharmacotherapy may be most effectively employed. The neural mechanisms underlying drug compulsive disorder and reward learning will be included. The newest molecular, behavioural and electrophysiological advances as well as therapeutic strategies will be proposed for drug addiction.

8:30-9:00 Verónica Álvarez (USA)
Dissecting the roles of dopamine D2 receptors in the basal ganglia and motivated behaviors
Dopamine actions in the nucleus accumbens are responsible for generating most of the behaviors triggered by stimulant drugs such as cocaine. This is in large part known because antagonists for the two main types of dopamine receptors expressed in the accumbens, D1 and D2 receptors, can block the behavioral response to cocaine. Dopamine D1 receptors are mainly expressed in the direct-pathway projection neurons of the striatum. D2 receptors, however, are expressed on the indirect-pathway projection neurons, as well as on cholinergic interneurons and the synaptic terminals of glutamate inputs and dopamine inputs to the striatum. Veronica Alvarez will present data from multiple studies in which her laboratory and that of Dr. Rubinstein used genetic tools to dissect out the specific contributions of the dopamine D2 receptors expressed in different cell-types in driving motivated behaviors; from the response to stimulant drugs, to alcohol induced sedation and stimulation.

9:00-9:30 Bruno Averbeck (USA)
Neural systems underlying reinforcement learning

To survive, animals must find food, avoid harm and reproduce. Learning is critical to solving these problems as environments often change, and animals have to adapt to these changes. Reinforcement learning (RL) is the behavioral process of learning from the outcomes of decisions to make better choices in the future. The neural systems underlying these processes are, therefore, critical for adapting to changes in the environment. However, when these systems are driven too far they also underlie disorders including addiction and acquired forms of anxiety like PTSD. The standard model of RL focuses on dopamine and its role in the striatum. Specifically, this model suggests that the activity of dopamine neurons, which codes errors in the prediction of rewards, drives plasticity on frontal-cortical synaptic inputs to the striatum. Through this process striatal medium spiny neurons represent and track the values of choices. However, recent work by our lab has shown that the amygdala also plays an important role in RL. Specifically, when animals have to learn the values of visual images, the amygdala and ventral striatum play important roles. However, when animals have to learn the values of actions, the dorsal striatum is important. In addition, the amygdala can rapidly update value estimates, whereas the striatum adapts more slowly. The slower striatal learning is, however, less sensitive to noise.

9:30-10:00 Martine Cador (France)

Opiate withdrawal memories: Behavior and neural network

Compulsive drug-seeking behavior and its renewal in former drug addicts is promoted by several situations, among which reactivation of drug withdrawal memories plays a crucial role. Opiate abuse induces a strong dependence which is characterized by the appearance of a withdrawal syndrome upon drug use cessation and in abstinent individuals, withdrawal-associated aversive memories are hypothesized to motivate drug seeking and relapse. In rats it was shown that re-activation of affective memories associated with the withdrawal state induced a negative emotional state influencing motivated behaviors and leading to drug seeking. In term of neuronal substrates, several structures of the mesolimbic corticostriatal circuit are reactivated by the simple re-exposure to environmental stimuli previously associated with naloxone-precipitated opiate withdrawal in dependent rats suggesting that the processing of withdrawal memories is underpinned by activity changes within these interconnected limbic structures. I will present behavioral, anatomical and in vivo gamma oscillation recordings showing that among these structures the nucleus accumbens (NAC), the basolateral amygdala (BLA) and the hippocampus (HPC) are of crucial interest in processing salience and valence of withdrawal associated memories.

10:00-10:30 Peter W Kalivas (USA)

Using the Neurobiology of Willpower to Treat Drug Addiction

All treatments for drug addiction are replacement therapies, such as methadone for opioids or varenicline for tobacco, that do not directly treat the changes in the brain produced by chronic drug use. The brain pathology produced by chronic

drug use is located in neuro-circuitry controlling decision making, which accounts for why drug addicts make poor choices in life that cause increasing drug use and addiction. We have identified this pathology and found ways to reverse the pathology in rodent models of addiction. Some of these therapeutic approaches have successfully moved into clinical trials.

Wednesday 24th - 15:30 – 17:30 SYMPOSIUM II / *Room A*

"**Emerging mechanisms in neuronal signaling: from cell biology to pathogenesis**"

Chairs: Gabriela Salvador *INIBIBB-UNS-CONICET, Bahía Blanca, Argentina.* Mauricio Martín *CONICET- INIMEC-UNC, Córdoba, Argentina*

C-Fos, a moonlighting protein: What we know about its lipid activator capacity in the nervous system

Beatriz L. Caputto, Cesar G. Prucca, Lucía Rodríguez-Berdini.
CIQUIBIC (CONICET), Dpto. De Química Biologica "Ranwel Caputto", Fac. de Cs. Químicas, UNC

It is expected that the synthesis of lipids, the quantitatively most important molecular species of cell membranes, be synchronized with the cell's diverse functional states. In cells actively involved in proliferation or in plasma membrane extension, processes that demand massive membrane biogenesis, lipid synthesis rates must be higher than those in cells that are neither dividing nor actively growing. However, the nature of the regulatory events underlying such processes is still poorly understood. In the past years, we have shown that the protein c-Fos is actively involved in these regulatory events.

The content of c-Fos, a member of the AP-1 family of inducible transcription factors, is tightly regulated in cells: c-Fos is at the limit of detection in quiescent cells whereas its expression is rapidly and only transiently induced when cells are stimulated to re-enter growth. It has been hypothesized that this c-Fos-AP-1 activity transmits short-termed, growth-promoting cellular signals into longer lasting changes by regulating the expression of growth related genes. We established that c-Fos is capable of regulating growth not only by its AP-1 activity but also by its capacity to act as a cytoplasmic activator of lipid synthesis in normal and pathological cell processes that demand high rates of membrane biogenesis. Such is the case in light-stimulated retina ganglion and photoreceptor cells, in growing NIH 3T3 cells, in differentiating PC12 cells and primary rat hippocampal neurons, and in tumors of the nervous system. Specifically blocking c-Fos expression or in c-fos -/- mice, proliferation and

growth of normal and tumor cells are slowed/halted without substantial changes in their AP-1 content. At present, we are examining in vivo, putative c-Fos deletion mutants that do not affect its AP-1 activity but act as negative dominants of its lipid synthetizing activity in the hope to limit the unrestricted proliferation and growth of these CNS tumor cells.

Specific Phospholipids Regulate the Acquisition of Neuronal and Astroglial Identities in Post-Mitotic Cells

Aneley Montaner, Consuelo Perez and Claudia Banchio
Instituto de Biología Molecular y Celular de Rosario IBR-CONICET Rosario, Argentina

Up to now, the known mechanisms underpinning cell-fate specification act on neural progenitors, afecting their commitment to generate neuron or glial cells. Here, we show that particular phospholipids supplemented in the culture media modify the commitment of post-mitotic neural cells *in vitro*. Phosphatidylcholine (PtdCho)-enriched media enhances neuronal differentiation at the expense of astroglial and unspecified cells. Conversely, phosphatidylethanolamine (PtdEtn) enhances astroglial differentiation and accelerates astrocyte maturation. The ability of phospholipids to modify the fate of post-mitotic cells depends on its presence during a narrow time-window during cell differentiation and it is mediated by the selective activation of particular signaling pathways. While PtdCho-mediated effect on neuronal differentiation depends on cAMP-dependent kinase (PKA)/calcium responsive element binding protein (CREB), PtdEtn stimulates astrogliogenesis through the activation of the MEK/ERK signaling pathway. Collectively, our results provide an additional degree of plasticity in neural cell specification and further support the notion that cell differentiation is a reversible phenomenon. They also contribute to our understanding of neuronal and glial lineage specification in the central nervous system, opening up new avenues to retrieve neurogenic capacity in the brain.

Fatty acids participation in neuronal differentiation of SH-SY5Y cells

Falomir Lockhart, Lisandro J.
Laboratory of Biophysics and Cell Biology of Lipid-Binding Proteins, INIBIOLP, CCT-La Plata, CONICET; Fac. de Cs. Exactas, Universidad Nacional de La Plata, Argentina.

Fatty acids (FAs) are classically associated with structural and metabolic roles, as they can be stored as triglycerides, degraded by oxidation or used in phospholipids´ synthesis, the main components of biological membranes. Recently, it has been shown that these lipids exhibit also regulatory functions in different cell types, and the neuronal tissue should not be strange to this role. For example, the central nervous system is enriched in poly-unsaturated FAs, such as arachidonic acid, which participates in the regulation of membrane fluidity, axonal growth, development and inflammatory response. Alterations in lipid metabolism have been associated with cognitive problems and neurodegenerative diseases, but the molecular mechanism behind these effects remains elusive. These "lipokines" bind to specific receptors triggering second messenger´s systems and regulating gene expression. Four plasma membrane, G protein-coupled receptors that recognize free FAs were identified since 2005, commonly known as FFARs. But their roles in neuronal tissues are yet not fully understood.

Our aim is to characterize the mechanisms by which different FAs modulate the differentiation of SH-SY5Y cells *in vitro*, a broadly used model system for studies of neurodegenerative diseases such as Parkinson's Disease. We evaluated the effect of supplementation with FAs, monitoring Akt expression and phosphorylation levels; Ca^{+2} release and neurite outgrowth. Our results support a positive role for FAs acting through FFARs in neuronal differentiation, although further studies considering other receptors like PPARs and/or FABPs should also be considered for a wider understanding of FAs´ neuronal effects.

Characterization of lipid receptors in the nervous system will provide a framework for a better understanding of their roles in neurophysiology and, potentially, new targets for drug design against aging and neurodegenerative processes.

Role of isoprenoids in autophagy and prion-like spread of Amyloid beta pathology.

Posse de Chaves, E., Smith, K., Viveiros, A and Mohamed, A.
Neuroscience and Mental Health Institute- Department of Pharmacology- University of Alberta-Canada
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The development of disease-modifying therapies for Alzheimer's disease (AD) is hampered by the poor understanding of early pathogenic mechanisms that lead to it. Brain accumulation of beta amyloid peptides (Aβ) drive AD pathogenesis. In addition, Aβ may be transmitted from cell to cell in a 'prion-like' spread that contributes to AD progression.

We discovered that $A\beta_{42}$ inhibits cholesterol and isoprenoids (farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP)) synthesis, reducing protein prenylation in neurons exposed to $A\beta_{42}$ and in TgCRND8 mouse brains.

Autophagy relies heavily on prenylated proteins such as Rabs. Autophagy is altered in AD and reversing autophagy dysfunction improves pathophysiology and rescues memory performance in TgCRND8 mice. We showed that autophagic flux is blocked in neurons treated with $A\beta_{42}$ and in TgCRND8 mouse brain. Autophagy dysfunction is caused by inhibition of prenylation because GGPP normalizes autophagic flux in cultured cells and in vivo. Rab7 is required for autophagy progression. Rab7 localization to autophagosomes is reduced in $A\beta_{42}$-treated neurons and GGPP corrects Rab7 prenylation and subcellular localization.

When autophagy is compromised, cells may resource to protein secretion to alleviate stress, although this also may favor "prion-like" spreading. Aβ is released in extracellular vesicles (EVs). Autophagy blockade may increase EVs secretion. We isolated EVs from N2a cells and $N2aAPP^{swe}$ cells by ultracentrifugation and density gradient and characterized them using light scattering asymmetric flow field fractionation electron microscopy and image flow cytometry. Using trypsin protection assays we have determined that the majority of Aβ is located at the EVs surface, but around ~25% is present inside EVs.

Our studies identify the reduction of protein prenylation as a key mechanism of autophagy dysfunction and prion-like spread in AD and will provide evidence of treatments in vivo with disease-modifying value.

Wednesday 24th - 15:30 – 17:30 SYMPOSIUM III / *Room B*

"**Chronic pain: basic research and translational perspectives**"
Chair: Susana González *IBYME – CONICET School of Medicine-Universidad de Buenos Aires, Argentina*

Role of 2-pore domain potassium channels in spontaneous pathological pain

Dr. Cristian Acosta
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Pathological pain affects 1 out of 5 adults worldwide and is often refractory to traditional therapies. Patients affected by this condition exhibit debilitating sensory abnormalities including spontaneous pain, hyperlagesia, allodynia and paresthesias. Changes in nociceptor excitability are essential for the initiation and maintenance of this pain. As neuronal excitability is highly dependent on the resting membrane potential (Em) we focused on 2-pore domain potassium channels (K2Ps) whom are main contributors to Em in primary afferent neurons. We studied systematically 12 out of the known 15 functional K2P channels in a model of cutaneous inflammation and found that they exhibit a complex pattern of expression at the mRNA level. We then focused on two K2P channels, TREK2 and THIK1. We characterised the expression pattern for these channels and examined their role in pathological pain. We found that they were both expressed by subpopulations of nociceptors and that down-regulating their expression in vivo resulted in exacerbated spontaneous pain in rats also in a model of cutaneous inflammation. Importantly, TREK2 appears to limit spontaneous pain by hyperpolarizing a subpopulation of IB4-binding C-nociceptors, while THIK1 seems to play a role in both, peptidergic and non-peptidergic nociceptors. Taken together, our findings put selective activation of K2P channels as a new potential target to treat spontaneous pain.

Role of pannexin 1 in the chronic pain: a preclinical study

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Pannexin 1 (panx1) is a large-pore membrane channel expressed in many tissues of mammals, including neurons and glial cells. Panx1 channels are highly permeable to calcium and adenosine triphosphatase (ATP); on the other hand,

they can be opened by ATP and glutamate, two crucial molecules for acute and chronic pain signaling in the spinal cord dorsal horn, thus suggesting that panx1 could be a key component for the generation of central sensitization during persistent pain. In this study, we examined the effect of three panx1 blockers, namely, 10panx peptide, carbenoxolone, and probenecid, on C-reflex wind-up activity and mechanical nociceptive behavior in a spared nerve injury neuropathic rat model involving sural nerve transection. In addition, the expression of panx1 protein in the dorsal horn of the ipsilateral lumbar spinal cord was measured in sural nerve-transected and sham-operated control rats. Sural nerve transection resulted in a lower threshold for C-reflex activation by electric stimulation of the injured hindpaw, together with persistent mechanical hypersensitivity to pressure stimuli applied to the paw. Intrathecal administration of the panx1 blockers significantly depressed the spinal C-reflex wind-up activity in both neuropathic and sham control rats, and decreased mechanical hyperalgesia in neuropathic rats without affecting the nociceptive threshold in sham animals. Western blotting showed that panx1 was similarly expressed in the dorsal horn of lumbar spinal cord from neuropathic and sham rats. These results constitute the first evidence that panx1 channels play a significant role in the mechanisms underlying central sensitization in neuropathic pain.

IMT504 for the treatment of chronic pain: Preclinical observations and translational perspective

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Chronic pain, which can be inflammatory or neuropathic in nature, affects millions of people around the World. Unfortunately, an important number of patients do not see a proper solution to their problem, in part due to the fact that most drugs currently available to treat pain have limited efficacy and/or exert serious adverse effects. Such scenario reinforces the need of further research and the identification of new analgesic drugs that could help chronic pain patients. IMT504 is an oligodeoxynucleotide (ODN) with immunomodulatory and tissue repair properties, as shown in various human disease animal models. Recently, we showed that IMT504 prevents or abolishes the progress of pain in rats with sciatic nerve crush, a self-limiting neuropathy

that exposes the injured animal to up to 21 days of pain. In this conference, results demonstrating the efficacy of IMT504 for the control of chronic inflammatory or neuropathic pain will be presented. The results suggest the potential of this ODN in diverse chronic pain conditions, in turn prompting the translation to humans suffering pain. Such potential will be elaborated by presenting the steps taken thus far in relation to the validation of IMT504 as a therapeutic agent for the treatment of inflammatory or neuropathic pain in humans, through the development of a phase I-II clinical trial.

Neuroactive steroids and central neuropathic pain

Dr. Florencia Coronel
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Neuropathic pain develops in nearly 70% of patients with spinal cord injury (SCI). These patients, already burdened with the disability of paralysis, emotional trauma and spasticity, must contend with severe unrelenting pain that is refractory to conventional treatment. The precise mechanisms underlying neuropathic pain after spinal injury remain elusive. However, central sensitization involving the hyperexcitability of dorsal horn neurons in the pain pathway is known to be mediated by N-Methyl-D-Aspartate receptor (NMDAR), and the activation of glial cells, with the subsequent release of pro-nociceptive mediators, also play a crucial role. Previous work from our laboratory and others has shown that progesterone, a neuroactive steroid, exerts neuroprotective and promyelinating actions in the injured spinal cord. Further, we have recently reported that this steroid may offer a promising perspective in pain modulation. In this work, we used a recognized model of central neuropathic pain to study the effects of progesterone on the expression of NMDAR subunits and protein kinase C (PKC), key players in the process of central sensitization at the spinal level. Injured animals receiving vehicle showed well-established mechanical and thermal allodynia (pain elicited by innocuous stimuli), and a significant increase in the spinal expression of all the NMDAR subunits and PKC. Interestingly, animals receiving progesterone did not develop mechanical allodynia and showed reduced sensitivity to cold stimulation. In these animals, the expression of NMDAR subunits and PKC remained similar to control levels. In addition, progesterone was also able to reduce glial cell activation and the production of proinflammatory cytokines

which strongly contribute to the pathology of central neuropathic syndromes. Our current investigations add new data to further stimulate the study of neuroactive steroids-based therapies and may open new avenues to prevent chronic pain after central injuries.

Thursday, 25th - 08:30 – 10:30 SYMPOSIUM IV/ *Room A*

"Oligodendrocytes: its role in myelination and remyelination"

Chairs: Juana Pasquini *Dept Química Biológica, IQUIFIB. Facultad de Farmacia y Bioquímica, UBA-CONICET.* Jorge Correale *Instituto de Investigaciones Neurológicas Dr Raúl Carrea, FLENI, Buenos Aires, Argentina*

Signaling mechanisms regulating cns myelination

Wendy B. Macklin, Kathryn Bercury, Hannah Hathaway and Teresa Wood
Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora, CO, USA

The mTOR signaling pathway is a ubiquitous signal integrator for numerous growth and survival factors, guidance cues and differentiation drivers. In the central nervous system (CNS), it impacts the development of neurons and glia. Oligodendrocyte differentiation and myelination are tightly regulated,and we have shown thatAkt and mammalian Target of Rapamycin (mTOR) are important regulators of CNS myelination in vivo. mTOR functions through two distinct complexes, mTOR complex 1 (mTORC1) and mTORC2, by binding to either Raptor or Rictor, respectively. In order to establish whether both mTORC1 and mTORC2 have unique functions during CNS myelination, we conditionally ablated either Raptor or Rictor in the oligodendrocyte lineage in vivo. Initial studies deleted proteins from oligodendrocytes using the 2',3' cyclic nucleotide phosphohydrolase (CNP) promoter. In CNP-Cre X Raptor fl/fl mice (RaptorcKO mice) myelination in the spinal cord was dramatically impaired. By contrast, when Rictor(mTORC2) was comparably deleted, it has far less impact on myelination. However, in recent studies we deletedRictor selectively in oligodendrocyte progenitor cells using the platelet derived growth factor receptor alpha promoter (PDGFR□-Cre). Interestingly, a significant reduction of myelination was seen in PDGFR□-Cre X Rictorfl/fl(RictorcKO) mice. Unexpectedly, this dysmyelination was seen in corpus callosum rather than in spinal cord. These studies suggest that there are regional effects of mTOR signaling in oligodendrocytes and that mTORC1 and mTORC2 are both important for myelination. These studies also indicate that the specific promoter used for deletion may change the impact of the deletion, and that

there may be compensation for loss of mTOR signaling, depending on when the deletion occurs during the differentiation of the cells. These studies were supported by NIH R37 NS082203.

NG2-glia: old friends or new strangers? Implications and roles in the adult brain

Leda Dimou
Molecular and Translational Neuroscience, Dept. of Neurology, Ulm University, Germany

Glial cells in the adult brain are very diverse and some of them represent the stem and progenitor cells of the CNS. My talk will focus on the adult oligodendrocyte progenitor cells, also known as NG2-glia, in the intact and injured mouse brain. The widespread interest in this glial cell population raises from their unique properties, as adult NG2-glia represent the only proliferating cell type in the adult brain parenchyma outside the neurogenic niches and continuously generate -in a region specific manner- mature, myelinating oligodendrocytes. However, their functions in the adult CNS and the mechanisms regulating their behavior under both physiological and pathological conditions are still not resolved. Additionally, it is still widely unknown whether NG2-glia comprise a homogeneous or heterogeneous population. Interestingly, NG2-glia were found to build postsynapses for neurons and axons, with still unraveled roles. To tackle these questions, we use various tools such as novel transgenic mouse lines, transplantation experiments, conditional depletion of proliferating NG2-glia, proteomic and transcriptomic analysis as well as *in vivo* live imaging of these cells in the adult mouse cerebral cortex. By these techniques we were able to reveal new insights into the functional role of NG2-glia in the intact and injured brain.

The dialogue between oligodendrocytes and axons in the process of neurodegeneration and neuroprotection

Dr. Jorge Correale
Instituto de Investigaciones Neurológicas Dr Raúl Carrea, FLENI, Buenos Aires, Argentina

Results from immunological, genetic and histopathology studies have demonstrated that Multiple Sclerosis (MS) is not only an inflammatory disease, but also a neurodegenerative condition.Growing knowledge indicates that

oligodendroglial dysfunction can contribute to neuropathology in classical neurodegenerative diseases and their respective mouse models. The study of oligodendrocyte (OGD)-dependent axonal function and survival represents a new aspect of CNS neurodegenerative pathophysiology.Although myelin is traditionally viewed as an inert insulating structure, it has become clear that myelin is metabolically active, allowing themovement of macromolecules into the periaxonal space, with important functional impact on axonal nutrition and neuronal survival. Disruption of oligodendroglial proteins participating in various cellular functions may interfere, directly or indirectly, with efficient metabolic coupling between OGDs and axons, ultimately altering axon integrity and function.Several studies have demonstrated that lactate is critical for neuronal energy supply during increased activity, and that interfering with its pathway will result in neurodegeneration. As astrocytes are essentially the only cells containing glycogen in the adult CNS, glycogen metabolism followed by glycolysis provides a source of lactate to other cells. Studies combining both astrocytes and OGDs have demonstrated that astrocytes transfer energy metabolites directly to OGDs, which in turn support the metabolism of neurons and axons. Connections between astrocytes and myelinating cells occur via gap junctions formed by connexins (Cx) in the plasma membranes of two adjacent cells; Cx form channels that allow the exchange of small molecules between connected cells. Although most of the alternative energy transported from astrocytes consists in lactate, ketone bodies and pyruvate can also be produced by astrocytes and thus contribute to neuron energy supplies. Overall, the role of OGDs in supporting axons at a metabolic level is of obvious relevance to various myelin diseases. The close link in the axon-myelin unit makes them cellular partners, and further contributes to the understanding of how pathological alterations can spread across white and grey matter boundaries.

Experimental demyelination models: effects of apotransferrin administration

Juana Pasquini, Vanesa Mattera and Jorge Correale
Dept Química Biológica, IQUIFIB. Facultad de Farmacia y Bioquímica, UBA-CONICET

Previous results from our laboratory showed the pro-differentiating effect of apotransferrin (aTf) (intracranially injected) on oligodendroglial cells both*in vivo* and*in vitro.* In addition, the remyelinating effect of aTf was demonstrated in two different models of demyelination such as cuprizone intoxication and hypoxia-ischemia (H/I) and in an iron deficiency model of hypomyelination.In H/I, we observed that the intranasal (iN) administration of human aTf provides neuroprotection to the brain. Treatment with aTf reduceswhite matterdamage,

neuronal loss and astrogliosis in different brain areas, increasing the proliferation of oligodendroglial precursor cells in the subventricular zone. All these data induced us to develop a less invasive technique to deliver aTf to the CNS. Exosomeswere isolated from human and mouse plasma, as well as from neuroblastoma (N2a) and oligodendroglioma (OLN-93) cell lines and astrocyte primary cultures. Exosome characterization was conductedby Western blot, dynamic light scattering (DLS) and scanning electron microscopy (SEM), all of which showed that the nanoparticles had been isolated in pure conditions and without integrity modifications and were thus able to be loaded with aTf. The presence of TfR was also detected in all the extracellular vesicles studied,as well as their ability to bindaTf.
Obtainingexosomes with a clearly defined active therapeutic cargo such as Tf and with a surface marker to ensure the targeting of recipient cells may constitutea promising approach to nanomedicine.

Thursday, 25th - 16:00 – 18:00 SYMPOSIUM V/ *Room A*

"**Move on! Neural circuits underlying sensorimotor transformations**"
Chairs: Violeta Medan *IFIByNE, CONICET. Buenos Aires, Argentina.* Martín Carbo Tano *Brain and Spine Institute, ICM Hôpital Pitié-Salpêtrière, Paris, France*

Spinal circuits for somatosensation and movement
Martyn Goulding
Salk Institute for Biological Studies Molecular Neurobiology Laboratory, La Jolla, USA

Animals use a variety of sensory modalities to interact with and explore the environment in which they move. Of particular importance is the somatosensory system, which monitors the internal and external state of the body during movement. Very little is currently known about how somatosensory information is processed and gated by the spinal cord. Using a sophisticated suite of genetic tools, we have begun to functionally dissect the cutaneous arm of the somatosensory system, which plays a central role in generating many of the protective and affective behaviors animals display. Our studies have led to the identification of a number of excitatory and inhibitory cell types that play key roles in processing and gating noxious and innocuous mechanosensory stimuli. This knowledge is now being used to determine how sensory afferent feedback interfaces with the spinal motor system to control movement and generate stimulus-specific motor reflexes.

Brainstem circuits for the control of locomotion

María Soledad Espósito
Silvia Arber Lab, Friedrich Miescher Institute for Biomedical Research, Bassel, Suiza

The ability to move between places is an essential animal behavior that fascinated researchers since the beginning of neuroscience. Today we know that spinal cord circuits control the basic locomotor pattern determined by intra and inter-limb coordination, however, supraspinal commands are indispensable in order to initiate locomotion. Classical experiments based on electrical microstimulation identified brain regions with the ability to elicit locomotion but in most cases, the coexistence of functionally different neuronal subpopulations may have led to controversial results. In my talk, I will describe recent findings on the cellular and functional organization of brainstem motor centers in which specific neuronal subpopulations control opposing aspects of motor behavior such as locomotion or immobility.

NEURONAL NETWORKS FOR MOTOR CONTROL

Lidia Szczupak
IFIByNE-CONICET-UBA, CABA, Argentina

Neural networks that control animal movement are, on one hand, hierarchically organized and, on the other hand, highly distributed. The study of such networks requires the implementation of experimental strategies that allow simultaneous recordings at multiple levels within the nervous system to evaluate how these levels interact to generate a coherent behavioral output.
The nervous system of leeches presents unique advantages for the understanding on how motor control networks function. Leeches display robust locomotive and defensive behaviors. The simplicity of the organism structure is reflected in the relative simplicity of its nervous system formed by a chain of identical ganglia flanked by two brains, one in the head and the other in the tail. Neurons in each ganglion are not type representative units but they play well-defined functions, that are complementary shared with as few as one other neuron to very few other neurons.
The study of how the crawling motor pattern is organized in the leech nervous system had shed light on the role played by motoneurons in motor control. Previously conceived as mere output units, motoneurons shape the crawling motor pattern via recurrent inhibitory circuits, and through the interaction with the central pattern generator. Thus in addition to well-known proprioceptive

feedback mechanism, the output of motoneurons participates in the pattern generation.
The results obtained throughout the analysis of the crawling network do not contradict the hierarchical nature of motor networks but shed light on how the processing of feedforward and feedback signals are essential to shape a behavioral output.

Neural mechanisms of leg proprioception and motor control in Drosophila

Jhon Tuthill
University of Washington, Seattle, USA

Animals rely on an internal sense of body position and movement to effectively control motor behavior. This sense of proprioception is mediated by diverse populations of internal mechanosensory neurons distributed throughout the body.
My lab is trying to understand how proprioceptive stimuli are detected by sensory neurons, integrated and transformed in central circuits, and used to guide motor output. We approach these questions using genetic tools, *in vivo* two-photon imaging, and patch-clamp electrophysiology in *Drosophila*. We recently found that the axons of fly leg proprioceptors are organized into distinct functional projections that contain topographic representations of specific kinematic features: one group of axons encodes tibia position, another encodes movement direction, and a third encodes bidirectional movement and vibration frequency. Whole-cell recordings from downstream neurons reveal that position, movement, and directional information remain segregated in central circuits. These feedback signals then converge upon motor neurons that control leg muscles.
Overall, our findings reveal how a low-dimensional stimulus – the angle of a single leg joint – is encoded by a diverse population of mechanosensory neurons. Specific proprioceptive parameters are initially processed by parallel pathways, but are ultimately integrated to influence motor output. This architecture may help to maximize information transmission, processing speed, and robustness, which are critical for feedback control of the limbs during adaptive locomotion.

Thursday, 25th - 16:00 – 18:00 SYMPOSIUM VI/ *Room B*

"Astroglial heterogeneity: an opportunity for neuroprotection and regeneration?"

Chair: Elaine Del-Bel *Department of MFPB-Physiology, FORP, University of São Paulo, Brazil*
Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), São Paulo, Brazil

Cellular targets of tyrosine kinase inhibitors in Amyotrophic Lateral Sclerosis

Luis Barbeito
Instituto Pasteur de Montevideo, Uruguay

Inhibitors of type III tyrosine kinase have demonstrated therapeutic benefit in oncologic, inflammatory and fibrotic diseases. We have previously shown evidence that post-paralysis survival of SOD1G93A rats can be significantly extended by the masitinib, a drug currently in phase 3 clinical trials for ALS. Masitinib is unique among many other ALS-developmental drugs because it exerts protection in SOD1G93A rats when treatment starts after overt paralysis onset, potentially reproducing the clinical setting in ALS patients.

Masitinib targets a highly selective profile of tyrosine kinases including CSF1R, KIT, PDGF-R, Fyn and Lyn. Through inhibition of CSF1R, masitinib strongly reduces gliosis and the emergence of aberrant glial cells in the ventral horn of symptomatic SOD1G93A rats. In the fast-fatigable muscle extensor digitorum longus (EDL), post-paralysis treatment with masitinib significantly decreases c-Kit-expressing mast cells that accumulate close to denervated motor plates. Masitinib treatment starting after paralysis onset dramatically reduces the number of degranulating mast cells and delays NMJ denervation, as compared with vehicle-treated rats.

In the sciatic nerve of symptomatic SOD1G93A rats, a subset of reactive Schwann cells expresses CSF1 and IL-34, which stimulate macrophage proliferation and activation through CSF1R. Additionally, a subset of invading macrophages express stem cell factor, which promotes the proliferation and differentiation of mast cell precursors through activation of c-Kit. Furthermore, a sub-set of chymase+ macrophages accumulate and pack together with neutrophils, likely exacerbating the focal nerve pathology. Treatment with masitinib for 15 days from paralysis onset, prevents the appearance of mast cell/neutrophil aggregates and reduces the number of non-phagocytic macrophages. Remarkably, the treatment also significantly decreases axonal pathology and demyelination, as compared to vehicle-treated rats.These findings further strengthen the rationale for treating ALS with tyrosine kinase

inhibitors, in particular masitinib, and indicate novel pathogenic pathways in the central and peripheral nervous systems involving inflammatory cells, the emergence of which is likely associated with paralysis progression.

Astrocyte Transforming Growth Factor Beta 1 Protects Synapses against Aβ Oligomers in Alzheimer's Disease Model.

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Alzheimer disease (AD) is characterized by progressive cognitive decline, increasingly attributed to neuronal dysfunction induced by amyloid-β oligomers (AβOs). Although the impact of AβOs on neurons has been extensively studied, only recently have the possible effects of AβOs on astrocytes begun to be investigated. Given the key roles of astrocytes in synapse formation, plasticity, and function, we sought to investigate the impact of AβOs on astrocytes, and to determine whether this impact is related to the deleterious actions of AβOs on synapses. We found that AβOs interact with astrocytes, cause astrocyte activation and trigger abnormal generation of reactive oxygen species, which is accompanied by impairment of astrocyte neuroprotective potential *in vitro* We further show that both murine and human astrocyte conditioned media (CM) increase synapse density, reduce AβOs binding, and prevent AβO-induced synapse loss in cultured hippocampal neurons. Both a neutralizing anti-transforming growth factor-β1 (TGF-β1) antibody and siRNA-mediated knockdown of TGF-β1, previously identified as an important synaptogenic factor secreted by astrocytes, abrogated the protective action of astrocyte CM against AβO-induced synapse loss. Notably, TGF-β1 prevented hippocampal dendritic spine loss and memory impairment in mice that received an intracerebroventricular infusion of AβOs. Results suggest that astrocyte-derived TGF-β1 is part of an endogenous mechanism that protects synapses against AβOs. By demonstrating that AβOs decrease astrocyte ability to protect synapses, our results unravel a new mechanism underlying the synaptotoxic action of AβOs in AD.

Astrocytes as active players of the innate immune system: Another layer of astroglial heterogeneity?

Dr. Alberto Javier Ramos -Argentina
Laboratorio de Neuropatología Molecular, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis", CONICET, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

Reactive gliosis involving activation and proliferation of astrocytes and microglia, is a widespread but largely complex and graded glial response to brain injury. Astroglial population has a previously underestimated high heterogeneity with cells differing in their morphology, gene expression profile, and response to injury. Over the last years we have been studying whether astrocytes may behave as facultative innate immunity cells after CNS injury. Classical innate immunity activation in the absence of infection relies on the Damage Associated Molecular Patterns (DAMP) release by dying cells. DAMPs behave as ligands of the Pattern Recognition Receptors (PRR), such as Toll-like (TLR), RAGE and others. Using a combination of mathematical modeling, in vitro and in vivo experimentation, we have been able to show that astrocytes essentially behave as facultative cells of the innate immunity response that classically follows brain damage. While classical innate immunity pathways such as those involving RAGE, TLR4/NFkB and TREM-2 are activated by released DAMPs, astrocytes are also key players in determining the interaction with local and peripheral professional immune cells. Moreover, detailed histological studies and ex-vivo culture experiments have shown that only a subset of astrocytes seems to have the immune and neuroinflammatory role in experimental focal brain lesions and they can be specifically targeted by dendrimeric nanoparticles. This additional layer of neurobiological complexity can also be explored for therapeutic purposes oriented towards controlling neuroinflammation in the injured brain.

Are neuroinflammation and astrocytes key elements in L-DOPA-induced dyskinesia in Parkinson's disease?

Prof. Elaine Del-Bel
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Inflammation in Parkinson's disease (PD) is a new concept that has gained ground due to the potential of mitigating dopaminergic neuron death by decreasing inflammation. The solution to this question is likely to be complex.

We propose here that the significance of inflammation in PD may go beyond the nigral cell death. The pathological process that underlies PD requires years to reach its full extent. A growing body of evidence has been accumulated on the presence of multiple inflammatory signs in the brain of PD patients even in very late stages of the disease. Because neuron-microglia-astrocyte interactions play a major role in the plasticity of neuronal response to l-DOPA in post-synaptic neurons, we focused this review on our recent results of l-DOPA-induced dyskinesia in rodents correlating it to significant findings regarding glial cells and neuroinflammation. We showed that in the rat model of PD/l-DOPA-induced dyskinesia there was an increased expression of inflammatory markers, such as the enzymes COX2 in neurons and iNOS in glial cells, in the dopamine-denervated striatum. The gliosis commonly seem in PD was associated with modifications in astrocytes and microglia that occur after chronic treatment with l-DOPA. Either as a cause, consequence, or promoter of progression of neuronal degeneration, inflammation plays a role in PD. The key aims of current PD research ought to be to elucidate (a) the time sequence in which the inflammatory factors act in PD patient brain and (b) the mechanisms by which neuroinflammatory response contributes to the collateral effects of l-DOPA treatment.

Friday, 26th - 08:30 – 10:30 SYMPOSIUM VII/ *Room A*

"Synaptic drive and neuromodulatory circuits in cognitive and emotional processes"

Chairs: Joaquin Piriz *IFIBIO, CONICET-UBA, Buenos Aires, Argentina,* Mariano Soiza Reilly *IFIBYNE, UBA-CONICET, Buenos Aires, Argentina*

"Experience-dependent synaptic plasticity in the lateral habenula"

Manuel Mameli,PhD
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In everyday life, proper behavioral responses when foreseeing an unpleasant event are necessary for survival. Neurons in the lateral portion of the epithalamic nucleus habenula (LHb) are excited upon a negative event. Furthermore, after conditioning, LHb neurons show excitation when the conditioned stimulus is presented (Matsumoto and Hikosaka, 2007). However, whether synaptic adaptations occur within the LHb during learning, allowing anticipating an aversive stimulus, remains unknown. We hypothesized that, during the formation of an association between an external stimulus and the successive administration of a punishment, plasticity at excitatory synapses occurs in the LHb. To investigate this issue, we interrogated synaptic transmission onto LHb neurons in acute brain slices from animals at different stages of learning using an active avoidance paradigm (30 trials/day, 5 days). The animals learned to avoid a footshock preannounced by a tone already from the second and third sessions ("learners"). Control mice instead received the footshocks and the CS randomly, not contingently. 24h after training session 2 we measured spontaneous excitatory postsynaptic currents (sEPSC) in acute brain slices containing the LHb. The frequency of sEPSCs, but not amplitude, was significantly increased in the LHb of learners, compared to control mice. Recording trains of EPSCs revealed similar paired-pulse ratios between learners and controls. We then measured AMPA and NMDA currents elicited by electrical stimulation within the LHb, observing a significant increase in AMPA/NMDA ratio in learners compared to controls. Furthermore, this AMPA/NMDA increase was observed when evoking EPSCs using uncaged glutamate in the proximity of dendrites. These data suggest that learning to predict an aversive stimulus engages post-synaptic strengthening at excitatory synapses in the LHb.

“Synaptic Tagging and Capture: From Synapses to Behavior”

Sadegh Nabavi PhD

Danish Research Institute of Translational Neuroscience (DANDRITE), Denmark Department of Molecular Biology and Genetics, Aarhus University, Denmark. snabavi@dandrite.au.dk

It is shown that long-term potentiation (LTP) is the cellular basis of memory formation. However, since all but small fraction of memories are forgotten, LTP has been further divided into early LTP (e-LTP), the mechanism by which short-term memories are formed, and a more stable late LTP (L-LTP), by which long-term memories are formed. Remarkably, it has been shown that an e-LTP can be stabilized if it is preceded or followed by heterosynaptic L-LTP. According to Synaptic Tagging and Capture (STC) hypothesis, e-LTP is stabilized by capturing proteins that are made by L-LTP induction. The model proposes that this mechanism underlies the formation of late associative memory, where the stability of a memory is not only defined by the stimuli that induce the change but also by events happening before and after these stimuli. As such, the model explicitly predicts that a short-term memory can be stabilized by inducing heterosynaptic L-LTP. A main project in our lab isto test this hypothesis. Specifically, weare testing two explicit predictions of STC model: 1) A short-term memory can be stabilized by induction of heterosynaptic LLTP. 2) This stabilization is caused by the protein synthesis feature of L-LTP. To do this, using optogenetics, weare engineering a short-term fear memory. Subsequently, weare examining if optogenetic delivery of L-LTP to a second pathway converging on the same population of neurons in the amygdala does stabilize the short-term fear memory. To be able to engineer natural memory by manipulating synaptic plasticity weare developingatwo-color optical activation system which permits selective manipulation of distinct neuronal populations with precise temporal and spatial resolution.

“Cholinergic mechanisms shaping VTA dopaminergic mal-adaptations to stress and nicotine”

Sebastian P. Fernandez, PhD

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The stress response per se is beneficial, however when responses are disproportionate or excessively long-lived, they become maladaptive. As such, traumatic experiences and social stress promote the onset of psychiatric disorders, including pathological anxiety, major depression and inability to socially perform. Perhaps not surprisingly nicotine dependence is 2-3 more

common in psychiatric patients. The prevalence of this comorbidity and the complex interactions that occur between the two underlying disorders questions the strategy that consists to deal with each entity separately or consider only that one increase the vulnerability. We demonstrate that the interaction between stress (a major factor in depression etiology) and nicotine dependence occurs at the level of the ventral tegmental area (VTA). We show that chronic social stress increases activity of VTA dopamine neurons, causally resulting in depressive-like behaviors such as social aversion and anhedonia. Strikingly, mice that received nicotine in the drinking water are more sensitive to stress, and both behavioral and cellular maladaptations are triggered by a single defeat episode. Blocking ß2 or α7 nicotinic acetylcholine receptors (nAChRs) prevents, respectively, the development and the expression of social stress-induced neuroadaptations. Using neuro-anatomical tracers and c-fos immunohistochemistry we identify the laterodorsal tegmental nucleus (LDTg) as a source of cholinergic input to the VTA that is activated by stress. Patch-clamp recordings in LDTg-to-VTA cholinergic neurons revealed that this cell populations increases firing in response to chronic stress, consistent with increased cholinergic tone. We then used conditional expression of inhibitory DREADDs via viral stereotaxic injections in the LDTg. Silencing of LDTg cholinergic cells during stress was sufficient to prevent dopaminergic cellular mal-adaptations and depression-related behaviors. Our results pinpoints to a specific circuit dysregulation in relation to stress disorders, nicotine addiction and depression.

“Prefrontal serotonin transporter shapes cortico-raphe circuits and long-term emotional deficits of early-life exposure to SSRIs”

Mariano Soiza-Reilly, PhD
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Loss or reduced function of the serotonin transporter (Slc6a4/SERT) during early development has paradoxical long-term effects in adult life by increasing vulnerability to depression and anxiety. However, the basis for these developmental effects is not known. Here, we show that during an early postnatal period, (P0-P10), Slc6a4/SERT is transiently expressed in a subset of layer 5-6 pyramidal neurons of the prefrontal cortex (PFC). PFC-SERT+ neurons establish glutamatergic synapses with a number of subcortical targets, including 5-HT and GABA neurons in the dorsal raphe nucleus (DRN). PFC-to-DRN circuits

develop postnatally, coinciding with the period of PFC Slc6a4/SERT expression. Complete or cortex-specific ablation of SERT increases the number of functional PFC glutamate synapses onto 5-HT and GABA DRN neurons. This PFC-to-DRN hyper-innervation is replicated by early postnatal exposure to the SSRI fluoxetine from P2to P14, which also causes long-lasting emotional deficits and dampens the activation of the PFC in response to stress. Targeting the PFC-SERT+ neurons with pharmacogenetic tools, we show that chemogenetic inhibition of these neurons enhances the emotional deficits caused by early life exposure to SSRIs. Overall, our data identify specific PFC descending circuits that are targets of antidepressant drugs during the perinatal period. We demonstrate that developmental expression of SERT in a subset of PFC neurons controls synaptic maturation of PFC-to-DRN circuits and that maladaptive changes of these circuits, induced by early exposure to SSRIs, play a central role in behavioral responses to stress.

Friday, 26th - 11:00 – 13:00 SYMPOSIUM VIII/ *Room A*

"Cell strategies in degenerative and regenerative processes of the nervous system"

Chair: Luis E. Politi *INIBIBB-CONICET. Bahia Blanca, Buenos Aires, Argentna*

Multipotent cells as mediators of peripheral nerve regeneration

Dr. Patricia Setton
IQUIFIB-CONICET-UBA, CABA, Argentina

Demyelination is one of the hallmarks of the Wallerian degeneration (WD) process and cell therapy is among the strategies under study to induce remyelination. Results from our group obtained in a reversible model of WD induced by the crush of the rat sciatic nerve demonstrated the spontaneous migration of endogenous or transplanted bone marrow mononuclear cells (BMMC) exclusively to the injured nerve. Once in the ipsilateral nerve, some BMMC colocalize with Schwann cell markers and nerve fiber markers. In this context, our group is currently digging into the regenerating effects of BMMC and adipose-derived mesenchymal stem cell transplant upon injury in terms of axon morphology and function, neuropathic pain amelioration and the corresponding underlying mechanisms. In addition, studies underway are seeking to optimize cell recruitment to the lesion area through pharmacological and nanotechnological resources. So far, results hint at a beneficial role for

multipotent cells in nerve injury and suggest they could be useful adjuvants to anti-inflammatory/analgesic drug treatments.

Restoring the connectomes of regenerated retinal bipolar neurons following a tissue-disrupting retinal lesion in adult zebrafish.

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We previously reported strikingly normal morphologies and functional connectivities of regenerated retinal bipolar neurons (BPs) in zebrafish retinas sampled 60 days after a ouabain-mediated lesion of inner retinal neurons (60 dpi) [McGinn et al., 2018, *J Neurosci* 38(1):120-136]. Here we report early steps in the birth of BPs and formation of their dendritic trees and axons in histologically regenerated retinas following retinal injury. Zebrafish were subjected to ouabain-mediated lesion that destroys inner retinal neurons and spares photoreceptors and Müller glia, and were sampled at 13, 17, and 21 dpi, a time frame over which plexiform layers re-emerge, and which corresponds to the initial appearance and accumulation of two populations of BPs (PKCα+ and *nyx::mYFP*+). Sequential BrdU, then EdU, incorporation reveals that similar fractions of PKCα+ BPs and Hu+ amacrine/ganglion cells are generated at the same times, suggesting that the sequence of neuronal production during retinal regeneration may not strictly match that observed during embryonic development. The sparsely distributed *nyx::mYFP*+ BPs were examined for morphological detail by confocal microscopy, tracing, morphometric analyses, identification of cone synaptic contacts, and rendering/visualization. Apically-projecting neurites (=dendrites) of regenerated BPs sampled at 13, 17, and 21 dpi are either truncated, or display smaller dendritic trees when compared to controls. In cases where BP dendrites reach the outer plexiform layer (OPL), numbers of dendritic tips are similar to those of controls at all sampling times. Further, by 13-17 dpi, BPs show patterns of photoreceptor connections that are statistically indistinguishable from controls, while those sampled at 21 dpi slightly favor contacts with double cone synaptic terminals over those of blue-sensitive cones. These findings suggest that dendrites of regenerated BPs that reach the OPL establish normal photoreceptor connectomes, albeit with some plasticity. Through 21 dpi, basally-projecting neurites (=axons) of regenerated *nyx::mYFP*+ BPs traverse long distances, branch into inappropriate layers, or appear to abruptly terminate, making them difficult to trace. Collectively, these findings suggest that, after a lesion that destroys BPs and their postsynaptic partners, but spares their presynaptic inputs, maturation and pathfinding of

regenerated BP axons is delayed compared to formation and maturation of their dendritic trees.

3D Retinal Organoids: New Frontiers for Stem Cell-based Clinical Applications

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Human induced pluripotent stem cells (hiPSC) provide a unique tool for the development of in vitro models of retinal diseases as well as therapeutic strategies to regenerate the diseased retina. Recent progress in our ability to generate hiPSC-derived three dimensional retinal tissue that closely mimic the in vivo retinal microenvironment and tissue organization open new frontiers for their use in clinical applications. This talk will present and overview of the current-state-of-the art in retinal organoids; discuss the challenges and opportunities these systems present for clinical applications; and describe new directions being pursued in the context of potential therapeutic approaches.

Friday, 26th - 15:30 – 17:30 SYMPOSIUM IX/ *Room A*

"Cellular and molecular mechanisms in retina degeneration"

Chairs: Nora Rotstein *INIBIBB, UNS-CONICET, Bahía Blanca, Buenos Aires.* Cecilia Sánchez *CIBICI-CONICET-UNC, Córdoba, Argentina*

Neuroprotection of photoreceptors as a therapeutic strategy in retinal degeneration

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Retinitis pigmentosa (RP) is a degenerative disease leading to photoreceptor cell loss. Mouse models of RP, such as the rd10 mouse have enhanced our understanding of the disease, allowing for development of potential therapeutics. Our group has demonstrated that the synthetic progesterone analogue 'Norgestrel' is neuroprotective in two mouse models of retinal degeneration. We have elucidated several mechanisms by which Norgestrel

protects photoreceptors, such as up-regulating growth factors and damping of glia cell activity. This presentation will outline the mechanism and action of Norgestrel's neuroprotective effects.
Dams of post-natal day (P) 10 rd10 pups were given a Norgestrel-supplemented diet (80mg/kg). Upon weaning, pups remained on Norgestrel. Tissue was harvested from P15-P50 rd10 mice. Norgestrel-diet administration provided significant retinal protection to P40 in mice. Alterations in microglial activity coincided with significant protection, implicating microglial changes in Norgestrel-induced neuroprotection.
Utilizing primary cultures of retinal microglia and 661W photoreceptor-like cells, we show that rd10 microglia drive neuronal cell death. We reveal a novel role of Norgestrel, acting directly on microglia to reduce pro-inflammatory activation and prevent cell death. Norgestrel effectively suppresses cytokine, chemokine and danger-associated molecular pattern molecule (DAMP) expression in the rd10 retina. Remarkably, Norgestrel up-regulates fractalkine-CX3CR1 signalling 1000-fold at the RNA level. Fractalkine-CX3CR1 signaling has been shown to protect neurons by regulating retinal microglial activation and migration. Ultimately, these results present Norgestrel as a promising treatment for RP.

Vascular and non-vascular alterations in retinopathies: towards a change in the therapeutic strategy

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Neovascular retinopathies are leading causes of irreversible blindness. Although vascular endothelial growth factor (VEGF) inhibitors have been established as the mainstay of current treatment, clinical management of these diseases is still limited. As retinal impairment involves abnormal neovascularization and neuronal degeneration, we evaluated here the retinal functionality and the behavior of neuro-glial injury markers using the oxygen-induced retinopathy (OIR) model in mice treated or not with anti-VEGF mAb.
Postnatal day 17 OIR mouse retinas showed the highest neovascular profile and exhibited neuro-glial alterations as well as retinal functional loss, which persisted until P26 OIR. Remarkably, although anti-VEGF treatment in P17 OIR

improved retinal vascularization, neither non-vascular nor functional alterations were attenuated. These results suggest that, in addition to neovascularization, retinal neurodegeneration should also be considered an important pathogenic component of the disease highlights the importance of non-vascular alterations in proliferative retinopathies and the need of seeking new therapeutic agents targeting both neovascular and neurodegenerative processes to treat this multifactorial disease.

Molecular Mechanisms of PEDF Peptides in Retinal Degenerations

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The generation of retinoprotective peptides that activate specific and selective targets in the eye is of interest due to their high potential therapeutic value in retinal dystrophies. The well-established actions of pigment epithelium-derived factor (PEDF)and its involvement in controlling retina homeostasis, make this protein a prime candidate for future ocular therapeutic applications. PEDF exerts neurotrophic, neuroprotective, antiangiogenic, gliastatic, antioxidant and antiangiogenic effects in the retina. It protects the retina from degeneration processes induced by cell death, pathological neovascularization, tumorigenesis and inflammation. Studies on protein structure and function have demonstrated that the multiple actions of PEDF rely on specific epitopes distributed throughout the protein and interactions with several targets, including specific surface receptors, orphan receptors or other proteins. Mapping of the biological active regions has made possible the isolation of individual and specific activities of this multifunctional protein. Protein fragmentation and chemical peptide synthesis have been employed in the design of small peptides that have retained independent activities of PEDF *in cellulo, ex vivo*and *in vivo*. Peptides of 17 residues designed fromthe PEDF neurotrophic domain recapitulate the properties of its full-length protein of about 400 residues. They hinder photoreceptor cell death by binding the PEDF receptor and stimulating its phospholipase activity to liberate fatty acids from phospholipids, which in turn act on downstream signaling cascades. Our findings point out that the neurotrophic PEDF peptidesact via the PEDF receptor on extrusion of intracellular calcium, attenuation of calpain activity and regulation of Bcl2, Bax, and Aif for photoreceptor survival. The current knowledge of the molecular mechanisms of PEDF will be discussed.

This work was supported in part by the Intramural Research Program of the National Eye Institute, National Institutes of Health. Commercial disclosures: NONE.

Friday, 26th - 15:30 – 17:30 SYMPOSIUM X/ *Room B*

"Epilepsy from bench to the patients"

Chairs: Jerónimo Auzmendi *IBCN "Prof. E. De Robertis" UBA-CONICET School of Medicine – UBA, Buenos Aires, Argentina* Alberto Lazarowski *Clinical Biochemistry Department, FFyB, UBA, Buenos Aires, Argentina*

Progressive P-glycoprotein overexpression and its relationship with SUDEP

Alberto Lazarowski
Clinical Biochemistry Department, FFyB, University of Buenos Aires, Argentina

Sudden unexpected death in epilepsy (SUDEP) is the major cause of death in those patients suffering from refractory epilepsy (RE), with a 24-fold higher risk relative to the normal population. SUDEP risk increases with seizure frequency and/or seizure-duration as in RE and Status Epilepticus (SE). P-glycoprotein (P-gp), the product of the multidrug resistant *ABCB1-MDR-1* gene, is a detoxifying pump that extrudes drugs out of the cells and can confer pharmacoresistance to the expressing cells. Neurons and cardiomyocytes normally do not express P-gp, however, it is overexpressed in the brain of patients or in experimental models of RE and SE. P-gp was also detected after brain or cardiac hypoxia. We have previously demonstrated that repetitive pentylenetetrazole (PTZ)-induced seizures increase P-gp expression in the brain, which is associated with membrane depolarization in the hippocampus, and in the heart, which is associated with fatal SE. SE can produce hypoxic-ischemic altered cardiac rhythm (HIACR) and severe arrhythmias, and both are related with SUDEP.Our results suggest that the highly accumulated burden of convulsive stress results in a hypoxic heart insult, where P-gp expression may play a depolarizing role in cardiomyocyte membranes and in the development of the ECG changes, such as QT interval prolongation, that could be related with SUDEP. We postulate that this mechanism could explain, in part, the higher SUDEP risk in patients with RE or SE.

Epigenetic changes induced by antiepileptic drugs and their relevance in epilepsy

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In the treatment of epilepsy, antiepileptic drugs (AEDs) represent a group of exogenous factors that can induce epigenetic modifications and alter the structure of chromatin. Epigenetic changes such as DNA methylation, histone modifications and synthesis, as well as the function of non-coding RNAs (ncRNA), are part of the cellular environment of the brain with epilepsy. However, many of these changes can be induced by the sole administration of AEDs. Alterations in the chromatin structure induced by the AEDs can result in changes in the gene expression of various factors involved in the pathology of epilepsy, both to the benefit of the disease and to the detriment of it. This presentation will focus on reviewing the epigenetic modifications induced by AEDs widely used in the clinic. It is important to consider that although AEDs are widely used to control epilepsy and other neurological diseases, their epigenetic effects are not considered. On the other hand, the knowledge of the epigenetic changes induced by AEDs represents new possibilities in the development or optimization of treatments for the patient with epilepsy.

Kainic acid as a preclinical experimental model for the study of new molecules for the treatment of epilepsy and neurodegenerative diseases.

Antoni Camins[1,3,4], Carme Auladell[3,4,5], Jaume Folch[2,3], Ester Verdaguer[3,4,5], Rubén Darío Castro-Torres[3,4,5,6], Miren Etchetto[1,2,3,4], Oriol Busquets[1,2,3,4]
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Kainic acid (KA) is a non-degradable analog of glutamate, and a potent neurotoxin that acts through glutamate receptors, showing affinity for non-NMDA ionotropic receptors, specifically kainate receptors (KAR). In rodents, local or systemic administration of KA triggers a pattern of repetitive seizures for several hours, followed by a latency period, and a subsequent spontaneous onset of seizures (Ben-Ari 1985, Ben-Ari and Cossart 2000, Nadler 1981). These

seizures cause brain damage, often associated with the aberrant formation of new synapses, simultaneously with an increase in the density of kainate receptors, glial activation, deregulation of cellular homeostasis and a consequent loss of hippocampal neurons (Blumcke et al. 2000, Cavazos et al 2004, Dudek et al 2002, Kondratyev and Gale 2004, Lee et al 2002, Niquet et al 1994, Pitkanen and Sutula 2002). These alterations are similar to those that develop in the most frequent epilepsy in adult humans, temporal lobe epilepsy (TLE) (Engel et al., 1989). In this way, the KA experimental model, in addition to reproducing the TLE, allows the understanding of neuronal death mechanisms present in neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (Pitt et al., 2000; Hynf et al., 2004; Meredith et al., 2009). In recent years, different studies have shown the participation of MAPK pathways in the mechanisms of neuronal death and inflammation, characteristic of neurodegenerative diseases (Chang and Karin 2001, Che et al 2001, Ferrer et al 2005 ; Harper and Wilkie 2003; Lin et al., 2013; Kamat et al., 2014). In particular, the JNK pathway has been broadly related to neurodegenerative disorders.Our studies have shown a reduction in neuronal death and absence of astrogliosis observed in the hippocampus of *Jnk3*$^{-/-}$ and Jnk*1*$^{-/-}$ mice after treatment with KA. The results obtained with *Jnk1*$^{-/-}$ mice are novel, since the role of this isoform in neurodegenerative processes is demonstrated for the first time. In addition, these results have allowed us to demonstrate the efficacy of a molecule Licochalcone A (Lic-A) through the inhibition of JNK1, caused a reduction in the seizure pattern in rodents. In addition, it reduced the phosphorylation levels of JNK, as well as its activity. In addition, Lic-A prevents neuronal degeneration of the hippocampus, increases pro-survival antiapoptotic mechanisms, reduces pro-apoptotic biomarkers, and reduces cell stress and neuroinflammatory processes. Therefore, our results suggest that the inhibition of JNK1 by Lic-A has neuroprotective effects and that; it could be a potential new approach for the treatment of epileptic status and neurodegeneration.

Identification of epileptogenicity markers from the register of individual neurons in patients candidates to epilepsy surgery

Silvia Kochen

Epilepsy Center, Ramos Mejía y El Cruce Hospital, EnyS-CONICET, Buenos Aires, IBCN-CONICET-UBA, Buenos Aires, Argentina

Epilepsy is the most frequent disease of neurological diseases. Patients who do not respond to pharmacological treatment (30-40%) may benefit from surgical treatment. In some cases, for the identification of the epilepsy zone (EZ), the electrical activity must be recorded during the crisis of epilepsy with intracerebral macro and microelectrodes (EEGi). The use of microelectrodes allows the registration of multiple neurons, as well as those of local field, simultaneously, with the registration of large neurons, participation in the different scales, more accurately identify the EZ and the new biomarkers. This line of research will affect the health of patients, the most selective surgery of the EZ with less risk of irreversible cognitive and / or motor sequelae. On the other hand, it is a tool to better understand the dynamics of the neural network.

YOUNG INVESTIGATOR LECTURES

Wednesday 24th

YIL1.-Studying synaptic transmission at the level of individual synaptic vesicles

Natali L. Chanaday R.
UT Southwestern Medical Center

Coupling of synaptic vesicle fusion and retrieval constitutes a core mechanism ensuring maintenance of presynaptic function. Recent studies have shown the coexistence of several endocytic pathways in neurons, with diverse kinetics and temperature dependencies. Using optical methods, we study the recycling of single and multiple synaptic vesicles in cultured hippocampal neurons., including their kinetics, calcium and temperature dependence. Our goal is to understand the underlying molecular mechanisms coupling different modes of exocytosis to different endocytic routes.

YIL2.-Dietary restriction promotes tissue-specific reprogramming of circadian gene expression

Victoria Acosta Rordiguez
UT Southwestern Medical Center

Caloric restriction (CR) extends lifespan in many species, yet the mechanisms are unclear. Our previous studies showed that CR protocols involve a 2h-temporal restricted (TR) feeding followed by 22h of fasting, all of which impact on health. Thus, it is unclear whether the timing, frequency or amount of food intake is the critical factor that improves metabolic fitness.
Here, we investigated how feeding conditions modulate the circadian (24h) profile of gene expression in the hypothalamus and 3 major metabolic tissues: liver, white and brown adipose tissues. We developed an automated feeders to fed mice either during the day or the night, with or without 30%CR.
We found complex tissue-specific circadian changes in mRNA expression induced by both timing and amount of food intake. While feeding time determined the circadian profile of core clock genes in the liver and WAT, it did not affect expression in the BAT and hypothalamus. Remarkably, despite the core clock machinery remaining unchanged; the profile of metabolic genes such as leptin followed feeding time in BAT. Thus, revealing misalignment within the BAT. Altogether, these results show that metabolic tissues integrate environmental (feeding and day/night cycles) and systemic signals in a tissue-specific manner.

Integrating these tissue-specific signatures with metabolic outcomes may help elucidate the mechanism by which dietary restriction extends longevity, revealing a link between circadian clocks and healthy aging.

YIL3.-Behavioral plasticity and action selection in *Drosophila*

Ezequiel Axel Gorostiza
IFEC-CONICET-UNC

Phototaxis is an iconic example for behaviors dominated by innate components or preferences. Such preferences likely reflect evolutionary adaptations to predictable situations, and the behaviors dominated by them have traditionally been conceptualized as hard-wired stimulus-response links. Perhaps therefore, the century-old discovery of plasticity in Drosophila phototaxis has received little attention. Experiments performed by McEwen demonstrated that wing defects, caused by mutation or damage, profoundly affect phototaxis in walking Drosophila1. The fact that manipulating an unrelated organ, such as wings, affects phototaxis contradicts the assumed hard-wired organization of this behavior, suggesting that it may not be a simple stereotypic and automatic response, but that it contains at least a certain element of flexibility. To explore this hypothesis in our laboratory, walking flies were tested for their light/dark preference in several different behavioral tests. Interestingly, light/dark preference tested in walking flies is dependent on various aspects of flight. If flying ability is temporarily compromise, photopreference reverses concomitantly. Neuronal activity in circuits expressing dopamine and octopamine, respectively, plays a differential role in photopreference, suggesting a potential involvement of these biogenic amines in this case of behavioral plasticity. We conclude that flies monitor their ability to fly, and that flying ability exerts a fundamental effect on action selection in Drosophila. This work suggests that even behaviors which appear simple and hard-wired comprise a value-driven decision-making stage, negotiating the external situation with the animal's internal state before an action is selected.

YIL4.-New players in cortical development: role of GDNF/ GFRα1

Antonela Bonafina
IBCN-CONICET-UBA

During development, neural stem cells and their derivative progenitor cells give rise to all the neurons of the nervous system. The transition of proliferative

progenitor cells to fully differentiated neurons is controlled by intrinsic programs, as well as extrinsic environmental cues, such as neurotrophic factors. In this work, we studied the role of glial cell line-derived
neurotrophic factor (GDNF) and its receptor, GFRα1, during the proliferation and differentiation of cortical neural precursors cells (CNPs) both in the developing cortex. We show that GDNF and GFRα1 are expressed in the mice neocortex during the period of cortical neurogenesis. We show that GDNF through its receptor GFRα1 inhibits self-renewal capacity of mouse CNPsinduced by FGF2, promoting neuronal differentiation. While GDNF leads to decreased proliferation of cultured CNPs, selective ablation of GFRα1 in glutamatergic cortical precursors enhances its proliferation. Moreover, analysis of conditional GFRα1-knockout mice shows an increase in the number of cycling cells during cortical development. We also show that GDNF treatment of CNPs resulted in a marked increase in neuronal population and promoted morphological differentiation even in the presence of FGF2. Analysis of newborn conditional GFRα1-deficient mice shows a reduction in dendritic length in a subpopulation of cingulate cortical neurons in vivo. This result is in agreement with our previous findings indicating that the GDNF/GFRα1 complex plays a crucial role in the development of hippocampal dendritic arbors (1). Together, these results indicate that GDNF/GFRα1 signaling plays an essential role in regulating the proliferative condition and the differentiation of CNPs to cortical or hippocampal neurons. The evidence obtained gives new opportunities to study the function of GDNF in neurodevelopmental diseases characterized by cognitive deficits.

YIL5.-Sex hormone effects in brain mitochondria: at the crossroads of neuroprotection and aging

Sandra Zárate
INBIOMED (UBA-CONICET), Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina

Sex steroids have pleiotropic effects in the brain, preserving neural function and survival. Loss of ovarian hormones after menopause is often associated with synaptic and cognitive impairments and increased risk of neurodegeneration, processes also highly linked to mitochondria (MT) dysfunction. In this line, we study the role of ovarian hormones in the maintenance of a healthy neural

function in the hippocampus, specially focusing on MT. To this aim, we use an animal model of surgical-induced menopause in Wistar rats.
Our data show that hippocampal MT from ovariectomized (OVX) rats exhibit reduced active respiration and ATP production rates. This MT dysfunction is correlated with changes in its membrane lipid profile resulting in a higher peroxidizability index and lower cardiolipin content with altered fatty acid profile. Our results suggest that ovarian hormone loss induces a MT phenotype similar to an aging-related one in terms of higher susceptibility to membrane peroxidation together with impaired MT bioenergetic capacity. Also, we are currently studying the expression and function of Humanin (HN), a mitochondrial-derived peptide with cytoprotective, metabolic, and anti-inflammatory effects. Our data in vivo show that HN colocalizes with astrocyte markers and its expression decreases in the hippocampus of OVX rats. Also, there is a positive correlation between the expression of HN and GFAP, suggesting that ovarian hormone loss promotes functional and morphological changes in astrocyes, which could affect astroglial support to neuronal function and may represent an underlying mechanism for synaptic dysfunction. In fact, we show that HN prevents synapse loss in cultured hippocampal neurons exposed to glutamate. Also, our results in cultured astrocytes show that ovarian hormones positively regulate HN expression and release. Our study could help find new therapeutic targets for interventions that may promote a healthier lifespan for post-menopausal women.

YIL6.-Tell me the way you live, I will tell the way you are: The impact of sensory and motor stimulation on the epigenetic control of steroidogenic-related genes in the rat hippocampus

María Florencia Rosseti
ISAL-CONICET-UNL

Environmental enrichment (EE) promotes neuronal protection through various mechanisms of action. Neurosteroids are steroid hormones synthesized de novo from cholesterol or steroidal precursors in various brain regions and they have positive effects on neurogenesis, synaptic connectivity and cognitive performance. We analyzed the effects of a short-term EE on the Mrna expression and DNA methylation state of steroidogenic enzymes in the hippocampus. For that, young adult (90-day-old) and middle-aged (360-day-old) female Wistar rats were exposed to sensory (SE) or motor (ME) enrichment

during 10 days and compared to animals housed under standard conditions (SC). SE was provided by an assortment of objects that included plastic tubes and toys; for ME, rodent wheels were provided. In young adult animals, both SE and ME increased the mRNA expression of P450(17α) and 3α-HSD enzymes and decreased the expression of P450arom. In addition, SE increased the transcription of 5αR-1. Interestingly, ME upregulated P450(11β)-2 gene expression in both young adult and middle-aged animals compared to SC. These results suggested that aged rats would require a more prolonged stimulus than young animals to observe a similar effect. We found hypomethylation at the 5αR-1 gene (site d) produced by SE and at the 5αR1 (site a) and 3α-HSD promoters produced by ME, in young adult rats. The fact that two different sites of the CpG Island 5αR-1 promoter altered their methylation patterns depending on the EE, suggest that these sites could be potential regulatory stimulus-specific sites. In middle-aged rats, ME decreased methylation levels at a cis-acting element Ad1 of the P450(11β)-2 promoter. Altogether, these results propose that sensory and motor stimulation differentially regulate the transcription of steroidogenic enzymes through epigenetic mechanisms associated with differential promoter methylation in the young and aged rat hippocampus.

Thursday 25th

YIL7.-Compartmentalization of antagonistic Ca2+ signals in developing cochlear hair cells

Marcelo Javier Moglie
INGEBI-CONICET

The normal maturation of the auditory pathway relies on a critical developmental period characterized by the firing of sensory-independent action potentials by cochlear inner hair cells (IHCs). Spiking activity produces the influx of Ca2+ through voltage-gated channels which in turn triggers the synaptic release of glutamate onto dendrites of the auditory nerve, leading to the propagation of the spontaneous activity throughout the auditory system. On the other hand, IHCs are the postsynaptic target of efferent cholinergic neurons from the brainstem. At this synapse, Ca2+ entry through nicotinic α9α10 receptors is coupled to the activation of Ca2+ -dependent K+ channels to hyperpolarize the IHC. Thus, efferent Ca2+ influx is inhibitory, opposing the

excitatory Ca2+ signal produced during IHC firing. The aim of our work was to investigate the mechanisms that allow segregation of excitatory versus inhibitory Ca2+ effects within the small and diffusionally compact IHCs. Electrophysiological recordings combined with swept–field confocal Ca2+ imaging experiments revealed the existence of multiple efferent Ca2+ entry hotspots which were closely positioned to afferent Ca2+ entry sites within a single IHC. This finding was confirmed by IHC reconstructions at a nanometer scale using serial section electron micrographs (EM), suggesting that efferent Ca2+ spread could invade afferent synapses. However, recordings from postsynaptic boutons of auditory nerve neurons showed that even high frequency stimulation of efferent fibers failed to cross-activate and trigger the synaptic release of glutamate. Efficient compartmentalization of Ca2+ signals was accomplished by: i) sub-synaptic cisterns revealed in EM reconstructions, juxtaposed to cholinergic contacts; ii) a fast Ca2+ extrusion pathway mediated by SERCA pumps; iii) and a very strong Ca2+ buffering in IHC cytoplasm. Thus, efferent fibers maintain its inhibitory signature and modulate spontaneous activity in the developing IHC.

YIL8.-Revealing expectancy signals in the barrel cortex using repetitive spatiotemporal multi-whisker stimulations

Matías Goldin
UNIC-CNRS

The central nervous system (CNS) processes incoming sensory information in a way that reflects its preparedness for an expected input. Perception is therefore built by selective brain operations where the body state, its actions and the sensory context are integrated to generate expectations. Neuronal signatures of those expectations and particularly to a violation of an expected stimulus have been recorded in animals and humans. Where are those signals generated? In the predictive coding hypothesis1, expectancy signals are generated in high cortical areas. However, it is debated if these signals are present in a primary sensory cortex. After a survey of the literature on expectancy signals in the CNS, I will present electrophysiological evidence for sensory responses in the primary somatosensory cortex (S1) related to expectation. We used the rat vibrissal system by applying highly predictable tactile inputs using a 24-whisker stimulator2. Multiple single-unit recordings, local field potentials and current source density were obtained in the whisker region of S1 of anaesthetized rats.

A stimulation pattern of successive whisker deflections (stimuli profile previously obtained3,4) from the front to the back of the whisker pad was repeated many times during a training phase and truncated patterns, where the target whisker was missing, were presented at random times (with 5 % chance) to follow the eventual build up of expectancy signals.
Our preliminary results show that the stimulus history can reconfigure the activity in the barrel cortex so that responses to truncated inputs resemble responses to the full pattern of stimulation. Ultimately, our project shall reveal how the brain compares sensory incoming information with inner representations of the world, an essential operation for identifying salient events.

YIL9.-ERP Correlates of recognition semantic memory after active versus passive memory retrieval

Jorge Mario Andreau
IBYME-CONICET

Most of the Event Related Potential (ERP) studies of memory utilize recognition tasks (e.g., old/new item memory [Curran et al., 2006 ; Rugg et al., 1998 ; Rugg & Doyle, 1994]). Recently, a cued memory recall task has been used to study associative memory retrieval. We introduced a modification to the latter and studied recognition memory process after an associative memory task. Twenty subjects were train to learn five pairs of arbitrary fractal images. We then evaluated semantic associative memory process through a delayed paired-association (DPA) task and a delayed match-to- sample (DMS) control task. EEG activity was recorded while subjects looked at a cue stimulus and, after 1s delay; decided if the target stimulus matched the cue (DPA condition), or if it was identical to the cue (DMS condition). Therefore, they resembled traditional old/new studies except the memory trace was different not only between the two conditions (par/no pair, same/different), but also between the two tasks (DPA/DMS). Critically, in DPA, the recognition memory required active memory retrieval, while the recognition in DMS did not. When comparing the ERP activity between the two tasks, no familiarity effect was found (e.g., FN400 component [Curran et al., 2006]) since all stimuli were equally familiar to the subjects. Interestingly, we found differences between 160-260ms, and 320-520ms with a posterior topography. Those differences could be consider as a neural correlate of active associative LTM retrieval.

YIL10.-Neuroendocrine regulation of postprandial dieresis in Rhodnius prolixus

Natalia Capriotti

Centro Regional de Estudios Genómicos, Universidad Nacional de La Plata, Argentina

Given that hematophagous insects ingest large quantities of blood in a single meal, they should undergo a rapid postprandial diuresis to maintain the homeostasis. The diuresis is regulated by serotonin and neuropeptides, which modulate the secretory activity of the Malpighian tubules and the fluid transport and peristaltic waves in the anterior midgut. Diuresis finishes 4 h. post blood-meal (PBM), when anti-diuresis processes begin. CCHamide is a brain gut neuropeptide precursor conserved in insect genomes. The physiological role of CCHamide has been studied in Drosophila melanogaster and Bombyx mori, where it modulates feeding behavior as an orexigenic factor. Here, we report that the neuropeptide RhoprCCHamide (RhoprCCHa) is involved in the regulation of the postprandial diuresis in Rhodnius prolixus, a triatomine insect which is a vector of Chagas disease. The expression of RhoprCCHa gene was downregulated by RNA interference in this insect, obtaining an 85% of gene silencing and we found a dual effect of RhoprCCHa in the diuresis. Our results point to an inhibition of immediate excretion (10 to 45 min. PBM) and a stimulation of dieresis towards the end of the process (90 to 240 min. PBM). Using in vitro approaches we confirmed an effect of RhoprCCHa inhibiting the fluid transport by the anterior midgut stimulated with 5HT and an increasing in the secretion rate by stimulated Malpighian tubules. The opposite role in different structures was not reported previously for any neuropeptidergic system in insects. It seems to reflect the necessity of a tight regulation of the volumes excreted in hematophagous, and thus avoiding defects in the diuresis that would endanger the homeostasis

ORAL COMMUNICATIONS

Thursday 25th – 14:30 – 15:30 / *Room C*

OC1.-Dopaminergic Neurodegeneration and Neuroinflammation: Modulation by IGF-I gene therapy

Macarena Lorena Herrera1, Andrea Otamendi1, Osvaldo Martín Basmadjian1, Leandro Gabriel Champarini1, Eugenia Falomir-Lockhart2, Franco Juan-Cruz Dolcetti2, VIctor Alejandro Molina1, María José Bellini2, Claudia Beatriz Hereñú1
1 Universidad Nacional de Córdoba, Facultad de Ciencias Químicas, Departamento de Farmacología, Instituto de Farmacología Experimental de Córdoba (IFEC)-CONICET, 2 Universidad Nacional de La Plata, Facultad de Ciencias Médicas, Instituto de Investigaciones Bioquímicas de La Plata (INIBIOLP), CONICET

Insulin-like growth factor 1 (IGF-1) is emerging as a powerful neuroprotective molecule since most brain disorders are accompanied by IGF-1 deficiency and/or resistance. IGF-1 has a wide variety of functions and its study could provide the basis to prevent the deleterious effects of neurodegeneration. The aim of this study is to explore the effects of IGF-1 gene therapy on different experimental models of neurodegeneration and neuroinflammation. Under an experimental model of PD, hippocampal IGF-1 gene therapy has important effects on neuronal activity that could explain, in part, the improvement in working memory dysfunction that we observed after 20 days of neurodegeneration in rats injected with 6-OHDA. ICV IGF-1 gene therapy induced a restorative effect in the hypothalamus of senile rats with DA dysfunction, and a significant improvement in motor performance in aged rats. Besides, in a clinical assessment of frailty in female and male mice we observed cognitive and motor improvements in the groups injected with IGF-I. Neuroinflammation comprises glial cells activation and the release of pro-inflammatory molecules, which is a normal response oriented to protect neural tissue. With regard to this, IGF-1 gene delivery to astrocytes in vitro reduces their inflammatory response to LPS. Besides, IGF-1 exerts neuroprotective actions in a TBI, which triggers the activation of glial cells in the cortex. Our results provide a support to develop new therapeutic approaches.

OC2.-Familiar face recognition in the primate brain

Sofia Landi, Winrich Freiwald
Rockefeller University

We have known for some time that there is a network of brain regions for face recognition. However, attempts at finding how and where face familiarity is encoded in the brain have proven inconclusive. We used functional magnetic

resonance imaging (fMRI) in macaque monkeys to measure brain activity as they looked at pictures of other monkeys' faces that were familiar and unfamiliar to them. Activity in the entire face-processing system increased in response to the faces of long-term acquaintances. Additionally, these faces prompted the activation of two previously unknown face-selective areas. One is located in the perirhinal cortex (PR), a region that has been associated with declarative memory and the other one is embedded in a region involved in audio-visual integration and social knowledge: the temporal pole (TP). These two areas showed a nonlinear response as blurred faces became gradually visible, becoming abruptly active when the faces of familiar monkeys became recognizable. We are now exploring the electrophysiological properties of single-cell and neural populations in these areas. Preliminary results confirm our fMRI study: we found a high fraction of face-selective cells tuned to familiarity. Individual cells encoded specific familiar faces, and unfamiliar faces that were similar in shape or appearance failed to elicit the same neural responses. TP and PR emerge thus as special regions within the macaque face processing system that encode individual familiar faces.

OC3.-Interoceptive associations in addiction to smoked cocaine

Laura Alethia de la Fuente1, Lucas Sedeño1, Sofia Schurmann3, Camila Ellmann3, Silvina Sonsogni2, Laura Bellucio2, Eduardo Canepa2, Enzo Tagliazucchi4, Teresa Torralva3, Agustin Ibañez1

1 LPEN-INCyT, 2 Laboratorio de Neuroepigenética-UBA, 3 NPS-INCyT, 4 COCUCO-UBA

Contemporary neurocognitive models of drug addiction underscored the role of interoception. In these models, interoception is defined as the sensing and processing of body signals to serve a homeostatic function related to the onset and maintenance of addictive-behavior. In this work we assess the relation between interoception and smoked cocaine dependence with a multimodal and multi-dimensional approach. We use the Hearbeat-detection (HBD) task and related Heart Evoked Potential (HEP) recordings at baseline (interoceptive accuracy) and during learning. We combined this behavioral and electrophysiological data with structural and functional connectivity analysis of the main interoceptive hubs. Smoked cocaine dependent subjects presented ongoing psychophysiological measures of enhanced interoception accuracy (HBD & HEP); accompanied by structural and FC tuning of interoceptive networks. Our findings support both specialized effects of smoked cocaine on interoception, and also provide direct empirical evidence for drug models suggesting that hyper-interoception processing is a key aspect in addictions.

Thus, multimodal assessment of interoception could serve as a potential domain to asses clinical and neurocognitive characterization of psychophysiological and underlaying neurophysiological adaptations in addiction.

OC4.-Memory deficits in transgenic McGill-R-Thy1-APP hemizygous rats

Daniela Salas1, Federico Filippin1, Edgar Kornisiuk1, Pilar Canal1, Anna Di Tomas Lioro1, Sonia Docarmo2, A. Claudio Cuello2, María Verónica Báez1, Diana Jerusalinsky1

1 IBCN, 2 Departamento de Farmacología y Terapéuticas Universidad McGill

McGill-R-Thy1-APP Wistar transgenic (Tg) rats, with human APP under the Thy1.2 promoter, bearing the Swedish and Indiana mutations corresponding to familial AD in homozygous condition, had been reported to show significant cognition deficits at 3 months of age. On the other hand, hemizygous Tg rats show a more subtle phenotype. In this work, 6 and 13 month old hemizygous Tg males and their WT litter mates rats were individually left to freely explore an open field (OF) for 5 min and tested at 24 h; the numbers of crosses in the floor were recorded. There were no differences between WT and Tg groups during the training and the number of crosses significantly decreased in the test compared with training. Rats were then trained in an inhibitory avoidance task (IA) of a mild electric foot shock and tested at 24 h to evaluate long-term memory (LTM). Latency to go accross a door to get into a dark compartment where the rat will get the shock, was recorded. There were no significant differences in training latencies between animal groups. 24 h later, test latencies were significantly higher than training latencies for WT rats, while there were no significant differences for Tg rats. Therefore, both Tg and WT rats are able to habituate to the OF, keeping LTM; on the other hand, WT animals learned and remembered the IA at 24 h, while the Tg were not able to remember it, evidencing deficits in these sort of associative memory involving aversive and spatial components.

OC5.-The interplay between behavioral pattern completion and pattern separation for retrieval in a cue-degraded context

Magdalena Miranda, Facundo Morici, Dinka Piromalli Girado, Francisco Gallo, Weisstaub Noelia, Pedro Bekinschtein

Laboratorio de Memoria y Cognición Molecular, INCyT

Because our environment is permanently evolving, it is crucial for episodic memory to remember our previous experiences despite environmental changes. Computational models have suggested the existence of a pattern completion process by which networks could retrieve entire memories from partial or degraded cues. The CA3 region of the hippocampus was proposed to mediate this computation by the plastic enhancement of the recurrent collateral connections of CA3 neurons that were active during learning. In this work, we manipulated the amount of cues available during retrieval (test phase) in a spontaneous object recognition task to investigate the function of CA3 NMDA-receptors (NMDAR) for pattern completion. We show that pharmacological intervention of hippocampal CA3 NMDAR receptors impairs retrieval of the object location memory only when cues are degraded, while similar manipulations in the dentate gyrus have no effect. Moreover, while the context alone is enough o guide retrieval of the object memory under partial cues, antagonists of NMDAR in the test phase prevent this retrieval. These findings suggest that NMDAR in CA3 are necessary for the retrieval of spatial memories when the amount of environmental information is reduced, and that plastic changes in the dentate gyrus and CA3 are important to define if behavioral pattern separation or pattern completion occurs when exposed to a modified context.

OC6.-*Dissoc*iating reconsolidation and extinction of contextual aversive memory in female rats using midazolam treatment and reinstatement paradigm: influence of reactivation time span

Jaqueline Maisa Franzen, MarceloGiachero, Leandro José Bertoglio
Department of Pharmacology, Federal University of Santa Catarina, Florianopolis, SC, Brazil

Females (FEM) have particularities in contextual aversive memory (CAC). Reactivated aversive memories may follow alternative outcomes which are dependent on duration of reactivation session. Although the time course of a CAC after retrieval has been well characterized in male rats, this temporal pattern is still unexplored in FEM. We aimed to investigate the passage from reconsolidation to extinction of memory combining CAC, different reactivation time span, midazolam and a reinstatement procedure in FEM. Rats were trained and, on the following day, rats were exposed to different re-exposure times (1, 2, 5, 7, 10 or 30 min) that were followed by MDZ administration. Given that FEM showed a decrease in freezing expression with the increase in the number of re-exposures to the CAC, we used a reinstatement strategy that allowed

dissociating the effect of MDZ on memory. Our findings showed that when the reactivation session lasted 2-5 min, memory returned to a labile state sensitive to disruption by MDZ and memory showed no reinstatement. When 30-min reactivation session was performed, memory was directed to extinction and MDZ was able to disrupt the retention of this process and memory showed reinstatement, but, memory was insensitive to MDZ effect when reactivation session lasted 7-10 min. In summary, combining post-reactivation MDZ treatment with a reinstatement protocol, we managed to dissociate the mutually exclusive processes of reconsolidation and extinction in FEM rats.

Friday 26th – 14:30 – 15:30 / *Room B*

OC7.-Temporal mapping of adult-born granule cells integration in two major local inhibitory populations of the hippocampus

Ayelen I. Groisman, Sung M. Yang, Alejandro F. Schinder
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Adult neurogenesis provides a continuous pool of new granule cells (GCs) that participate in information processing in the dentate gyrus of the hippocampus. We studied how GCs become integrated toward maturation into the preexisting circuit of the adult mouse dentate gyrus. We chose two major population of GABAergic interneurons (INs) of the hippocampus: Parvalbumin expressing cells (PV) and Somatostatin expressing cells (SST). We combined optogenetics and acute slice electrophysiology to activate PV or SST and GCs, retrovirally labeled, at different stages of maturation and studied their connectivity in both directions, interneuron to GCs and viceversa. We built a temporal map of synaptogenesis for each IN population and observed that connectivity between PV and GCs (input and output) reached maturation when GCs were >6 weeks old. For SST, the inhibitory postsynaptic current increased gradually with GCs development, while the GC output connectivity developed much later (>11 weeks) compared to PV. We found that PV synapses onto GCs were located perisomatically and contributed to both feedforward and feedback inhibitory loops within the granule cell layer. In contrast, SST contacted GCs in proximal and distal dendrites and contributed only to feedback inhibition. These data demonstrates that integration of new GCs within the preexistent dentate GABAergic network is specific of each IN population and that adult neurogenesis promotes a long-term plasticity for circuit remodeling.

OC8.-The varieties of the psychedelic experience: association between reported subjective effects, bindings, affinity profiles and molecular structures of eighteen psychoactive compounds

Federico Zamberlan[1], Camila Sanz[3], Rocio Martinez Vivot[1], Carla Pallavicini[2], Fire Erowid[4], Earth Erowid[4], Enzo Tagliazucchi[1]

[1] COCUCO - IFIBA - CONICET, [2] FLENI, [3] DF - UBA, [4] Erowid Center

Classic psychedelics are substances of paramount cultural and neuroscientific importance. The observation of cross-tolerance and a series of empirical studies support partial agonism at the serotonin 5-HT2A receptor as a common mechanism for the action of psychedelics. The diversity of subjective effects elicited by different compounds has been attributed to the variables of "set" and "setting", to the binding affinities for other serotonin receptor subtypes, and to the heterogeneity of transduction pathways initiated by conformational receptor states as they interact with different ligands ("functional selectivity"). Here we evaluated the hypothesis that such variety is related to the binding affinity profiles for a range of different neurotransmitter and transporters including (but not limited to) serotonin receptors. Building on previous experimental binding affinity data in combination with natural language processing tools applied to a large repository of reports of psychedelic experiences (Erowid's Experience Vaults), we established that the similarity between the receptorome of eighteen psychoactive compounds correlates with the closeness of their associated subjective effects. We also showed that the highest correlation could be achieved by considering a repertoire of receptors. Our methodological developments open the way to the systematic exploration of the relationship between the binding affinity profiles and subjective effects of other psychoactive compounds.

OC9.-Leukocytes as key players in optic nerve neuroinflammation

Marcos L. Aranda[1], Florencia Altschuler[1], María F. González Fleitas[1], Diego Guerrieri[2], Hernán H. Dieguez[1], Damián Dorfman[1], Ruth E. Rosenstein[1]

[1] Laboratorio de Neuroquímica Retiniana y Oftalmología Experimental, Departamento de Bioquímica Humana, Facultad de Medicina, CEFyBO, UBA/CONICET., [2] Laboratorio de inmunomoduladores y regeneración de órganos, Facultad de Medicina, CEFyBO, UBA/CONICET

Optic neuritis (ON) is a condition involving primary inflammation, demyelination, and axonal injury in the optic nerve which leads to retinal ganglion cell (RGC) loss, and a decrease in pupil light reflex (PLR) and visual evoked potentials (VEPs). Neuroinflammatory diseases are characterized by

disruption of the blood-brain barrier (BBB) and increased leukocyte infiltration. The aim of the present work was to analyze the involvement of cell infiltration on visual damage induced by experimental ON. LPS or vehicle were injected into the optic nerve from adult male Wistar rats. BBB integrity was analyzed through Evans blue perfusion on WT-GFPþ/WT chimeric rats. At 6 h post-LPS injection an increase in albumin-Evan's blue leakage and in optic nerve cellularity were observed. At 24 h post-injection, e-GFP(+) cells (likely macrophages and neutrophils) were identify in LPS-injected optic nerves. Experimental ON induced an increase in the chemokine CCL2-immunoreactivity. The injection of Bindarit (a CCL2 inhibitor) and bone marrow depletion (by gamma irradiaton) significantly prevented the effect of ON on PLR, VEP amplitude, and RGC number. In order to induce BBB breakdown, tissue plasminogen activator (tPA) was injected into the optic nerve. tPA microinjection mimicked the effect of ON on PLR and RGC number. These results indicate that BBB integrity loss and leukocyte recruitment plays a key role in the visual damage induced by experimental ON.

OC10.-Light-regulation of ArylalkylamineN-Acyltransferase (AANAT) and a new potential rol in vertebrate retina

Maximiliano Nicolas Rios, Mario Eduardo Guido
CIQUIBIC – UNC

A key regulatory step in melatonin synthesis is that at which serotonin is converted to N-acetyl-serotonin (NAS) by the enzyme Aralkylamine N-Acetyltransferase. AANAT is present in the retina and other regions while NAS can activate the TrkB receptor to generate neuroprotective effects. In photoreceptor cells, AANAT activity peaks during the dark (D) and at subjective night while activity is significantly decreased by light (L). By contrast, melatonin synthesis, AANAT expression and activity are high during the subjective day or L phase in chicken retinal ganglion cells (RGCs). Here we investigated the expression of AANAT and of nonvisual opsins in enriched embryonic RGC cultures exposed to different L conditions. Cultures expressed Opn4 (melanopsin), Opn3 and Opn5 which may confer intrinsic photo sensitivity. Moreover, cultures exhibited blue L (BL) induction of AANAT immunoreactivity and mRNA as compared with D or red L treatedcells. In addition, expression of this enzyme was significantly increased by adenylate cyclase activator forskolin (10 uM) in D. Interestingly, AANAT showed a localization change, from the cytoplasm to nucleus, increasing in BL, and this effect was reversible in darkness condition after L exposure; in addition the nuclear importation of AANAT was

blocked with protein synthesis inhibitor cycloheximide (50uM) in BL. Results suggest that AANAT is a blue L-induced enzyme in RGCs controlled by cAMP, likely playing important roles in inner retinal cells.

Friday 26th – 14:30 – 15:30 / *Room C*

OC11.-Lrig2 promotes dendritic complexity, spine morphogenesis, and excitatory synapse formation in hippocampal neurons

Ana Paula De Vincenti, Fernando Cruz Alsina, Antonella Soledad Rios, Fernanda Ledda, Gustavo Paratcha

Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis" (IBCN) UBA-CONICET

Dendrite size and morphology are key determinants of the functional properties of neurons, and brain disorders are due primarily to structural abnormalities of dendrites and their connections. Distinct leucine-rich repeat (LRR) transmembrane proteins are highly expressed in the brain, especially in the hippocampus, where they play a critical role in the organization and function of neural circuits, regulating neurotrophin signaling, coordinating pre- and postsynaptic compartments during excitatory and inhibitory synapse formation and regulating synaptic plasticity.

Recently, the LRR protein Lrig1, has been described as an essential regulator of neurotrophin signaling and dendrite arborization of hippocampal neurons. However, the physiological contribution of Lrig2 for neuronal development remains to be determined. Taking advantage of the postnatal expression of Lrig2 by hippocampal developing neurons, we used gain and loss of function assays to examine how altered Lrig2 expression impacts dendrite morphology and synapse formation in search for specific LRR proteins involved in neurodevelopmental disorders.

Here we show that Lrig2 overexpression exacerbates dendrite complexity by promoting growth and branching, in a LRR domain-dependent manner. Our results also indicate that Lrig2 is expressed in pre- and post-synaptic fractions, where it controls the density of dendritic spines and increases the number of excitatory synaptic contacts in hippocampal neurons.

OC12.-Role of cytoplasmic c-Fos as an activator of lipid synthesis during neuronal differentiation

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Cytoplasmic c-Fos activates phospholipid synthesis by associating with particular lipid synthesizing enzymes at the endoplasmic reticulum (ER). This activity of c-Fos supports the high rates of membrane genesis required for neuronal differentiation. In hippocampal cultures, blocking either c-Fos expression or its activity promotes an impairment in differentiation with no observable development of axonal processes. In addition, the expression of N-terminal deletion mutants of c-Fos capable of blocking only its cytoplasmic activity produces a similar effect. Moreover, using an in utero model to evaluate neuronal cortical migration, neurons electroporated with a shRNA targeting c-Fos fail to migrate and are mostly visualized in the ventricular/subventricular zones. Since we found c-Fos strongly co-localizing with ER markers in neuronal processes, we examined if its lipid synthesis activator capacity is exerted in neurons by examining CDP-diacylglycerol synthase (CDS), previously described as one of the enzymes activated by c-Fos, and CTP:phosphocholine cytidylyltransferase-β2 (CCTβ2), that is responsible for CDP-choline formation in the brain. A strong interaction between c-Fos and the enzymes was found by FRET experiments together with a marked increase in CDS enzymatic activity in the presence of recombinant c-Fos. These results support our hypothesis that c-Fos plays a main role in neuronal differentiation and this might be achieved through phospholipid synthesis regulation.

OC13.-Differences on the effect of proteins of the same tethering complex on neuronal polarity

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The initial signals that determine polarity are largely unknown, placing the mechanisms underlying the axon formation under the scope of our investigation. Two interconnected process are essential for axon formation: the axonal biochemical specification and the rapid membrane outgrowth. The

exocytic pathways that function to translocate membrane patches to plasma membrane, undergoes by regulated non secretory exocytoses. It has been shown in hippocampal neurons that the axolemmal expansion occurs by the insertion of plasmmalemal precursor vesicles (PPVs) at the growth cone, a process regulated by IGF1. A previous physical interaction between the vesicle target and the membrane is necessary to fusion. This process is mediated by thethering complexes. The exocyst complex is an candidate for the regulation of fusion of PPVs, of which the total composition is still unknown in neurons. It has been reported that IGF-1 triggers translocation to the plasma membrane of the exocyst component exo70 in the growth cone, being one of the steps at the complex formation. We determined that several proteins of the exocyst complex are present at hippocampal cultures in early stages of development. More over two proteins of this complex have opposites effects on neuronal differentiation. The implication of silencing sec3 in hippocampal cultures and in utero electroporation develop abnormalities. In constrast, the effect of suppressing sec8 remains neuronal migration and polarity non affected.

OC14.-Inter-hemispheric hypo-connectivity and regional metabolic hyper-activity in an experimental model of autism

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Autism spectrum disorders (ASD) are a group of neurodevelopmental disabilities characterized by alterations in brain connectivity and neuroinflammation. In accordance with the long-distance hypo-connectivity and local hyper-connectivity hypothesis, previous studies in our laboratory with the valproic acid (VPA) model demonstrate connectivity alterations and reactive gliosis in the prefrontal cortex and hippocampus of VPA rats. The aim of this work was to evaluate the brain metabolic activity and the structure of the corpus callosum (CC) in VPA animals. For this purpose, glial cells in the CC were studied at PND 36 by CC1, PDGFαR, GFAP and tomato lectin staining. Also, CC ultrastructure was assessed by electron microscopy (EM). Evaluated by positron emission tomography, glucose uptake was increased in local areas along the brain of VPA rats, while it was decreased when considered the whole forebrain.

In the CC of VPA rats, the number of CC1+ cells diminished and number of PDGF+ cells increased, in the absence of astrogliosis or microgliosis. Concomitantly, EM showed less myelinated axons and aberrant myelin in the CC of VPA rats. To sum up, VPA animals exhibit hyper-metabolism in circumscribed brain areas along with global hypo-metabolism. Concurrently, CC myelination in VPA animals is disrupted, accompanied by an altered balance in the oligodendroglia lineage. Taking together, our findings support the local hyper-activity and long-distance hypo-connectivity hypothesis in ASD.

POSTER ABSTRACTS

P1.-UNQ-BAW the IV: the last in the line of succession

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The Brain Awareness Week at the University of Quilmes (UNQ) was carried out in two dates: June 9th and June 15th. It was the fourth BAW event held on the south of the metropolitan area of Buenos Aires.

On June 9th, we offered the workshop "Neurosciences applied to Education", where four lectures were given to around 100 teachers, directives and education students. The lectures were presented by specialists in the field: Dra. Juliana Leone (U. Di Tella), Dra. Cecilia Calero (U. Di Tella), Lic. Carolina Fracchia (CEMIC) and Lic. Veronica Ramirez (CEMIC).

On June 15th, we organized a "Neuro-Fair" consisting on stands prepared by neuroscience research laboratories, covering topics such as memory, visual and auditory perception, biological rhythms, development of the nervous system, animal models and brain anatomy, among others. The displays were specifically designed for a high-school level audience, aimed to inform as well as to promote scientific careers. Moreover, special talks were offered by recognized researchers as Dr. Rodrigo Laje, Dr. Santiago Plano featuring the illusionist/mentalist Maximiliano Giaconnia, Dr. Diego Golombek and Dra. Maria Luz Gonzalez Gadea. We estimate that the event was visited by around 3000 people.

We received financial support from the Argentinian Society for Research in Neuroscience (SAN) and the UNQ.

P2.-Musical learning: music and sounds as evocative of memories and emotions in our brain

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Music has always represented an important part of every human culture, both past and present. It is a strong modulator of mood and social interactions. Nowadays advances in neuroscience enable researchers to quantitatively measure just how music affects the brain and neuronal networks. Individual sounds are capable of evoking different emotions and memories, depending on the context and the background of the hearer. We designed and developed our scientific communication project according to the guidelines for the Brain Awareness Week (BAW). Our goal was to introduce children between 8 and 10 years old to the exciting world of neurosciences. In order to carry on our purpose, we visited fourth and fifth grades in Valentín Bonetti and Saint Andrew's Schools in the city of Mendoza, Argentina. We designed workshops to explain how the brain is modified by its interaction with sounds and music. We also provided dynamic talks and games so that children could learn while playing them. In this way, we sought to explain the links between sounds stimuli and how our brain is able to interpret and respond to them. The children easily associated different sounds with emotions and memories they perceived; they also learnt that a numerical sequence was easier to remember with a background melody. They enthusiastically manipulated rat and cow fixed brains in order to learn brain anatomy. Fortunately, we received a positive feedback from the children who were really excited to receive us.

P3.-BAW 2018 in Misiones: DO WE KNOW OUR BRAIN? A CHALLENGE OF SENSES

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One of the most important challenges of the current scientists is to bring their knowledge, methods, procedures and results to the society. Education is a main resource that students have to shape their future. So, it is fundamental to create bridges between science and education, through new forms of science divulgation. The objective of this BAW project was to improve students knowledge about the brain functioning, brain protection and also how to become neuroscientist in Argentina. For that purpose, during Brain Awareness Week (BAW) in March 2018, we visited three secondary schools located in Misiones province: Instituto Roque González (Posadas), Instituto Madre de la Misericordia (Posadas), Escuela Provincial de Educación Técnica (E.P.E.T.) Nº 50 (Leandro N. Alem). We developed the project through guide questions, group games, sense tests and a final talk with a total of more than 200 students. We focused on the participation of the students: they were able to experience themselves and many questions arose during the talks, which were very dynamic and varied among the different schools. Children, together with the professors and school directors, enjoyed and took advantage of the opportunity of having neuroscientists in the schools. Teachers repeatedly thanked us for bringing our research and knowledge to very distant provinces like Misiones. Support by grants of SAN (BAW); Transportes Rio Uruguay; E.P.E.T. Nº 50 and G. Rosciszewski family.

P4.- What do you have in mind?

Paula Bonaccorso, Belén Mulle, Vanesa Bazzocchini, Vanina Bugueño, Sebastián García

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In the last decades the study of the brain and the mind has become an important topic of science. Everyday we ask ourselves questions about we what do we have in mind. The main objective of our project is to answer those interrogants by explaining learning, emotions and memory, transfer public scientific knowledge and promote interest and critical thinking. We are a multidisciplinary team of psychologists, biochemistries, biologists and bioengineers.
During the Brain Awareness Week (BAW,12-18 May 2018) we perform talks, publications and contests on our facebook page (Qué tienes en Mente?).
We published five weekly news and articles related to the topic and five neuroscientists joined our proposal to talk about their specialties. Finally, by making contests and giving the winners a book, we made understandable neuroscientific approaches and open dialogue spaces that produced integral e-learning. This project collaborated to stimulate and reinforce neuroscience divulgation.

P5.-Activities for the brain awareness week organized by the Institute of Neurosciences and Complex Systems

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During the Brain Awareness Week 2018 -March 12th to 16th- we organized several activities that took place at Hospital "El Cruce - Dr. Néstor Kirchner" (HEC), Arturo Jauretche National University (UNAJ) and Florencio Varela Museum. Two Workshops were held, one on "Healthy Aging", in which problems related to cognitive diseases prevention and treatment in older adults were tackled, and another on Mental Health and Neurosciences. The former was addressed to health and social development workers, and the latter, to the general public. Various talks addressed to secondary schools teachers and students, university students, and the community were also delivered under the following titles: "Why do we feel pain?", "The internal clock that controls us ", "What happens to our memories while we sleep?", "Why do we remember and forget?". Two movies were shown, followed by a talk-debate. At the end of the week an exhibition called "Everything you wanted to know about how your brain works and you were encouraged to ask … but was not enough" was organized. Around 300 people participated in the activities, which were also disseminated through institutional websites and social networks.

P6.-Getting in contact with schools: the synapsis between students and neuroscientists

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The brain is our most intriguing organ. An important function is to detect and interpret events taking place in the environment through senses and command a response. How are these processes seen from the eyes of children? As imagination is their powerful tool, we proposed to sail in the students´ sea of marvellous theories. In this journey, we showed them though games what scientists already know. Framed around Brain Awareness Week 2018, an international campaign to educate general public and to support brain investigation, a group of researchers carried out the fourth edition of "Neuroscience of Senses visits the classrooms of fourth grade". This project, created and organised by Nicolás Unsain, was possible thanks to SAN financial support through its annual call for BAW projects. In addition, CCT-CONICET Córdoba and the Ministry of Science and Technology of Córdoba provided school contact, scheduling and transport. We visited 37 classrooms of 19 schools from Córdoba city and six nearby towns. Before the visit, teachers asked students to draw a neuroscientist, describe them and write questions they would like to ask. In the visit, we displayed an interactive lecture mixed with exciting games. Students participated actively asking questions and discussing concepts acquired by their own experience. Finally, we took a microscopic sight of the brain with immunolabeled neurons and compared fixed caw and rat brains; activities that allowed children to discover the role of brain.

P7.-MOLECULAR CHANGES IN GLUN2A KNOCKDOWN OF MATURE PRIMARY NEURONAL CULTURES

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NMDA Receptors (NMDAR) are glutamatergic receptors involved in synaptic plasticity, learning and memory processes as well as in several neuropathologies. NMDAR are composed by two GluN1 obligatory subunits and two regulatory subunits: GluN2 (A-D) or GluN3 (A-B). In cognitive related brain structures GluN2A and GluN2B are the most expressed regulatory subunits, that undergoes a tightly regulation at transcriptional and translational level. Whereas GluN2B expression is characteristic of immature synapses, GluN2A is present in mature and stable synapses. In order to better understand the role of GluN2A in synapsis, we transduced mature neuronal cultures with AAV-eGFP vectors: one codifying a specific shRNA anti GluN2A, AAV-sh2A, and the other carrying a shRNA scramble as control, AAV-shSc. As we verified that AAVsh2A knockdown GluN2A mRNA and protein levels (GluN2A KD), we analyzed the other NMDAR subunit expression in this cultures, as well as REST, a transcription factor that regulates GluN2A/GluN2B relationship. The GluN2A KD induced a decrease in REST levels without significant changes in GluN2B expression. On the other hand, GluN1 protein levels were significantly low in GluN2A KD cultures in spite of control mRNA levels. Furthermore, GluN1 splicing variants proportion was altered. These results suggest that GluN2A KD induce a rearrangement of NMDAR and REST expression similar to those observed in more immature states at neuronal differentiation.

P8.-The impact of DNA methylation/demethylation machinery on hippocampus of female weaned mice and their dams in a protein malnutrition model

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The developing brain requires a specific sequence of molecular steps that must be finely regulated. Adverse environmental, like perinatal protein malnutrition, impacts brain development in mice leading to functional changes. Moreover, the gestation and post-partum period presents the mother with a wide hormonal, physiological and metabolic changes that could be windows of susceptibility to all kinds of adverse factors. However, little is known about molecular mechanisms related with alterations describe above on malnourished weaned mice and their dams.
CF1 dams received low protein diet (8% casein) or normal protein diet (20% casein) during gestation and lactation. After this period, dams and PD21 female mice was euthanized and hippocampus was extracted to study RNA and protein expression.
We observed a significant effect of nutritional condition on genes related with epigenetics mechanisms both in dams and weaned mice. We found an increase in DNMT3b and Gadd45b RNA expression in malnourished weaned mice, but there is no difference in DNMT3a and GR. Also, we evidence a greater expression of GR RNA and Gadd45b protein in dams who received low protein diet, but we don´t observed difference on DNMT1 RNA and GR protein expression.
We suggest that protein malnutrition during gestation and lactation alters the neurological development of female weaned mice and the anxiety and depressive-like behavior of dams through genes related with epigenetic mechanisms.

P9.-Sphingosine kinases and NPC1 decrease would contribute to altered function in old hippocampal neurons

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It is now recognized that sphingolipid metabolites regulate many cellular processes important for health and disease. One of the most important of these metabolites is sphingosine-1-phosphate produced by two sphingosine kinase isoenzymes, SPHK1 and SPHK2. Sphk1 and Sphk2 have been implicated in neuronal function and memory formation. In hippocampal neurons, SPHK1 participates in excitatory synaptic transmission and has profound effects on spatial learning. SPHK1 is activity-dependent recruited to presynaptic terminals and promotes neurotransmitter release. Decreased levels of SPHK1 have been also associated to sphingosine accumulation leading to defects in endocytic trafficking. In the nucleus, SPHK2 regulates transcription of memory genes by producing S1P, which acts as an endogenous inhibitor of histone deacetylases.

Our results show that during aging, the levels of SPHK1 and SPHK2 are dramatically decreased in mouse hippocampus. According to these data, the accumulation of sphingosine was observed in hippocampal neurons aged in vitro. Furthermore, decreased expression of the Npc1 (Niemann Pick C1) gene, required for intracellular cholesterol redistribution and one of the SPHK2 targets, was found in the hippocampus of old mice.

All these results suggest that defects of neuronal function during aging would be due, at least in part, to deficits in S1P signaling and endocytic defects mainly consequence of cholesterol accumulation in the endolisosomal compartment.

P10.-Do not perturb me while I crawl

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Leeches crawl on solid surfaces by successive elongation and contraction of its body, anchored on the front and rear suckers. These movements would exert mechanical forces on the skin, innervated by three types of mechanosensory neurons. Because activation of the mechanoreceptors elicit a series of defensive behaviors, the mechanosensory signals could perturb the rhythmic displacement.

Recordings of low threshold tactile (T) mechanosensory neurons in isolated midbody ganglia during dopamine-elicited fictive crawlings (crawling) show that T cells receive inhibitory signals in phase with the activation of the motoneurons that cause the contraction. The inhibition is probably due to the activation of a synaptically-driven chloride conductance. Because the study was produced in the absence of the periphery this inhibition must be originated by the nervous system, probably downstream of the central pattern generator.

To confirm that inhibition of T cells is necessary to the smooth occurrence of crawling we analyzed the effect of exciting these neurons during the contraction phase and during the elongation phase. The results show that activation of T cells interrupts the burst of the motoneuron that controls contraction, but has no effect during elongation.

We interpret that the circuit that controls crawling sends an efference copy to the sensory neurons, to counteract the discharge caused by the mechanical forces exerted during contraction.

P11.-Analysis of the regulatory mechanisms that affect Gpm6a expression levels in the hippocampus of chronically stressed rats

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The neuronal membrane glycoprotein M6a (Gpm6a) is a member of myelin proteolipid protein (PLP/DM20) family that functions in the processes of neuronal remodeling and plasticity, such as neurite outgrowth, filopodium formation, and synaptogenesis. Pathological conditions have been linked to the alterations in Gpm6a expression levels or sequence. Downregulation of Gpm6a mRNA has been shown in the hippocampus of depressed suicide victims as well as in animal models of chronic stress. Regulatory mechanisms that affect Gpm6a expression levels during chronic stress exposure and in pathological conditions are not clearly understood. Different epigenetic mechanisms have been described to regulate Gpm6a mRNA levels: i) direct posttranscriptional regulation by miR-133b or ii) by miR-124, as well as iii) transcriptional regulation through miR-124 and miR-9 mediated effect on Hdac5-regulated transcriptional factor Mef2c.

Here, we use qPCR to demonstrate that in the hippocampus of chronically stressed rats, the exposure to restraint stress decreases levels of Gpm6a mRNA as well as the expression levels of miR-133b, miR-124a, but not miR-9-5p. Moreover, we detect altered levels of Hdac5 and Mef2c suggesting that chronic stress affects Gpm6a levels through miR-124 mediated effect on Hdac5 and Mef2c. Overexpression of miR-124 in cultured hippocampal neurons leads to increased neuronal arborization as assessed by Sholl analysis and increases Gpm6a protein levels.

P12.-A deeper view into the effects of repetitive traumatic stress on aging

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An attack, or even the perception of a predator elicits a rapid “fight-or-flight” response to enhance the animal’s chance of survival. In mammals, the acute fight-or-flight response leads to the release of catecholamines (CA). Perpetuated activation of this acute stress response, as is the case of patients suffering from post-traumatic stress disorder (PTSD) is associated with accelerated aging.

Nevertheless the molecular and cellular mechanisms that underlie this detrimental effect remain largely obscure. Taking advantage of its relative simple anatomy, genetics, high degree of conservation and short lifespan, we introduced a model of the nematode C. elegans, to go deep into these mechanisms.

C. elegans coordinates stress response by releasing the CA tyramine (TA), the structural and functional counterpart of adrenaline in mammals. We here determined that TA-deficient animals (tdc-1) exhibit increased healthspan and lifespan. On contrary, animals permanently exposed to acute stressors, have reduced lifespan and deteriorated general fitness. These detrimental effects are not observed in tdc-1 mutants suggesting that they depend on TA release. We are currently performing experiments in order to explore how neuronal architecture and function are affected by persistent activation of the fear-related response. This study was aimed to unravel how the stress response impacts on the structural, cellular and functional changes that normally occur with aging.

P13.-Role of Aβ/APP interaction in the increase of APP and BACE 1 convergence induced by Aβ.

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Alzheimer's disease (AD) is the most prevalent form of dementia linked to aging and its cause is related to the accumulation of the beta amyloid (Aβ) peptide in brain. Aβ derivates from sequential cleavage of amyloid precursor protein (APP) by BACE 1 and γ-secretase. Both, APP and BACE 1, are transmembrane proteins which present a dynamic intracellular traffic. Moreover, the site of convergence of both proteins and its modulation is yet unclear. Exist some evidence that suggest that Aβ is capable of induce its own production. In this study, we try to delineate, using confocal microscopy and quantitative colocalization analysis, which is the basal distribution of APP and BACE 1 in HELA cells and how this arrangement is affected by Aβ treatment. We saw that initially APP and BACE 1 have a low colocalization which is increased after a 24 hs treatment with Aβ 10 uM as result of a re-distribution of APP and BACE 1 in recycling endosome. Also we verified that this effect is a consequence of the Aβ/APP interaction in such a way that when it is expressed a deletioned APP that lacks binding domain to Aβ (APPΔβ), the increase of convergence of APP and BACE 1 induced by Aβ is avoided. Finally, we saw that the increase in the encounter between APP and BACE 1 after Aβ treatment is the consequence of the activation of a signaling pathway mediated by APP/Go/βγ proteins since galein, a specific βγ inhibitor, is capable to preclude it.

P14.-NEURONAL GLYCOPROTEIN M6A AS A KEY REGULATOR OF SYNAPTIC PLASTICITY DURING EXTRA UTERINE BRAIN DEVELOPMENT

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During the early stages of development and in adulthood, neurons of the central nervous system suffer changes in the formation, maintenance and elimination of synapses. This process, synaptic pruning, is linked to many neurological diseases as Alzheimer's disease and schizophrenia. The neuronal membrane glycoprotein M6a had been widely related to neuronal structural plasticity. In hippocampal cultured neurons, M6a promotes neurite and axonal outgrowth, filopodia/spines formation and enhance the number of synapses. Variations in GPM6A gene expression and SNPs are linked to mental disorders such as depression, schizophrenia, mental retardation and Alzheimer's disease. However, there is no evidence linking M6a to the synaptic pruning process, nor potential ligands of M6a that modified their levels. Therefore, we aim to analyse the variation of M6a levels throughout brain development. To this end, Sprague-Dawley rats were sacrificed from the day of their birth, P0 (postnatal, zero), to adulthood, P90 and samples from hippocampus, prefrontal cortex, cerebellum and striatum were taken. We observed that the levels of M6a vary from P0 to P90 and this variation depends on the tissue analyzed. Moreover, we showed that M6a is expressed in the striatum, which had not been yet described. We also generated and characterized a recombinant protein that will allows us to identify M6a ligands for understand how this protein is related to the synaptic pruning.

P15.-IGF-1 expression in the cerebellum of the developing Spontaneously Hypertensive Rat (SHR)

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The Spontaneously Hypertensive Rat (SHR) grows in a chronic hypoxic environment due to placental insufficiency. This situation resembles that of the IUGR, one of the major problems in perinatal medicine representing one of main causes of perinatal mortality and morbidity. Insulin-like growth factor 1 (IGF-1) serves as a promoting factor for Purkinje cell postnatal survival and dendritic growth, and it stimulates repair mechanisms after hypoxic damage. An increase in IGF-1 levels has been associated with enhanced reactive astrocytosis. The refinement of neuronal circuits during postnatal (P) cerebellar development is critical to their subsequent function and abnormalities in this process can result in neurodevelopmental disorders, as shown by the SHR rats. We examined the expression of IGF-1 by RT-PCR in the cerebellum of SHR and of the normotensive counterparts of the WKY strain, at P7 and P14. We also measured GFAP immunofluorescence in the cerebellum white matter (WM) and c. callosum (CC) of littermates. We found an increase IGF-1 expression in the WM of the SHR at P14 ($p<0.01$ vs WKY). In a preliminary assay we detected GFAP immunolabeling in WM and CC at P7 and P14 in both strains. This reactivity is apparently more intense in the SHR animals. These results indicate that the SHR brain may show signs of brain repair and remodelling as a consequence of an adverse gestational environment. SHR rat could be proposed as a valid animal model for studying IUGR.

P16.-Molecular mechanisms associated with impaired peripheral nerve repair mediated by anti-ganglioside antibodies

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Guillain Barré Syndrome is an acute monophasic polyneuropathy characterized by the presence of ascending muscular paralysis and arreflexia. In a subgroup of patients, paralysis is related to the presence of high titers of antibodies targeting gangliosides (anti-Gg); glycosphingolipids containing sialic acid. These antibodies are generated in response to antigenic determinants with structural homology to gangliosides present in the wall of causative agents of gastrointestinal or respiratory infections that commonly precede the disease. Passive transfer studies with a mAb anti-Gg (anti GD1a-GT1b, clone 1B7) in a murine model of axon regeneration confirmed that these antibodies are able to inhibit nerve repair by negative modulation of actin and tubulin cytoskeleton in growth cones. In vitro studies demonstrated that this effect is mediated through the activation of RhoA/ROCK signaling pathways. Recent findings in this model show that nerves from animals exposed to anti-Gg display a significant failure in the clearance of tissue debris, suggesting a possible effect on non-neural cells. Chronic administration of a pharmacological inhibitor of the RhoA/ROCK pathway, Y-27632; was able to reverse this effect. Preliminary experiments display that mice treated with mAb 1B7 show a reduced number of extravasated macrophages in sciatic nerves respect to the control. These results suggest a new RhoA/ROCK-dependent inhibitory effect of anti-Gg on nerve repair by targeting non-neural cell.

P17.-Neuroprotective effect of Yerba mate (Ilex paraguariensis) on cultured dopaminergic neurons, from in vitro to Drosophila models of Parkinson's disease

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Parkinson's disease (PD) is the second worldwide neurodegenerative disorder in prevalence. Its origin is unknown, but its pathophysiological characteristic is the progressive degeneration of dopamine-releasing neurons (nDA) of the Substantia nigra pars compacta. Recently, a study conducted in Argentina revealed that the consumption of yerba mate (YM) has an inverse association with the risk of developing PD.

With the aim of demonstrating the putative neuroprotective properties of YM on nDA, we are undertaking experimental approaches both in vitro and in vivo. First, we studied the survival of mouse nDA on primary cultures treated with YM extract, and found that YM provides higher neuroprotection over nDA than other known agents, such as caffeine. To delve into the basis of this neuroprotection, we have also tested some of the major compounds of the YM extract, such as chlorogenic acid and theobromine.

Given these promising results, we hypothesized that the YM extract could also protect nDA in vivo from the degeneration caused by the expression of a-syn in a Drosophila melanogaster model of PD, and improve the related locomotor deficit. To reach this goal, we have set up the administration of YM to these flies and produced preliminary behavioral and histological data. Our results demonstrate that YM protects nDA in vitro and set the grounds to study such effect on a simply, but very powerful, in vivo model of PD.

P18.- CHARACTERIZATION OF FUNCTIONAL ASPECTS OF THE RETINA IN A MOUSE MODEL OF LASER-INDUCED CHOROIDAL NEOVASCULARIZATION (CNV)

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Age-related macular degeneration (AMD) in its neovascular form is the leading cause of vision loss among adults above the age of 55. In the present study, we validate an established CNV mice model, which resemble human neovascular AMD. Thus, this study was performed in this mouse model of CNV, in order to characterize the neovascular process and its impact on the retinal functionality as well as the inflammatory profile. The CNV lesion were induced with four spots of argon green laser photocoagulation per eye on C57BL/6 mice. After 7 days of laser burn, we analyzed the retinal functionality by scotopic electroretinography (ERG). The a- and b-wave amplitude as well as the implicit time were evaluated. The results demonstrated that both, a- and b-wave amplitude, were decreased in the CNV mouse model. Then, the NV on choroid–RPE flatmounts was studied by isolectin B4 (IB4) staining. At the same time, different types of cells in the lesion area were characterized by specific cell markers: CD105 (ECs), NG2 (pericytes), F4/80 (microglia), and the inflammatory and pro- angiogenic profile were analyzed by qPCR. The lesion area showed an increased number of ECs, pericyte and microglia, accompanied with high transcriptional levels of pro-inflammatory and pro-angiogenic factors. In conclusion, the functionality of cells localized in the outer and inner nuclear layers of retina was affected by the choroidal neovascularization process.

P19.-Terminal differentiation of late-born spinal cord neurons

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Understanding the ontogenetic mechanisms that control cellular diversity is a central problem in developmental neurobiology. It still remains unclear how the timing of differentiation contributes to neuronal diversity, which are the properties of late-born neurons and how their identity is controlled. We have shown that CerebroSpinal Fluid-contacting Neurons (CSF-cNs), located in the spinal cord central canal, originate from unique late neurogenic events. We found that CSF-cNs robustly express Gata3 and Gata2 transcription factors, downstream of Ascl1. To determine their function, we performed loss of function experiments by generating Gata2/3 conditional mutant mice. We found that after Gata3 deletion, the dorsal group of CSF-cNs (CSF-cN') is missing, while the ventral subset (CSF-cN") remains unaffected. In Gata3/2 double mutants we found a complete loss of CSF-cNs suggesting that Gata2 acts redundantly with Gata3 during CSF-cN" differentiation. A close inspection on the temporal activation of Gata3 and Gata2 showed differences in the induction of these transcription factors during the development of both subpopulations. To better characterize CSF-cNs and their axonal topography, we performed mosaic genetic labelling using Ascl1CreER mice in combination with membrane-bound-YFP reporters. These experiments, in combination with retrograde fluorescent marking, indicate that CSF-cN are rostrally-projecting neurons.

P20.-The neddylation pathway regulates axo-dendritic development by controlling cytoskeletal dynamics

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Neuronal development is controlled by signaling cascades regulated by a myriad of posttranslational modifications. Although the role of ubiquitin has been well established in the maturation of nerve cells, the function of other members of the ubiquitin-like protein family remains poorly understood. Nedd8 is the UBL with the highest homology to Ub, and we demonstrated that Neddylation is highly abundant in the brain and is critical for synapse formation and maintenance. Blocking Neddylation with genetic and pharmacological tools reduced axonal and dendritic growth both in cell culture and in-utero electroporation approaches. These effects were partially reverted by Cyto-D and Taxol. These results suggest that cytoskeleton dynamics are involved in the effects of Nedd8 on axodendritic growth. To identify the structural details underlying the effects of Nedd8 we employed live-imaging, superresolution, and fluorescent microscopy. Neddylation blockade with MLN-4924 strongly reduced microtubular polymerization, induce ectopic lamellipodia formation and increased the growth cone size in early neurons. In biochemical screenings, we have identified several neddylated targets that are regulators of cytoskeleton structure and function. We evaluated the function of neddylation on those targets performing molecular replacement strategies in primary neuronal cultures and in-utero electroporated mouse brains. The effect of neddylation on dendritic growth and arborization will be discusses.

P21.-LOW LED LIGHT EXPOSURE AS A MODEL OF RETINAL DEGENERATION IN ALBINO RATS

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Excessive exposure to artificial light [light pollution (LP)] can accelerate the course of certain genetic diseases, induce the death of rod cells and promote circadian asynchrony, triggering the development of retinal degeneration (RD).

Previously we developed a RD model by constant exposure of albino rats to low intensity LED light (LL). This model is characterized by the death of rods, an increase in rhodopsin (Rho) phosphorylation and changes in the expression and localization of Opn4 and 5 in the internal retina.

Based on this background, we decided to study the kinetic of rod cells death, so, we evaluated the levels of oxidative stress (OS), the composition of fatty acids in membranes, ERG responses and whether Rho phosphorylation is a reversible mechanism.

Our results show that the treatment with light produces a significant increase of OS levels after 4 days of LL. The changes in OS metabolites are followed by a significant reduction of docosahexaenoic acid, indicating the oxidation of membrane outer segment. Nevertheless, ERGs showed retinal activity completely abolished after LL3, suggesting an interruption of rods activity before OS. Finally, Rho phosphorylation was reversible if the animals were exposed to darkness for 48 hours after LL treatment.

These results give evidence of a possible role of OS in the development of RD and the putative role of Rho phosphorylation/dephosphorylation. This model of constant light exposure may provide knowledge of LP effects.

P22.-A key function for Microtubule-Associated-Protein 6 in activity-dependent stabilization of actin filaments in dendritic spines

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Emerging evidence indicates that microtubule-associated proteins (MAPs) are implicated in synaptic function; in particular, mice deficient for MAP6 exhibit striking deficits in plasticity and cognition. How MAP6 connects to plasticity mechanisms is unclear. Here, we address the possible role of this protein in dendritic spines. We find that in MAP6-deficient cortical and hippocampal neurons, maintenance of mature spines is impaired, and can be restored by expressing a stretch of the MAP6 sequence called Mc modules. Mc modules directly bind actin filaments and mediate activity-dependent stabilization of F-actin in dendritic spines, a key event of synaptic plasticity. In vitro, Mc modules enhance actin filament nucleation and promote the formation of stable, highly ordered filament bundles. Activity-induced phosphorylation of MAP6 likely controls its transfer to the spine cytoskeleton. These results provide a molecular explanation for the role of MAP6 in cognition, enlightening the connection between cytoskeletal dysfunction, synaptic impairment, and neuropsychiatric illnesses.

P23.-Serotonin and Catecholamines Neuronal Circuits regulate opposing behaviors in Caenorhabditis elegans

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Patients with anxiety disorders, such as post-traumatic stress disorders (PTSD) and panic attacks, exhibit high levels of catecholamines (CA), even in the absence of stress. Selective serotonin (5-HT) reuptake inhibitors (SSRIs), which increase the 5-HT level in the synaptic gap, are the most suitable drugs to treat these patients. This means 5-HT plays an important role in these disorders, but its relationship with CA is still unknown and difficult to study in the complex human nervous system. Given its simplicity and the highly conserved neurological pathways, C. elegans can be used to provide insights into the crosstalk between 5-TH and CA.
When C. elegans encounters food, it releases 5-HT to inhibit locomotion. We exposed tdc-1 and tbh-1 null mutants (unable to synthetize the analogous of mammalian CA tyramine (TA) and octopamine (OA), respectively) to exogenous 5-HT and found that they are hypersensitive to paralysis. These results strongly suggest that 5-HT acts antagonistically to CA. In addition, we studied the hypersensitivity to exogenous 5-HT of mutants in TA and OA receptors. We observed that tyra-3, ser-3 and ser-6 null mutants do not recover completely from the serotonin-induced paralysis. We are now digging into the molecular and cellular underpinning of these antagonistic effects by analyzing mutants in 5-HT receptors. These opposite actions could be conserved in mammals and explain the efficiency of SSRIs in PTSD and panic attack treatments.

P24.-Downregulation of arginyltransferase (Ate1) enhances bortezomib-induced cell death in human glioma cells

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The enzyme Ate1 mediates the post-translational addition of an Arg to proteins bearing acidic N-terminal amino acids that are mainly target to proteasomal degradation or macroautophagy. Previous studies reported that Ate1 downregulation suppresses cell death induced by different stressors. In addition, Ate1-knockout fibroblasts exhibit tumorigenic properties, including exacerbated contact-independent growth and chromosomal aberrations. We recently reported that increased cell membrane exposure of an Ate1 substrate (arginylated calreticulin) modulates the sensitivity to proteasomal inhibitor bortezomib (BT) of human oligodendroglioma (HOG) cells. Hence, further assessment is required to determine the Ate1 implication in the tumorigenic progression of BT treated cells. HOG cell death induced by BT comes through a mechanism that involves activation of the unfolded protein response (UPR) mediators, including the transcriptional activation of the spliced mRNA xbp1 and concomitant upregulation of DR5-R membrane expression. Moreover, we do not observed changes in autophagy flux at different time and drug doses. Strikingly, we found that Ate1 knockdown in HOG increases their sensitivity to BT in a macroautophagy independent way, suggesting that apoptosis of glioma cells induced by BT is strongly influenced by Ate1 expression. We postulates that Ate1 is an essential enzyme that regulates stress response and cell fate controlling the tumorigenic progress of cancer cells.

P25.-Role of Gata3 in the Development and Maintenance of Serotonergic Neuron Identity

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The serotonergic system, located in the Raphe's nuclei, controls different aspects of behavior and physiological processes. During embryonic development, serotonergic neurons are produced from progenitors in the most ventral domain of hindbrain, which also generate visceral motoneurons. Genetic studies have identified that the transcription factors Pet1, Lmx1b and Gata3 are important for the proper assignment of serotonergic identity. By performing genetic tracings in young and adult mice in combination with expression analysis we found that Gata2 and Gata3 expression is retained in mature serotonergic neurons. To assess the role of Gata3 in postnatal Raphe neurons, we generated inducible Gata3 conditional knockouts and found reduced expression of Pet1, Tph2 and Sert in the dorsal raphe nucleus. Moreover, we found a decrease in serotonin synthesis, which is accompanied with a loss of habituation in open-field tests, suggesting an anxiety-like phenotype. On the other hand, the deletion of Gata3 during advanced embryonic neuron maturation did not show altered expression of Pet1, Sert and other genes related to serotonergic function. These results indicate that Gata transcription factors not only are important for serotonergic neurons specification, but are also involved in maintaining serotonergic identity throughout life.

P26.- Differences on the effect of proteins of the same tethering complex on neuronal polarity

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The initial signals that determine polarity are largely unknown, placing the mechanisms underlying the axon formation under the scope of our investigation. Two interconnected process are essential for axon formation: the axonal biochemical specification and the rapid membrane outgrowth. The exocytic pathways that function to translocate membrane patches to plasma membrane, undergoes by regulated non secretory exocytoses. It has been shown in hippocampal neurons that the axolemmal expansion occurs by the insertion of plasmmalemal precursor vesicles (PPVs) at the growth cone, a process regulated by IGF1. A previous physical interaction between the vesicle target and the membrane is necessary to fusion. This process is mediated by thethering complexes. The exocyst complex is an candidate for the regulation of fusion of PPVs, of which the total composition is still unknown in neurons. It has been reported that IGF-1 triggers translocation to the plasma membrane of the exocyst component exo70 in the growth cone, being one of the steps at the complex formation. We determined that several proteins of the exocyst complex are present at hippocampal cultures in early stages of development. More over two proteins of this complex have opposites effects on neuronal differentiation. The implication of silencing sec3 in hippocampal cultures and in utero electroporation develop abnormalities. In constrast, the effect of suppressing sec8 remains neuronal migration and polarity non affected.

P27.-TREM-1/TREM-2 ROLE IN REACTIVE ASTROGLIAL POLARIZATION TO THE PROINFLAMMATORY PHENOTYPE

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Reactive gliosis is a generic astroglial response to brain injury. Reactive astrocytes can further polarize into an A1 proinflammatory-neurodegenerative phenotype. We have recently described that TLR4/NFkB signaling facilitates astroglial conversion to the A1 phenotype (Rosciszewski et al., Mol. Neurobiol. 2017). Having in mind that TREM1/TREM2 and DAP12 participate in the fine-tuning of the inflammatory response by controlling TLR/NFkB signaling in immunocompetent cells, we here studied the expression of these receptors and DAP12 intracellular adaptor in vivo after brain ischemia and in vitro in glial cell cultures exposed to oxygen-glucose deprivation for 6 h. Using an experimental model of brain ischemia in rats, we detected TREM2 and DAP12 expression in glial cells, with a peak between 3-7 DPI with a specific localization in the ischemic penumbra. In vitro, we observed that OGD exposure increases TREM2 expression in astrocytes and microglia; reduces TREM1 in both cell types; while DAP12 expression is not significantly altered by OGD. Finally, we performed co-culture experiments of ischemic explants (3DPI) on primary glial cells. After 5 DIV, we observed that infiltrated cells from ischemic explants and mainly microglia expressed TREM2. Our results show that ischemia or OGD induces the expression of TREM1 and TREM2 in microglia but also in a subpopulation of reactive astrocytes and the DAP12 adaptor is available to signal in these cells. Grants: PICT 2015-1451; UBACYT.

P28.-Expression of aggressiveness modulate mesencephalic c-Fos activation during a social interaction test in Japanese quail (Coturnix coturnix) reared in enriched or plain environments

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Display of aggression is associated with both the animal's propensity to behave aggressively and their opponent´s behavior. Recently, a social interaction test (SI) that focuses only on the experimental bird aggressiveness by assessing its behavior against a non-aggressive opponent (photocastrated counterpart) was developed. The avian Intercollicular-GCt complex (comparable with periaqueductal gray) is a node in the descending pathways that organize behavioral and autonomic aspects of defensive responses and aggressiveness. Using SI, we evaluated whether mesencephalic areas are involved in the expression of aggressive behaviors in adult males and whether the mesencephalic activation is related to the male performance (aggressive vs. non-aggressive) during the trial, and to the environmental stimulation received during birds´ breeding/rearing (standard vs. enriched). Five mesencephalic areas (at two anatomic levels) were studied by determining C-Fos expression. Aggressive males showed increased c-Fos labeling in all areas in comparison to non-aggressive and control birds. Non-aggressive and test control males showed similar c-Fos labeling. Environmental stimulation did not appear to influence c-Fos expression. Results suggest that the mesencephalic areas are involved only when males are actively expressing aggressive behaviors. The phenomena is shown regardless of both the environmental stimuli received during the birds´ rearing, and the stressful stimuli during the trial.

P29.-Characterization of the antagonistic actions of histamine on homomeric GABAAρ1 receptors

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Histamine may exert its effects not only through its canonical (G-protein coupled) receptors, but also by other mechanisms which are currently being studied. It was shown that histamine can modulate the activity of different ligand-gated ion channels including several subtypes of GABAA receptors. For example, it gates homomeric GABAAβ2-3 and acts as a positive modulator on heteromeric GABAAα1-5β2γ2 receptors, but its effects on GABAAρ1 receptors had never been studied before. We previously reported that histamine inhibited GABAAρ1 receptor responses in a dose-dependent, reversible and voltage-independent manner. This was the first evidence of histamine mediating an inhibitory action on a ionotropic GABA receptor and contributed to explore the role of histamine in the retina. In the present study we analyzed the mechanism of action involved in this modulation. GABAAρ1 receptors were expressed in Xenopus laevis oocytes and GABA-evoked chloride currents recorded by two-electrode voltage-clamp. Dose-response curves for GABA performed in the presence of histamine were shifted to the right, with no changes in the slope, nHill or maximum response. No use dependent effects were observed. These results are compatible with a competitive antagonism operating on the GABAAρ1 receptors. Computational docking studies and single-oocyte binding assays with tritiated GABA are being conducted to confirm the mechanism of action proposed here.
Supported by FONCYT and CONICET

P30.-Are transferrin pro-differentiating effects on neurons mediated by iron?

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Transferrin (Tf) is a glycoprotein best known for its role in iron delivery, although it has also been attributed trophic functions. Tf has been reported to favor the proliferation and differentiation of different cell types, and previous studies by our group have shown apoTransferrin to particularly accelerate the differentiation of oligodendrocytes in vitro as well as in vivo (Paez et al., 2005). In the present work, we aimed to determine the effects of apoTf treatment on neurons in vitro. For this purpose we used two different systems: N2a cells, a neuroblastoma cell line which is frequently used to study the neuronal differentiation process, and primary cultures of cortical neurons.

After examining the Tf-Tf receptor system in our models and verifying that both N2a and neurons are capable of internalizing Tf added to the culture medium, we assessed Tf effects on the degree of cell differentiation and whether these effects are linked to iron metabolism. We conducted morphological and immunocytochemical assays using primary antibodies as antigen markers of specific stages of lineage progression and established that Tf has pro-differentiation effects in these cell types.

P31.-Alpha-MSH modulates hippocampal neural precursor cell proliferation and differentiation

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Hippocampal neurogenesis is essential for learning and memory. Neural precursor cells (NPCs) in the subgranular zone of the hippocampal dentate gyrus proliferate and differentiate into either glial cells or dentate granule cells. Alpha-melanocyte-stimulating hormone (a-MSH) improves learning and memory, neuronal survival and plasticity in models of neuroinflammation, brain ischemia and Alzheimer's disease and is a mitogen for adult rat subventricular zone neural stem cells. Here, we studied the effect of [Nle4,D-Phe7]-a-MSH (NDP-MSH) on hippocampal NPC differentiation. Postanatal hippocampal NPCs were propagated in vitro as neurospheres. Cells were dispersed and cultured without growth factors. NDP-MSH was added on days 0 and 3. After 6 days in culture, a large proportion of NPCs become quiescent, evidenced by loss of nuclear Ki-67 expression. Treatment with NDP-MSH prevents the exit from cell cycle, increasing the proportion of Ki-67+/Nestin+ cells (putative type 2 precursors), and promotes cell proliferation evidenced by BrdU incorporation. In turn, there is a decrease in the expression of neuroblast marker DCX and in the proportion of NS-1+ cells (oligodendrocytes), as well as GFAP+/Ki-67- cells (putative astrocytes or quiescent type 1 precursors). Additionally, NDP-MSH stimulates microglial phagocytosis of dead neurons. To conclude, NDP-MSH modulates the hippocampal neurogenic niche by regulating NPC fate while acting on local microglia to promote clearance of dead cells.

P32.-MAG as a therapeutic target for neurodegenerative diseases related to glutamate overload

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This research project analyzes the protective effect of oligodendrocytes (OLs) against glutamate (Glu) overload, focusing on their critical role as white matter modulators of extracellular glutamate. Our group has previously demonstrated that mAb-mediated crosslinking/activation of MAG triggers a phosphoinositides/PKC-dependent intracellular signaling which results in reduced oxidative stress and protection of OLs and nearby neurons against Glu overload. Based in these previous findings, our current aims are: To study the role of Ca2+-dependent signaling pathways and to perform wide RNA sequencing on OLs under MAG activation. We seek to develop new therapeutic bioactive ligands of MAG derived from the structure of its axonal receptors. Also, to evaluate their efficacy in animal models displaying axonal damage secondary to Glu-mediated toxicity and to demonstrate its efficacy in modulating Glu levels in the CNS. We propose multiple approaches in order to characterize such pathways and to assess therapeutic effects: OL-enriched primary culture, cerebellar organotypic culture, myelinating oligodendrocyte-neuronal co-culture, gene expression analysis using RNA-seq and animal models of the human diseases Multiple Sclerosis and Stroke. These studies can help to describe more precisely intracellular signaling pathways involved in axon-myelin interactions that provide stability and survival of both neurons and OLs. Moreover they can contribute to the development of novel neuroprotective therapies in order to mitigate axonal damage secondary to demyelination as observed in Multiple Sclerosis.

P33.-Studying synaptic transmission at the level of individual synaptic vesicles

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Coupling of synaptic vesicle fusion and retrieval constitutes a core mechanism ensuring maintenance of presynaptic function. Recent studies have shown the coexistence of several endocytic pathways in neurons, with diverse kinetics and temperature dependencies. Using optical methods, we study the recycling of single and multiple synaptic vesicles in cultured hippocampal neurons., including their kinetics, calcium and temperature dependence. Our goal is to understand the underlying molecular mechanisms coupling different modes of exocytosis to different endocytic routes.

P34.-Altered brain global translation in TDP-43 transgenic mice: evidence from polysome profiling and SUNSET method

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TDP-43 is a RNA-binding protein that participates in a plethora of functions, including mRNA metabolism, and it is a major component of inclusions observed in neurodegenerative diseases like frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). We aimed to deepen our understanding about the role of TDP-43 in the regulation of mRNA translation and protein metabolism, using two complementary approaches. To assess if TDP-43 regulates active translation we performed subcellular fractionation of brain cortex by sucrose gradient centrifugation. The polysome profile of hTDP-43-expressing brains was significantly altered by a shift towards light fractions as compared to wild-type littermates, indicating a decrease in global mRNA translation. In brain slices, application of SUNSET method (which assesses ongoing translation by antibody detection of incorporated puromycin into newly synthetized proteins) indicating that hTDP-43 overexpression leads to decreased puromycin labeling. No puromycin-positive cells were observed in vehicle-incubated slices. Together, these results suggest that manipulating TDP-43 levels lead to changes in global translation and that the cytotoxic effects observed in FTD/ ALS might be related to alterations in proteostasis by TDP-43. We are currently evaluating if TDP-43 regulates the unfolded protein response, a process that modifies global protein synthesis. These findings will contribute to understand the etiology of TDP-43 proteinopathies.

P35.-Development of a low cost 3D printable Mouse Brain Matrix

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A Mouse Brain Matrix allows to slice a mouse brain into coronal or sagittal sections, enabling precise and reproducible removal of small brain regions for biological experiments. These matrices are commercially available, but are expensive and designed for a defined species and age. Reproducibility is a hallmark of good science but usually involves high costs when designs and hardware are proprietary. Open science hardware allows for greater reproducibility while improving accessibility when materials are low cost and easy to obtain, such as in 3D-printable designs.

3D printing is now within reach of many scientific laboratories allowing for rapid and inexpensive prototyping of custom laboratory equipment. We therefore aimed to produce a simple design that could be used to section brain tissue in a reliable and reproducible manner using freely available software and a consumer grade 3D printer.

We have designed a matrix for adult mouse brains from an MRI scan processed with 3D modelling open source software: 3D Slicer, Meshlab and OpenScad. Our matrix is specifically designed for the dissection of the dorsal and ventral hippocampus, prefrontal cortex, nucleus accumbens and amygdala using ordinary razor blades and plastic micropipette tips. However, the design can be adapted to slice different regions or brain sizes, and printed in any available material. The mouse brain matrix is freely available at https://www.thingiverse.com/thing:3077272

P36.-Physical interaction between dopamine receptor type-1 (D1R) and CaV2.2 channels increases CaV2.2 function

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D1R co-localizes with voltage-gated calcium channel CaV2.2 in rat PFC neurons, and the sole expression of D1R increases CaV2.2 membrane expression in a heterologous expression system. It has been proposed that this effect of D1R on CaV2.2 distribution depends on a physical interaction between CaV2.2 channels and the loop-2 region of D1R, but the effect of this D1R-CaV2.2 complex on CaV2.2 function remains unclear. Here, we investigate how D1R expression impacts CaV2.2 function and whether the D1R-CaV2.2 complex plays a role. We recorded whole-cell calcium currents in transfected HEK293t cells and found that low D1R expression (D1R:CaV2.2 molar ratio of 0.1) increased both CaV2.2 current density (170% of control, P=0.0029) and the number of functional CaV2.2 channels in the membrane (257% of control, P=0.0216 as measured by ON gating currents). Next, we generated mammalian expression vectors containing the sequence for the loop-2 or loop-1 region of D1R, with an IRES-YFP tag to test for expression. Competitive expression of D1R loop-2 occluded the increase in CaV2.2 current caused by D1R expression, while competitive expression of D1R loop-1 did not, indicating that the gain in CaV2.2 function due to D1R expression relies on a physical interaction between D1R and CaV2.2. Thus, we demonstrate that the D1R-CaV2.2 complex impacts not only CaV2.2 distribution, but also CaV2.2 function. Future experiments in PFC neurons will illuminate the physiological impact of these results.

P37.-Toll-like receptors -2 and -4 in the reactive gliosis propagation after traumatic brain injury

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Astrocytes respond to CNS injury with a process named reactive gliosis. It is still unknown how reactive gliosis rapidly propagates reaching very distant regions in the CNS after a focal brain injury. It is proposed that damage proteins released by dying neurons acting on TLR/NFκB pathway could be involved in the reactive gliosis propagation. To address this question, we here performed a penetrating traumatic brain injury by stab wound in wild-type (WT), TLR4KO and TLR2KO mice and used monolayer and 3D glial cells cultures. While stab-wounded WT animals showed a clear astrogliosis gradient at 3-7-14 days post-injury (DPI); TLR-deficient animals showed an exacerbated gradient of astrogliosis at 3-7 DPI. However, at 14 DPI, the TLR4KO animals showed a similar gradient to WT animals. At 3-7 DPI, microglial cells near to injury core showed an increased reactive phenotype in TLR-deficient animals compare to WT animals. In vitro, scratch wound produced a gradient of NFκB activation in astroglial cultures, and the LPS exposure increased this gradient. Astroglial 3D cultures injected with TLR agonists LPS and HMGB1 responded with re-orientation of their process to the injected site in a dose-dependent manner. These results show that reactive gliosis propagation is a complex phenomenon that involves both astrocytes and microglia and that absence of TLR2 or TLR4 does not preclude reactive gliosis propagation, but affects it. Supported by grants PICT 2015-1451 and UBACYT.

P38.-Age-related changes in Ang II receptor´s immunolocalization and expression in the Substantia nigra

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Substantia nigra (SN) is the main source of dopamine and a critical area in Parkinson Disease (PD). Overstimulation of Ang II AT1 receptors could produce oxidative stress, which affect the sensitive area of the SN. Thus, we evaluated developmental changes in Ang II receptor´s expression and localization in this area. Animals of P21, P100 and P365 days were used. For RNA extraction, the SN was dissected from slides obtained with a cryostat at the adequate level. RT-PCR assays allowed us to observe a decrease in the expression level of both AT1 and AT2 receptors with age. AT1 receptors decreased about 80% at P100, while AT2 receptors showed no significant difference between P21 and P100. Both receptors diminished at P365. Immunofluorescence staining of AT1 and AT2 receptors showed at P21 and P100 higher density of AT2 stained cells than AT1 labeled cells, with citoplasmatic and perinuclear localization. The number of stained cells diminishes at the stage P365. These results might account for the natural process encompassing aging. There are no previous reports regarding Ang II receptor localization in the SN by immunofluorescence at different ages. A new role has been proposed for Ang II AT2 receptors as neuroprotector, since its actions counteracts the damage cause by oxidative stress due to AT1 receptors. Our present results confirm the presence of both receptors during aging with a lower level of AT1 receptors and provide information of potential use for future treatments.

P39.-A model for Parkinson Disease: administration of rotenone by using microvesicles

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Parkinson Disease (PD) is one of the most frequent neurological diseases in elderness. Rotenone is an herbicide known to produce neurotoxic effects. Several methods of delivery have been explored, some of them with high mortality. Thus, we decided to administer rotenone by using microvesicles of a copolymer of PLGA. Microvesicles allow a slow delivery of the drug and thus a long treatment with a single dose administration. Resuspended microvesicles (25 um) were administered by subcutaneous injection in a dose of 50 mg/kg. Rats were weighted every day and no significant difference with control animals was observed during the whole treatment at the dose assayed. Animal´s behavior was evaluated by using the bar test, grid test and rearing test. Significant changes were observed on behavior tests after 5 weeks of treatment ($p< 0.01$) for the three test assayed. Latency in the behavior during the bar and grid test do correlate with catalepsy. Rigidity was tested with the rearing test. Physiological symptoms such as rigidity and immobility did appear after 5 weeks of treatment. An accurate experimental model of PD should reproduce the slow, progressive, and selective nigrostriatal dopaminergic degeneration seen in the disease. The lack of mortalitity in the treated group supports a good selection in the dose of rotenone applied. Although nigrostriatal degeneration can be confirmed by the specific staining, the behavioral results strongly suggest that animals developed PD.

P40.-Ghrelin receptor (GHSR) and dopamine receptor type 2 (D2R) co-expression modifies each receptor´s effects on voltage gated calcium channel CaV2.2

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Presynaptic CaV2.2 are activated by action potentials, and their calcium current induces neurotransmitter release. In this context, regulating CaV2.2 is critical, and one of the most important mechanisms for doing so is through G-protein coupled receptor (GPCR) activity. Two such GPCRs are the ghrelin receptor (GHSR) and the dopamine receptor type 2 (D2R). We have previously demonstrated that GHSR constitutive activity reduces CaV2.2 trafficking to the plasma membrane and that ghrelin-induced GHSR activity inhibits CaV2.2 currents. On the other hand, dopamine-mediated activation of D2R also inhibits CaV2.2 currents. It has been recently shown that D2R and GHSR hetero-dimerize in hypothalamic neurons. Here we explore how co-expression of GHSR and D2R modulates the effect that each GPCR has individually on CaV2.2. We found that GHSR-D2R co-expression increases the basal inhibition of CaV2.2 by GHSR constitutive activity, since less GHSR is needed to reduce CaV2.2 currents when D2R is co-transfected. By contrast, the acute inhibitory effect of ghrelin on CaV2.2 currents is unaffected by GHSR-D2R co-expression. Meanwhile, GHSR-D2R co-expression decreases inhibition of CaV2.2 by dopamine-evoked D2R activity (increase in EC50), since a higher dopamine concentration is needed to inhibit CaV2.2 currents when GHSR is co-transfected. This last effect depends on GHSR constitutive activity, since it is occluded by pre-incubation with Substance-P analog 1 μM, a GHSR inverse agonist.

P41.-Lrig2 promotes dendritic complexity, spine morphogenesis, and excitatory synapse formation in hippocampal neurons.

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Dendrite size and morphology are key determinants of the functional properties of neurons, and brain disorders are due primarily to structural abnormalities of dendrites and their connections. Distinct leucine-rich repeat (LRR) transmembrane proteins are highly expressed in the brain, especially in the hippocampus, where they play a critical role in the organization and function of neural circuits, regulating neurotrophin signaling, coordinating pre- and postsynaptic compartments during excitatory and inhibitory synapse formation and regulating synaptic plasticity.

Recently, the LRR protein Lrig1, has been described as an essential regulator of neurotrophin signaling and dendrite arborization of hippocampal neurons. However, the physiological contribution of Lrig2 for neuronal development remains to be determined. Taking advantage of the postnatal expression of Lrig2 by hippocampal developing neurons, we used gain and loss of function assays to examine how altered Lrig2 expression impacts dendrite morphology and synapse formation in search for specific LRR proteins involved in neurodevelopmental disorders. Here we show that Lrig2 overexpression exacerbates dendrite complexity by promoting growth and branching, in a LRR domain-dependent manner. Our results also indicate that Lrig2 is expressed in pre- and post-synaptic fractions, where it controls the density of dendritic spines and increases the number of excitatory synaptic contacts in hippocampal neurons.

P42.-Alpha-synuclein aggregation and toxicity: structural biology meets cell biology

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Amyloid aggregation of alpha-synuclein (αS) in Parkinson's disease (PD) results in cellular toxicity and neuronal death. Several mutations in αS gene are associated with familial PD, supporting a central role for the protein in the development of the disease. However, the precise contribution of αS aggregates to neuronal impairment and death is not well understood. Previous work in our lab demonstrated that aromatic side chains of the N-terminal tyrosine residue at position 39 (Y39) of αS plays a critical role in its fibrillation pathway. In order to understand the key role of Y39 residue on αS aggregation and toxicity, we designed different point mutants of the protein. Through the combination of biophysics and cell-based assays, we demonstrated that replacement of Tyr by Ala or Leu at position 39 led to protein variants with different amyloidogenic potential. Interestingly, strong correlation was observed between the in vitro and in cell studies. Altogether, our data highlight the importance of combining structural and cell biology strategies, and open new perspectives to elucidate the molecular basis behind the amyloid aggregation of the protein αS.

P43.-IgGs from sporadic Amyotrophic Lateral Sclerosis patients induce neurodegeneration and microglia activation in mouse-isolated spinal cord model

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Amyotrophic Lateral Sclerosis (ALS) has as a target upper and lower motoneurons. Our previous studies have demonstrated the pathological role of autoimmune mechanisms mediated by antibodies in sporadic ALS patients. In the present study, we tested the effect of IgG from a group of sporadic ALS patients on the mouse-isolated spinal cord preparation, which was incubated with different ALS and control sera for 6 h. The purpose of the present study was to characterize (by immunohistochemistry) the localization of IgG in neurons and their role in microglia activation. Our results demonstrated significant IgG immunoreactivity in interneurons from dorsal and ventral spinal cord areas, and motoneurons. Furthermore, after applying ALS sera the number of ventral neurons was significantly decreased. On the contrary, while no changes in the number of microglia were observed, analysis of morphological parameters of microglial cells showed branche length to be significantly decreased following ALS serum incubation. Indeed, a significantly increase in CD68 staining, a marker for activated microglia, was observed that was consistent with post-transcriptional microglia activation while no effect was observed in the CD68 mRNA analysed by RT-PCR. These findings indicate the presence of a neuroinflammatory process in the pathological event induced by sporadic ALS sera and support the hypothesis of autoimmunity in the development of this neurodegenerative disease.

P44.-GLIAL METABOTROPIC GLUTAMATE RECEPTOR (mGlu3R) DYSFUNCTION IN ALZHEIMER´S: IMPLICATIONS FOR sAPPα-MEDIATED Aβ CLEARANCE

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Astroglial mGlu3R promotes neuroprotective effects, such as releasing neurotrophin sAPPα and increasing Aβ uptake. We aimed to study whether mGlu3R alterations could be associated with AD progression in an AD mice model. Evidence for mechanisms involved in sAPPα-mediated Aβ elimination is provided here as well.

mGlu3R protein levels remain stable during aging in non-transgenic (NTg) mice, whereas they progressively decrease with age in PDAPP-J20 (Tg) animals ($p<0.05$). It is known that a truncated version of the receptor, called mGlu3Δ4R, acts as a negative modulator of mGlu3R. mGlu3Δ4R levels increase with age in NTg mice, and they are significantly elevated in 5 months-old Tg mice ($p<0.001$). When analyzing mGlu3Δ4R/mGlu3R ratio, we found a significant increase in this ratio in 5 month-old Tg mice ($p<0.05$). Also, we found decreased mGlu3R levels ($p<0.01$) and increased mGlu3Δ4R/mGlu3R ratio ($p<0.05$) in cultured astrocytes and neurons exposed to Aβ. On the other hand, sAPPα increases Aβ uptake in cultured astrocytes in a SRA-dependent manner. However, when -after 24h sAPPα incubation- medium was replaced by a mix of sAPPα/Aβ instead of Aβ alone, phagocytosis was inhibited ($p<0.05$). Therefore, we postulate that Aβ clearance requires Aβ binding to sAPPα- SRA dimers at astrocyte surface.

In conclusion, altered mGlu3Δ4R/mGlu3R ratio could constitute a novel early biomarker for AD and could lead to reduced sAPPα production by astrocytes and then to deficient Aβ elimination.

P45.-Cholesterol loss triggered by aging stabilizes the epigenetic repressor CDYL in old hippocampal neurons

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Aging is characterized by a progressive decline in cognitive capacities, however, it is unlikely that this decline arises from the altered expression or activity of a single factor. Over the past decade, accumulated evidence has indicated that one of the most dramatic changes that occur at the molecular level in the aging brain is the alteration of epigenetic mechanisms controlling gene expression. Epigenetic mechanisms regulate a plethora of brain functions including activity-dependent transcription of memory genes, synaptic plasticity, learning and memory. Hippocampal aging is accompanied by the overexpression of the enzyme cholesterol-24-hydroxylase (CYP46) in cortex, cerebellum and hippocampus. This enzyme converts cholesterol to 24-hydroxycholesterol, which is eliminated from the brain. As a consequence of CYP46 overexpression, cholesterol levels are reduced in old neuronal cells. We found that cholesterol loss impairs downstream signaling from NMDA receptors leading to nuclear accumulation of the transcriptional repressor CDYL. CDYL is part of a repressor complex, which includes REST and the H3K9 methyltransferase G9a, among others, and targets several genes related to memory formation such as the gene encoding the neurotrophin BDNF. Thus, we propose that altered synaptic activity in old neurons, is promoted in part by cholesterol loss and leads to the formation of a transcriptional repressive structure at the promoter of memory genes.

P46.-MECHANISM OF CALCIUM RELEASE DURING UNFOLDED PROTEIN RESPOSE

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The Endoplasmic Reticulum (ER) plays a critical role in different processes, where the ER Ca2+ acts as a key messenger. Under resting conditions, the luminal Ca2+ concentration reflects a balance between uptake by Ca2+-ATPases and efflux pathways of which the translocon can play a prominent role. The translocon is an aqueous pore, formed by the Sec61 core spanning the ER lipid bilayer, blocked by the ribosome (cytosolic side) and by BiP (luminal side). During the acute phase of the UPR (Unfolded Protein Response), immediately after unfolded protein are accumulated in the lumen, the Ca2+ ER eflux through the translocon would increased. We performed cytosolic Ca2+ measurements in primary human astrocytes, expressing the Ca2+ indicator GCaMP6 tethered to the ER membrane, after UPR induction with Tunicamycin. We observed focal release of Ca2+ in stressed astrocytes that was significantly inhibited by translocon blockers (emetine or anisomycin). The Tm-induced Ca2+ signal was amplified by pre-treatment either with AB5 cytotoxine (hydrolyses BiP) or with the translocon opener puromycin. This effect was corroborated by co-immunoprecipitations. The likehood of obtained Tm-induce local Ca2+ events, increase by using either the slow Ca2+ chelator EGTA-AM or Xestospongin C and Ryanodine, InsP3 and Ry Receptors inhibitors, respectively. Finally, InsP3 Receptor null HEK-293 cell line exhibited Tm-evoked Ca2+ release near ER microdomain, which is inhibited by BiP over-expression.

P47.-Chemical chaperone reduces Endoplasmic Reticulum Stress in a GM2-gangliosidosis cell model

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The accumulation of misfolded proteins within the endoplasmic reticulum (ER) triggers a cellular process known as the Unfolded Protein Response (UPR), in which the cell attempts to restore ER homeostasis. If ER damage is persistent or excessive, an apoptotic response is initiated. PERK is an early ER stress sensor that attenuates protein synthesis. We demonstrated that Calcineurin (CN) associates with PERK, enhancing inhibition of protein translation and cell viability. But PERK signaling, including pro-apoptotic transcription factor CHOP, persists activated under prolonged stress. Chronic UPR is proposed to contribute to the pathology of many neurodegenerative diseases. GM2-gangliosidosis are characterized by a progressive neurodegeneration due to deficiency in B-hexosaminidase activity. However, the mechanisms that determine how GM2 accumulation triggers neuronal cell death remain unknown. Recently, we demonstrated in primary cultured neurons, that GM2 accumulation induces ER Ca2+ depletion and, in turn activates PERK signaling,

Here, we show that the selective PERK inhibitor GSK2606414 as well as CN and CHOP knockdown, effectively modulate neurite atrophy and apoptosis induced by GM2 accumulation. Moreover, we determinate that, the chemical chaperone UDCA (acid ursodesoxicolic) protects neuroblastoma cells Neuro 2a (N2a) againts ER stress, decreasing CHOP expression as well as the susceptibility of neurons to undergo apoptosis.

P48.-Tetraspanin promotes NGF signaling by controlling TrkA receptor proteostasis

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A key question in developmental neurobiology is understanding how axons and dendrites from different neuronal populations develop to generate specific patterns of neuronal connectivity. This process is regulated by the interaction of extrinsic signals, such as neurotrophins (NTs); and intrinsic factors, such as endogenous regulators of their receptors.
NTs are a group of secreted molecules that play a crucial role in the development and survival of neurons. They bind to tyrosine kinase receptors belonging to the Trk family and promote the differentiation and survival of specific populations of neurons. The cooperation between NTs and other soluble factors, are mechanisms that give specificity during the development of the nervous system.
Recent studies also show the importance of intrinsic factors, which regulate the activity of these receptors and allow to broaden the repertoire of signals induced by NTs, conferring another level of regulation and control in the establishment of neuronal connectivity.
In our work, we have identified members of the Tetraspanin superfamily that regulate the NGF-mediated TrkA signaling. We have shown that Tetraspanin is a specific intrinsic regulator of TrkA activation, its downstream signaling and its effect on neuronal differentiation. We also provide a novel homeostatic mechanism to control biosynthetic trafficking and degradation of TrkA.

P49.-NEUROPROTECTIVE EFECT OF THE PROBIOTIC BACTERIUM BACILLUS SUBTILIS AGAINST PARKINSON´S DISEASE IN CAENORHABDITIS ELEGANS

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A clear association between disorders in the microbiota and the onset and progression of Parkinson disease (PD) is known. Probiotic bacteria produce beneficial effects on host health so we wondered if the consumption of probiotics might be a strategy to prevent or treat PD. To test this hypothesis, we used the animal model Caenorhabditis elegans and the bacteria Bacillus subtilis DG101 and Escherichia coli OP50 (probiotic and non-probiotic, respectively). The studied C. elegans strains were the wild-type N2 and the PD-reporter strains: NL5901 (expressing YFP fused to human α-synuclein), UA57 (expressing GFP fused to dopaminergic neurons and presenting age-dependent neurodegeneration) and VC1024 (affected in synthesis of PDR, a homolog of human PARK2). The aggregation of α-synuclein (Lewy body, LB, formation), in 7 day-old NL5901 worms fed on DG101, was reduced by 75 % compared to worms fed on OP50. Seven day-old UA57 worms fed on DG101 showed higher neural integrity, and VC1024 and NL5901 worms exhibited an extended lifespan (74% and 88%, respectively), compared to worms fed on OP50. The behavioral worm characterization (i.e. food-sensing behavior, chemotaxis, fecundity and defecation) confirmed the suitability of DG101 to improve PD prognosis. The overall results showed that B. subtilis was able to stop the formation of LB, impaired neurodegeneration of dopaminergic neurons and significantly increased the healthy lifespan of Parkinsonian worms to levels of healthy worms.

P50.-The TM2-TM3 loop of the α10 subunit in the potentiation of the cholinergic nicotinic receptor α9α10 by extracellular calcium

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The α9α10 nicotinic acetylcholine receptor (nAChR) is expressed in cochlear hair cells. This nAChR mediates the inhibitory synapse between efferent fibers and outer hair cells. The inhibition results from calcium entry through the nAChR, in the presence of acetylcholine (ACh), followed by the activation of a Ca2+ dependent potassium current. This nAChR is composed of α9 and α10 subunits assembled into a pentameric cation-permeable ion channels. Each nAChR subunit comprises a large extracellular amino-terminal domain, four transmembrane domains (TM1-TM4) and a long cytoplasmic loop between TM3 and TM4. Expression of rat α9 and α10 nAChR subunits in Xenopus laevis oocytes yields functional α9 and α9α10 receptors, but not α10 homomeric nAChRs. One of the functional differences between α9 and α9α10 nAChRs is their modulation by extracellular Ca2+. α9 receptor responses to ACh are blocked by extracellular Ca2+. In contrast, α9α10 responses are potentiated at sub-mM Ca2+ concentrations and blocked by higher concentrations of this ion. In order to determine the structural determinants responsible for these differences, we generated chimeric subunits, expressed them in Xenopus oocytes and performed electrophysiological recordings under two electrode voltage clamp. Our results suggest that the TM2- TM3 loop of the α10 subunit contains key structural determinants responsible for the potentiation of the α9α10 nAChR by extracellular Ca2+.

P51.-SOX-11 regulates LINE-1 retrotransposon activity during neuronal differentiation

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Human Long interspersed nuclear elements-1 (LINE-1) retrotransposons activity occurs mainly in early embryonic development and during hippocampal neurogenesis. SOX-11 is a transcription factor relevant to neuronal development with unknown functions in the control of LINE-1 retrotransposon activity during neuronal differentiation. To study the dependence of LINE-1 activity on SOX-11 during neuronal differentiation, we differentiated human SH-SY5Y neuroblastoma cells and adult human adipose-derived mesenchymal stem cells (hASCs) into neuron fate and found increased LINE-1 activity. Our results show also that SOX-11 protein binding to the LINE-1 promoter resulted higher in differentiated neuroblastoma cells, while knock-down of SOX-11 inhibited the induction of LINE-1 activity in differentiating conditions. These results suggest that activation of LINE-1 retrotransposition during neuronal differentiation is mediated by SOX-11.

P52.-Effects of the Val66Met polymorphism on the BDNF gene in neuronal development and structure

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There is a single nucleotide polymorphism (SNP) in the BDNF gene (rs6265) which is associated with increased susceptibility to develop neuropsychiatric disorders in human carriers. This SNP is present in ~25% of the world population, and induces a substitution of a valine (Val) for a methionine (Met) in the BDNF prodomain (pBDNF), an abundant peptide in the central nervous system. pBDNF Met can trigger acute changes in 30 to 60 minutes to neuronal structure. However, the effects of pBDNF Val and Met for longer administrations periods, and in different stages of neuronal development, remains yet unknown. Thus, we studied the effects of both polymorphic variants of pBDNF on hippocampal neurons in culture at different stages of differentiation. In immature neurons, we did not detect alterations in the establishment of polarity nor in the development of dendrites and axons induced by either pBDNFs. On the other hand, in mature neurons, pBDNF Val and Met were able to significantly reduce the density of synaptic contacts. This is the first study to describe an effect of the Val variant of pBDNF (present in 75% of human population) on neuronal structure using a physiologically relevant dose. These results suggest that pBDNF is a modulator of synaptic contact density and that, together with mBDNF actions, might act as a regulator of precise circuit maturation.

P53.-TGFb effect during the demyelination and remyelination process

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Adult neural progenitor cells (NPCs) from the subventricular zone (SVZ) can differentiate into oligodendrocytes, a key aspect during the remyelination process following a demyelinating event. We have demonstrated that TGFβ induces oligodendrocyte precursors cell (OPCs) proliferation through an increase in Jagged1 expression in astrocytes and oligodendrocyte maturation by direct action on OPCs. The current work studies the effect of TGFβ during demyelination through in vitro and in vivo experiments. SVZ NPCs obtained from control or 7-day cuprizone (CPZ)-treated rats were cultured in the presence of TGFβ or its vehicle for 4 days. Immunocytochemistry showed no changes in Nestin+, Nestin+/GFAP+ or GFAP+ populations in any of the experimental groups. Cultures obtained from demyelinated animals showed a higher proportion of PDGFRα+ cells than those obtained from control animals. The presence of TGFβ increased the proportion of PDGFRα+ cells in control cultures and showed a slight increase in cultures from demyelinated animals. Furthermore, preliminary results obtained from corpus callosum Western blot analyses of animals intracranially injected TGFβ showed an increase in MBP+ cells concomitantly with a decrease in PDGFRα+ cells both in control and CPZ-treated animals. These results indicate that TGFβ might contribute to OPC differentiation during demyelination. More experiments are needed to evaluate the real impact of TGFβ during the whole demyelination/remyelination process.

P54.-Aβ oligomers detection by a specific scFv codified in an AAV vector

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Alzheimer's disease (AD) is a neurodegenerative disorder of the Central Nervous System that affects millions of people in the world. AD involves progressive lost in cognitive functions due to neuronal death in hippocampus and other related areas. AD was first characterized by the presence of amyloid plaques composed by Aβ peptides aggregates. Although it has been shown that neither Aβ peptides nor amyloid plaques were directly responsible for synaptic failures and neuronal death, it was suggested that soluble Aβ aggregates (from 4to 50 monomers), the Aβ oligomers (AβOs), were the main toxins at early steps of this pathology. Moreover, elevated AβOs levels have been reported in AD rat models, even before neurodegeneration signs appear. In this context we built an Adeno Associated Vector (AAV) for transiently expressing a single chain variable fragment antibody (scFv) that specifically binds AβOs and bears a signal peptide to be secreted (AAV-scFv-NUSC1Glu). N2A y B104 cell lines were infected with AAV-scFv-NUSC1Glu and the supernatant was then collected. First, we checked scFv expression at mRNA level, by PCR, and protein level by westernblot. Then, we attempted to detect synthetic AβOs levels by ELISA essays. We designed two different essays: A Direct ELISA and a Competitive one. Preliminary results have shown that only the competition essay was useful to discriminate the tested AβOs levels.

P55.-Iron deficiency strikes again: oligodendroglial and astroglial casualties

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Iron deficiency (ID) applied to developing rodents has proven to be an excellent model to understand the generalmyelination process and specific glial cell requirements. Previous work demonstrated that ID oligodendrocytes (OL) were mostly found in an immature stage, failing to attain complexity and a more mature morphology. In addition, ID astrocytes (AST) proliferated more than control ones and were more immature, much like OL.
To further describe ID effects, we explore the hypothesis that low iron availability constrains OL maturation by impairing glial cell metabolic pathways.
Pregnant mice were fed a control (C; 40mg iron/kg diet) or an ID diet (4mg iron/kg diet) from gestational day 5; brain cortexes of P0-2 pups born to those mice were used for OL and AST primary cultures. ID metabolic signature was assessed using a Seahorse extracellular flux analyzer. Measurements of glycolysis and mitochondrial respiration showed a dysregulated pattern of proteins involved in the TCA and mitochondrial dysfunction following gestational ID; both ID OL and ID AST maximum respiration rate was lower than control ones. In addition, ID AST exhibited a lower basal glycolitic capacity than controls which could be explained by a diminished of glycogen storage. These findings further prove that the regulation of cell metabolism may impact cell fate decisions and maturational status.

P56.-MILD STRESS INDUCED BY MATERNAL MANIPULATION DURING LATE GESTATION AND INFANTILE ETHANOL CONSUMPTION INDUCE CHANGES IN PRO-DYN, MU AND KAPPA OPIOID mRNA EXPRESSION

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Fetal ethanol experience generates learning and memories, capable of enhance ethanol consummatory behaviors during infancy. Opioid system seems to mediate alcohol reinforcement aspects. We proposed to study ethanol prenatal and infantile effects on opioid precursor peptides (POMC, Pro-enk and Pro-DYN) and receptors (MOR, DOR and KOR) mRNA expression, in hypothalamus. Pregnant rats received (GDs) 17-20, a daily intragastric (i.g.) administration with 2g/kg ethanol or water, or remained undisturbed (Unmanipulated group). An intake test was conducted at PDs 14-15. Three groups were performed: control (no intake test), water and 5% ethanol. At the end of intake test hypothalamus sections were obtained to perform qRT-PRC assessments. Alcohol intake was higher in animals whose dams received an i.g. manipulation, whenever water or alcohol. Prenatal manipulation possibly acts as a mild stressor capable of enhance consumption of alcohol, after birth. To test this alternative hypothesis we regrouped prenatal manipulation in: unmanipulated and manipulated (pups from water and alcohol groups). qRT-PCR data, assessed only in unmanipulated group, demonstrated that ethanol intake experiences down-regulate the expression of Pro-Dyn mRNA and gradually up-regulate mRNA expression of MOR and KOR. Also, MOR mRNA expression was attenuated by prenatal i.g. manipulation, supporting the idea that possibly plays a role as a mild stressor.

P57.-Leptin-mediated transcriptional regulation of Pomc in hypothalamic neurons

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Although it is well accepted that the adipostatic hormone leptin activates Pomc expression in hypothalamic neurons, the mechanisms controlling this interaction remain unexplored. In the brain, leptin binds to the long form of the leptin receptor stimulating the intracellular phosphorylation of STAT3 which acts as a transcription factor of several genes by acting on STAT3 binding motifs. We have detected that the neuronal Pomc enhancer 1 (nPE1) contains two canonical STAT3 binding motifs (5'-TTCCNGGAA-3') which are highly conserved in mammals. To challenge the hypothesis that these sites participate in leptin´s induced Pomc expression we generated mutant mice lacking both STAT3 sites from nPE1 using CRISPR/Cas9 technology. To maximize leptin´s effect on hypothalamic Pomc expression we previously reduced circulating leptin levels using two different experimental strategies. Our first approach was to study the effect of refeeding on mice previously fasted for 24 h and analyze body weight variations and hypothalamic Pomc mRNA levels. Our preliminary results indicate a greater weight loss in mice lacking STAT3 sites after fasting and a more rapid regain of previous body weight. The second approach involves crossing nPE1(STAT3-less) mice with leptin-deficient (ob/ob) mice. Further progress of these experiments will give us the possibility to evaluate the implication of STAT3 binding sites in the regulation of hypothalamic expression of POMC induced by leptin.

P58.-The role of sleep in the consolidation of new words in Temporal Lobe Epilepsy: Preliminary results

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New memories are reactivated during sleep reinforcing cortico-cortical connections favoring memory consolidation and integration. There are contradictory results concerning the role of sleep in new word integration. In healthy subjects, some studies reveal a fast integration independent of sleep while others show sleep-dependent integration of new words. However, these results may not be contradictory. We hypothesize that there is a fast cortical integration at short time after learning, but for this information to persist in time it becomes dependent of a period of sleep. Thus, for this to be possible, a normal hippocampal-cortex communication is needed. Patients with Temporal Lobe Epilepsy show a diminished hippocampal-cortical synchronization which explains the impaired declarative long term memory consolidation during sleep. Thus, these patients turn out to be an optimal model to test our hypothesis. Here we show preliminary data, using a word-learning task to evaluate the role of sleep in consolidation of new information and integration with the pre-existing lexical networks.

P59.-Impact of the Val66Met polymorphism on the BDNF gene on the structure and function of dopaminergic neurons

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A single nucleotide polymorphism (SNP) in the BDNF gene is present in more than 25% of the human population, and it results in a valine (Val) for methionine (Met) substitution (Val66Met) within its prodomain sequence. This SNP is associated with increased susceptibility to develop certain psychiatric and neurodegenerative disorders. Some of the associated diseases involve dopaminergic (DA) neuron dysfunction such as schizophrenia, addictions and, in some populations, Parkinson's disease. It has been demonstrated that the Met variant of the BDNF prodomain affects hippocampal neuron structure, but its effects on DA neurons remain to be studied. We hypothesized that the Met variant of the BDNF prodomain affects DA neuron structure and function. Interestingly, we found that stimulation with the Met prodomain (but not the Val variant) induces superior cervical ganglion DA neuron death in culture. Moreover, mesencephalic DA neurons cultured from BDNF Met/Met knock-in mice displayed shorter processes as compared to the Val/Val littermates. Finally, BDNF Met/Met mice show increased spontaneous ipsilateral turns after the unilateral injection of the specific DA neurotoxin 6-hydroxydopamine, suggesting that DA neurons from this genotype are more susceptible to degenerate compared to Val/Val mice. Altogether, these results suggest a molecular explanation for the increased incidence of DA-related central nervous system disorders in Val66Met carriers.

P60.-CAFETERIA DIET TEMPORARILY AFFECTS BRAIN REWARD DOPAMINERGIC PATHWAY THROUGH DNA METHYLATION MECHANISMS

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We analysed the short and long-term effects of a highly palatable cafeteria diet(CAF) intake on the expression of key genes of the reward dopaminergic pathway of the brain(RW). Female rats were fed chow or CAF for 4(CAF4) or 11(CAF11) weeks. Ventral Tegmental Area(VTA), Accumbens Nucleus Core(NAC) and Shell(NAS), and Ventral Pallidum(VP) were isolated by micropunching technique. For mRNA analysis, qPCR was performed. Digestion with methylation-sensitive restriction enzymes followed by qPCR was used for epigenetic studies. Serum leptin was assessed by RIA. CAF4 increased energy intake and adiposity. In VTA, CAF4 enhanced dopamine active transporter(DAT) and decreased both isoforms of glutamate decarboxylase(GAD), without altering Tyrosine Hydroxylase levels. CAF4 decreased dopamine receptor 2 mRNA in NAS and increased GAD2 levels in VP. The changes in DAT mRNA were related to a decrease in the methylation status of its promoter region. CAF11 further increased energy intake and adiposity, leading to hyperleptinemia, and increased mRNA of leptin receptor in VTA, without affecting the expression of any gene of the RW studied. Our results indicate that, in the short-term, CAF deregulates the RW, at least in part via epigenetic changes, possibly reflecting a state of RW hyposensitivity, which might promote the excessive intake of palatable foods to compensate this status. This is reverted in the long-term, when the hypercaloric intake could respond to an altered homeostatic control.

P61.-The NFκB alternative pathway is activated by antidepressant drug treatment

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Almost 30% of patients suffering from Depression (MDD) remain resistant to the current medication and exists pressing need to discover new targets for antidepressant drug development.

Our primary goal is to find new intracellular pathways regulated by antidepressants which could be potential targets for drug development. We focused on kinases and phosphoproteins which are well-known for being drugable targets.

As a first step, we carried out a protein array screening to reveal changes in the signalosome and phosphoproteome in the hippocampi of animals chronically treated with paroxetine. We extracted RNA from the same material and performed microarrays in order to compare mRNA and protein levels of the candidate molecules. We found strong changes in a number of interesting candidates including several members of the NF-κB pathway.

We focused on this pathway and studied its role in emotional behavior and antidepressant action. To do that, we generated a conditional KO mouse line carrying a deletion of the NF-κB kinase IKK-α specifically in excitatory (glutamatergic) neurons of the forebrain. The effects of antidepressant drugs on different endophenotypes were analyzed on this mouse line at different levels, including adult neurogenesis, glial activation, depression-like behavior and spine density of principal neurons of the hippocampus. These results point towards a relevant function of the NF-κB pathway on the mechanism of action of antidepressant drugs.

P62.-Mesenchymal stem cells therapy reversed hippocampal atrophy, neurodegeneration, loss of presynaptic proteins, reactive microglia and behavior impaired in a rat model of sporadic Alzheimer's disease

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Sporadic Alzheimer's disease (SAD) is a progressive neurodegenerative disorder with no efficient therapy. We are interested in developing therapeutic strategies to overcome the degenerative changes in SAD. In this context, we explored the neuroprotective effect of human mesenchymal stem cells (MSC), using a SAD rat model by intracerebroventricular injection of streptozotocin (icv-STZ). Animals were divided into 3 experimental groups: Sham, STZ and STZ+MSC. STZ and STZ+MSC received 3 mg/kg icv-STZ and, 24 days after, STZ+MSC received, every 18 days, 1x106 MSC in a tail vein. During the last two weeks until the end of the study (3 months post-icv-STZ), we performed different behavioral tests. Our results show that STZ treated rats were behaviorally impaired, whereas the STZ+MSC group improved its spatial memory and decreased the anxiety. Immunohistochemistry in the Stratum Radiatum (SR) of the hippocampus revealed that neurons, astrocytes and microglial cells were affected by STZ, and MSC therapy reversed the observed changes in neurons, microglial cells, and in the volume of the SR, previously atrophied by the STZ. Interestingly, Western Blots of hippocampal lysates on presynaptic proteins (SYT1, SYT2, SYP and SV2) and GABAergic neuron markers (GAD65/67) show that all these proteins levels decreased in the STZ group, whereas MSC therapy led to a recovery of SYT2, SV2 and GAD65 levels. We conclude that MSC therapy is a suitable biological tool in neurodegenerative disorders.

P63.-On the role of the γ2 subunit in the modulation of GABAA receptors by endogenous redox agents

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Endogenous reactive oxygen species and antioxidants participate in neuronal signalling and plasticity in normal physiology, during aging and in the development of neurodegenerative disorders. GABAergic neurotransmission was shown to be sensitive to redox agents. We demonstrated that tonic responses mediated by GABAAρ1 receptors can be modulated by H2O2, ascorbic acid (Asc), glutathione and nitric oxide through thiol modification of cysteines. We also identified endogenous redox agents that modulate GABAA receptors involved in fast inhibitory neurotransmission in the retina and hippocampus, but the molecular mechanisms implied remain elusive. Now we analyzed the effects of H2O2 and Asc on GABAAα1β2 and GABAAα1β2γ2L receptors expressed in Xenopus laevis oocytes using two-electrode voltage-clamp recording of GABA-evoked Cl- currents. H2O2 and Asc modulated GABAAα1β2 responses. H2O2 exerted a dose-dependent, reversible and voltage-insensitive potentiating effect which was not prevented by irreversible alkylation of sulphydryl groups with NEM, whereas Asc induced a dual modulation with an early inhibition and a subsequent phase of potentiation. In contrast, GABAAα1β2γ2L receptors activity was not altered during superfusion of H2O2 and Asc, suggesting that the γ2 subunit conferred a relative insensitivity to these two endogenous agents. Additional experiments to elucidate the mechanisms of action underlying the effects of H2O2 and Asc on GABAAα1β2 receptors are being performed.

P64.-Approaching a physiological method for studying neuronal activity-regulated gene expression

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Neuronal activity-dependent transcription is an integral part of the neuronal response to environmental stimulation and it is crucial for different molecular mechanisms underlying synaptic plasticity (LTP/ LTD), learning and memory, behavioral responses and neuronal survival. The nature of transcriptional response to electrical activity (target genes and their temporal induction profile) has been broadly studied during the last few years. Previous investigations were done activating neurons by applying protocols of chemical neuronal depolarization (KCl high concentrations, TTX withdrawal) that are highly artificial and far from any physiological condition.
In this project, we aim to develop novel strategies to study neuronal activity-regulated gene expression both ex vivo (in brain slices) and in vitro (in primary neuron culture). We used electrical and optogenetic stimulations at different frequencies and patterns of depolarizing stimuli mimicking brain electrical oscillations and bursting activity. We were able to observe different levels of gene expression and temporal dynamics of three known activity-regulated genes (Npas4, cFos and Arc) upon these stimulation protocols.
Together, the results indicate that activity patterns can determine the temporal dynamics of activation of gene expression and that the study of activity-dependent transcription should be refined and assessed with more physiological methods.

P65.-Glyphosate exposure impairs neuronal connectivity and spatial learning in rats

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The developing nervous system is highly susceptible to damage caused by exposure to environmental contaminants. Glyphosate (gly) is the active ingredient of a number of broad-spectrum herbicide formulations, widely used all over the world to control weeds. Previous studies have demonstrated that gly induces neurotoxicity in mammals. Therefore, the cellular mechanism of this alteration needs to be determined.

We evaluated hippocampus-dependent spatial learning by the Morris water maze test and found that acquisition is impaired in rats exposed to gly during a critical period of synaptogenesis (first three postnatal weeks of life). These animals also showed alterations in the expression of synaptic proteins in the hippocampus such as PSD-95 and Synapsin I.

To further analyse the effect of gly on neuronal connectivity we used hippocampal cultured neurons to study the maturation of dendrite arbors in 17 days in vitro (DIV) control and treated neurons. We observed that gly exposure markedly decreased dendritic length and complexity in a dose dependent manner.

Then, we studied whether the herbicide impairs the development of dendritic spines in 17 and 20 DIV cultured neurons. Results showed that exposure to gly induces a decrease in spine density and maturation. Furthermore, we observed a defect in the number of synaptic clusters.

In conclusion these findings suggest that gly exposure alters neuronal connectivity both in vivo and in vitro impairing complex cognitive behavior.

P66.-Stress granules and Processing bodies oscillate in mammalian fibroblasts

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Stress granules (SGs) and Processing bodies (PBs) are cytoplasmic membraneless organelles in which ribonucleoprotein complexes accumulates. SGs are formed by translational machinery components, like minor ribosomal subunits and translation initiation factors. SGs assemble when cells undergoes stress. PBs are formed by factors involved in mRNA translation inhibition and decay. It has been observed that several components of both SGs and PBs are rhythmically expressed, in a circadian fashion, thus we hypothesized that these foci oscillate. We show that the number and area of SGs induced by oxidative stress, as well as the PB number, exhibit daily oscillations in NIH3T3 cells. TIA-1, a protein with a prion-like domain that induces SG nucleation, is also expressed rhythmically. To test whether SG temporal changes were controlled by the transcriptional translational feedback loops (TTFLs) that form the molecular circadian clock, we analyzed SGs in wt and Bmal1-/- fibroblasts. Bmal1 is an essential and non-redundant component of TTFLs. Unexpectedly, we found oscillations in the number, area and signal intensity of SGs in both genotypes. The period and phase of the oscillations were similar in both cell lines, but the amplitude was higher in Bmal1-/- cells, suggesting that the TTFLs modulate the strength of the response at different times. We thought that the SG rhythms could be generated by redox or translational rhythms that have been shown previously in Bmal1-/- cells.

P67.-Role of atypical GTPase RhoD during the development of neuronal polarity

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Neurons are highly polarized cells typically extending a long thin axon and multiple short branched dendrites. These specialized compartments are developed through the coordination of cellular and molecular mechanisms in order to ensure the proper functioning of the nervous system, and are highly regulated by several small Rho GTPases with their effectors controlling different aspects of neuronal morphology. Among others, these events include actin and microtubules cytoskeleton assembly, and the addition of membrane in neuron specialized regions. Even though most of studies have been focused on classical Rho GTPases (RhoA, Rac1 and Cdc42), other less studied members of this family such as RhoD suggest to have unique effects on cytoskeleton and membrane dynamics. In this study we have analyzed the role of RhoD during the development of axonal polarization and neurite extension. Our results reveal that the expression of RhoD active mutant in hippocampal neurons induces the generation of multiple axons and increase neuritic outgrowth and complexity. These results suggests that RhoD plays an important role during neuronal differentiation and neuritic outgrowth. In addition, we have designed an unimolecular activity RhoD biosensor based on resonance energy transfer (FRET) to study the space-time dynamics of this Rho GTPase in cultured hippocampal neurons. Finally, we have evaluated how RhoD affects different dynamic parameters of microtubules cytoskeleton in fibroblast cells.

P68.-Modifications of the membrane-associated periodic skeleton (MPS) in axons during injury-induced axonal degeneration

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Axonal fragmentation is a regulated process that depends on various signaling molecules, proteases and other regulators to actively disintegrate the axonal compartment. In this work, we studied the change and possible role of the axonal membrane-associated periodic skeleton (MPS) during injury-induced degeneration. The injury model consisted on sensory neuron explants sections with a scalpel blade, producing axonal degeneration in the distal portion of the sectioned axons. The MPS is organized in periods of 190 nm, hence unobservable by diffraction-limited conventional fluorescence microscopy. Here we used two different super-resolution techniques: Expansion Microscopy (ExM) and Stimulated Emission Depletion Nanoscopy (STED). We show that the MPS abundance and organization decays at an early time point after injury, well before the onset of axon fragmentation. In addition, pharmacological treatments that prevent axonal fragmentation, such as NAD+, also prevent early loss of the MPS. We further show evidence demonstrating the effect of dismantling the MPS with the actin depolymerization drug Latrunculin A on axonal fragmentation in control and injured axons. In summary, our work suggests that the MPS is necessary for stabilization of the axon compartment during injury-induced degeneration.

P69.-Ghrelin receptor impairs inhibitory neurotransmission in hippocampal neurons in a ghrelin independent manner

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GHSR is a G-protein coupled receptor that displays high constitutive activity, independent from its endogenous ligand, ghrelin, relying exclusively on GHSR expression levels. It is widely expressed in the nervous system, including regions with restricted ghrelin access, as the hippocampus, but the mechanisms underlying neuronal modulation by GHSR remain elusive. Our previous work demonstrated that presynaptic voltage-gated calcium channels (CaV2), which allow the calcium influx that triggers neurotransmitter release, are highly sensitive to GHSR constitutive activity. Our aim here was to study the impact of CaV2 modulation by GHSR on hippocampal neurotransmission. We performed electrophysiological recordings in hippocampal primary cultures from E16-18 wild type and GHSR-deficient mice after manipulating GHSR expression levels by lentiviral transduction. We found that GHSR constitutive activity impairs CaV2 currents, being CaV2.2 the most affected subtype. Moreover we found that GHSR constitutive activity decreases inhibitory but not excitatory post-synaptic currents, without affecting CaV2-independent forms of neurotransmitter release

We show that GHSR constitutive activity modulates inhibitory neurotransmission in hippocampal neurons through a presynaptic mechanism mediated mainly by CaV2.2 currents impairment that specifically affects GABA release. Our work provides insights in assessing the role of GHSR in neurotransmission and plasticity at hippocampal synapses.

P70.-Transferrin transport through the endosomal-exosomal pathway in oligodendrolioma cell line OLN-93

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Studies by our group have shown that apoTransferrin (aTF) has maturational effects on oligodendroglial precursor cells, which allows its use as a potential therapeutic agent in Central Nervous System (CNS) demyelinating diseases. Exosomes are nanoparticles of 20-200 nm secreted by cells which allow intercellular communication through long distances. In this context, the aim of our work is to analyze the effects of intranasally administered exosomes as Tf nanocarriers in a demyelination model. Given that some exosomes contain the Tf receptor (TfR), our interest is to find an easy and quick pathway of intracellular loading of aTf through its binding to the receptor. Oligodendroglioma cells OLN-93 were incubated for 30 min in the presence of human aTf, washed and subsequently incubated for 24 h in DMEMF12 without FCS. Western blot analyses were used to characterize the isolated exosomes with different exosome markers and also revealed the presence of the Tf-TfR complex. These results were corroborated using a special type of beads coated by exosomes to be detected by flow cytometry. Coated beads were treated with an anti-CD63 exosome marker and a fluorescent anti-Tf marker.

P71.-Two opposite effects of dopamine receptor type-1 (D1R) expression on CaV2.2 calcium currents

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Voltage-gated calcium channels type CaV2.2 co-localize with D1R in prefrontal cortex (PFC) neurons and CaV2.2 currents are modulated by dopamine-mediated activation of D1R. However, D1R is also known to display constitutive activity and studies showed that the sole expression of D1R increases CaV2.2 surface expression. Thus, our aim is to study the role of D1R agonist-independent activity on CaV2.2 function. We transfected HEK293t cells with increasing D1R:CaV2.2 molar ratios and verified expression levels using YFP-tagged D1R. We recorded whole-cell calcium currents and found an increase in CaV2.2 current density at low D1R expression levels (170% of ctrl, P=0.0029). Unexpectedly, at high D1R expression levels CaV2.2 current density was reduced (61% of ctrl, P=0.0005). To explore the role of D1R constitutive activity, we treated cells with haloperidol (D1R inverse agonist) and cholerotoxin (Gs protein inhibitor). We found that the increase in current at low D1R:CaV2.2 molar ratio depends on D1R constitutive activity, while the reduction of current at high D1R:CaV2.2 molar ratio does not. The latter may involve the formation of D1R complexes. In summary, we show two agonist-independent and opposite effects of D1R on CaV2.2 current, depending on D1R expression levels. Future experiments are required to understand the role of this effect on PFC neurons, where CaV2.2 have critical post-synaptic functions and where changes in D1R density are associated with cognitive deficits.

P72.-EPHA3 AND EPHA4 REGULATE EPHEXIN1 AND RHO GTPASES ACTIVITY DURING AXON GROWTH OF RETINAL GANGLION CELLS

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The Eph/ephrin system is involved in the chicken retinotectal mapping. We demonstrated that tectal EphA3 stimulates axon growth of nasal retinal ganglion cells (RGCs) toward the caudal tectum preventing them from branching in the rostral tectum. Moreover, we demonstrated that ephrin-A-mediated EphA4 forward signaling decreases the level of axon growth and increases the density of axonal interstitial filopodia of nasal RGCs whereas the tectal EphA3 ectodomain produces the opposite effects by decreasing the EphA4 signaling pathway by competing with EphA4 for ephrin-As binding.

Our purpose was to determine whether the EphA4 forward signaling and EphA3 stimulation regulate the activity of Rho GTPases.

We cultured chicken embryo retinal explants exposed to control conditions, to the EphA3 ectodomain (EphA3-Fc) or to KYL (EphA4 inhibitor) to evaluate the axon growth and the level of expression and activity of ephexin1 (GEF of Rho GTPases); RhoA and Cdc42. We also performed total homogenates of chicken embryo nasal retinas previously exposed to the same experimental conditions. We evaluated the level of expression and activity of ephexin1, RhoA and Cdc42 by Western blot.

The results showed that EphA4 forward signaling decreases axon growth by increasing ephexin1 and RhoA1 activity and decreasing Cdc42 activity; whereas EphA3 ectodomain increases axon growth by decreasing ephrin-A-induced-EphA4 signaling, ephexin1 and RhoA1 activity and increasing Cdc2 activity. PIP441, UBACYT0526

P73.-Amygdala stimulation promotes recovery of behavioral performance in a spatial memory task and increases GAP-43 and MAP-2 in the hippocampus and prefrontal cortex of male rats

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The relationships between affective and cognitive processes are an important issue of present neuroscience. The amygdala, the hippocampus and the prefrontal cortex appear as main players in these mechanisms. We have shown that post-training electrical stimulation of the basolateral amygdala (BLA) speeds the acquisition of a motor skill, and produces a recovery in behavioral performance related to spatial memory in fimbria-fornix (FF) lesioned animals. BLA electrical stimulation rises bdnf RNA expression, BDNF protein levels, and arc RNA expression in the hippocampus. In the present paper we have measured the levels of one presynaptic protein (GAP-43) and one postsynaptic protein (MAP-2) both involved in synaptogenesis to assess whether structural neuroplastic mechanisms are involved in the memory enhancing effects of BLA stimulation. A single train of BLA stimulation produced in healthy animals an increase in the levels of GAP-43 and MAP-2 that lasted days in the hippocampus and the prefrontal cortex. In FF-lesioned rats, daily post-training stimulation of the BLA ameliorates the memory deficit of the animals and induces an increase in the level of both proteins. These results support the hypothesis that the effects of amygdala stimulation on memory recovery are sustained by an enhanced formation of new synapses.

P74.-CircTulp4: A circular RNA that controls excitatory neurotransmission

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Exonic circular RNAs (circRNAs) are a recently characterized class of noncoding RNAs. These molecules derive from exonic sequences and are generated by an alternative mechanism of splicing known as backsplicing, which yields a single-stranded RNA molecule with covalently joined ends. Due to their recent identification, the function of circRNAs is still almost unexplored. We have recently accomplished a systematic high throughput identification of numerous circular transcripts derived from nerve tissue samples. From these data, we have selected a circular RNA transcript derived from the Tulp4 (Tubby-like protein 4) gene to perform a functional characterization. We observed in loss-of-function experiments, both in primary neurons and in brain slices, that circTulp4 regulates excitatory neurotransmission and affects the number of glutamatergic synaptic contacts.

To study the role of circTulp4 in vivo, we have generated a transgenic knock-out mouse line mutating a splicing acceptor site using CRISPR/Cas9 technique. Preliminary results show that mice lacking circTulp4 have impaired neurotransmission and exhibit memory deficits.

P75.-Role of the types 1 and 2 receptors for Angiotensin II (AT1R/AT2R) in inflammation-induced nociceptor neuritogenesis

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Types 1 and 2 receptors for Ang II (AT1R/AT2R) may play a role in neuropathic pain. Albeit Ang II induced neuritogenesis in primary sensory neurons has been offered as an explanation, the underlying mechanisms remain unknown. Our previous work showed that AT2R expressing neurons were C and A-δ nociceptors and that its expression increased in small neurons at CFA1, whereas at CFA4 increased only in medium neurons. Here we examined the expression pattern of AT1R during cutaneous induced inflammation. We used immunocytochemistry and selective AT1R and AT2R antagonists to examine their involvement in axonal growth and branching in normal and inflammatory conditions. We also tested in vivo neuritogenesis in IB4-nociceptors innervating the skin. In vitro, an inflammatory soup induced AT2R mRNA expression, while Ang II triggered TNF-α mRNA synthesis only when AT1R was blocked. Ang II promoted axonal growth and branching through both AT1R and AT2R. Their expressions correlated positively except when AT2R was inhibited. These suggest that the 2 receptors work together and are needed to sustain Ang II mediated neuritogenesis. In vivo, AT1R expression did not change with inflammation in nociceptors, but it did in large neurons at CFA4. 4 weeks treatment with antagonists against either AT1R or AT2R showed little impact on nociceptor neuritogenesis at skin level after inflammation. Thus, AT1R/AT2R seem to be required for the purported action of Ang II in the context of neuropathic pain.

P76.-Pigmented Epithelium Derived Factor (PEDF) prevents apoptosis and acts as a neurotrophic factor for retinal neurons

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PEDF has been shown to be cytoprotective on the R28 retinal progenitor cell line, but its effects on retinal neurons remain largely unknown. We investigated its effects in cultured photoreceptors and amacrine neurons. Pure neuronal cultures from 1-day old rat retinas were grown in a serum-free, chemically defined media, and incubated at day 2 with PEDF, small fragments from its neurotrophic (44-mer and 17-mer) or antiangiogenic (34-mer) domains, PEDF plus the blocking peptide P1, the PEDF-Receptor (PEDF-R) inhibitor, atglistatin; or vehicle (control) for 3 days. Apoptosis, cell death, opsin expression and axonal outgrowth were then analyzed. PEDF and the fragments from its neurotrophic domain prevented apoptosis, preserving mitochondrial functionality, and promoted both opsin localization in photoreceptor apical ends and neurite outgrowth, mainly in amacrine neurons. Retina neurons expressed PEDF-R, which showed a high degree of colocalization with membrane markers. Pre-treatment with either P1 or atglistatin abolished PEDF effects whereas the fragment from PEDF antiangiogenic domain had no effect. In summary, this work suggests that PEDF is an effective survival factor for retinal photoreceptors during development in vitro. It also implies that PEDF plays different roles in neuronal differentiation, promoting the polarization and differentiation of photoreceptors and stimulating axonal outgrowth in amacrine neurons through the activation of its membrane receptor.

P77.-SEX DIFFERENCES IN GABA-MEDIATED CALCIUM INFLUX IN HYPOTHALAMIC NEURONS

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GABAA receptor (GABAAR) activation exerts trophic actions in immature neurons through depolarization of resting membrane potential gating the opening of voltage-dependent calcium channels. Previous results from our lab have shown gender-biased GABAAR responses in cultured hypothalamic neurons. These differences were found before brain masculinisation by gonadal hormones. Considering these, in this work we evaluated the GABAAR-mediated Ca2+ entry in cultured neurons segregated by gonadal type. Hypothalamic cells were obtained from embryonic brains at E16 (both male and female), two days before the peak of testosterone production by the foetal testis, and cultured for 2 days. To measure calcium signals, neurons were loaded with the calcium indicator Cal-520, followed by a time-lapse recording on live cells using a spinning disk microscope. Our results show that there are more male than female neurons responding to GABAAR stimulation. Additionally, almost 50% of male neurons did not recover basal calcium level after stimulation, in contrast to only 20% observed in females. Moreover, although nifedipine blocks intracellular calcium entry equally, it was stronger in males. Together, these results highlight the influence of neural sex differences irrespectively of sexual hormone exposure.

P78.-The cuprizone model under neurosphere´s scrutiny

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Cuprizone (CPZ) is a copper-chelating agent which induces demyelination in mice. Although its neurotoxic mechanism is still unknown, CPZ has been shown to produce astrogliosis, microglial activation and loss of oligodendrocytes throughout the brain resulting in demyelination and neurotoxicity.

Neural stem and progenitor cells (NSC/NPC) are able to generate all neural cell types and can be cultured as neurospheres (NS). NS can be maintained in a proliferative and undifferentiated state or alternatively be forced to differentiate into neurons, astrocytes or oligodendrocytes. In the present work we used NS cultures to evaluate CPZ effects on NSC/NPC survival, proliferation, migration and differentiation.

Although NS generation was not affected when cultures were initiated in the presence of CPZ, we observed a slight decrease in NS size at higher CPZ concentrations. Migration was also affected in the presence of CPZ, which generated changes in migration patterns and an increase in the maximal migration distance reached by cells detached from NS.

Treatment of dissociated NS during differentiation did not change mature oligodendrocyte, astrocyte or neuron proportions. However, CPZ treatment after cell differentiation produced a dose-dependent decrease in the number of MBP-positive cells.

The detection of oligodendroglial precursor cells in these conditions suggests that CPZ has a deleterious effect on mature oligodendrocyte cells without affecting their precursors.

P79.-Protein synthesis regulation during the behavioral tagging process in memory reconsolidation

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In the last years we have shown that memory reconsolidation is achieved through a behavioral tagging process. In other words, that the event that triggers the reconsolidation induces the setting of a tag, that determines were to store an updated memory, and the synthesis of plasticity related proteins (PRPs) that once captured at the tagged sites will allow the reconsolidation to occur. Now we are focused in identifying the neurotransmitter systems and brain structures that regulate the synthesis of PRPs.

Using the spatial object recognition (SOR) task, we show that the infusion of the D1/D5-dopaminergic receptor antagonist SCH23390, or the β-adrenergic receptor antagonist propranolol, 15 min before the reactivation of SOR memory induced long-term retrograde amnesia. Interestingly, the exploration of a novel OF 6o min before the reactivation session was able to rescue memory reconsolidation and prevent the amnestic effect of both antagonists. Now, we are combining the electrical stimulation of the ventral tegmental area (VTA) and/or the locus coeruleus (LC), with pharmacological interventions, to analyze if these structures are specifically recruited to regulate the synthesis of PRPs during SOR memory reconsolidation.

At the moment we show that D1/D5-dopaminergic and β-adrenergic receptors, in the hippocampus, are required to trigger the synthesis of PRPs during memory reconsolidation, and suggest that the VTA and the LC are the structures responsible of this regulation.

P80.-Postgraduate Students Stress

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Introduction. Emotional disorders (ED) have a high prevalence worldwide and have been related to chronic stress. In addition, graduate students go through a work environment conducive to triggering this type of stress. Objectives: to verify the association between burnout and ED; to compare the levels of chronic stress, anxiety and depression between graduate students and a control group. Finally, the relationship of these variables with salivary cortisol (C) levels will be studied. Method. Sample 86 Argentinian workers. Of the total sample, 56 were graduate students and the rest were workers from private companies. Instruments were applied to measure chronic stress (MBI-GS), generalized anxiety (GAD 7) and depression (PHQ 9) and salivary (C) was analyzed by ECLIA at 3 different times. The results show a moderate to strong correlation between the central dimensions of the burnout and the ED. Specifically, exhaustion correlated strongly and positively with both Anxiety ($r=.64$, $p<.01$) and Depression ($r=.63$, $p<.01$). Cynicism presented moderate and positive correlations with Anxiety ($r=.42$, $p<.01$) and Depression ($r=.37$, $p<.01$). Conclusion: Graduate students presented higher levels of Exhaustion, Cynicism, Anxiety and Depression. In sum, the results show that burnout, anxiety and depression are more prevalent in the graduate student population.

P81.-Ghrelin-evoked GHSR activity impairs low voltage activated Ca2+ channel (CaV3) currents in hypothalamic neurons

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CaV3 play a critical role in shaping burst firing and controlling pacemaker activity in neurons. Despite the importance of these channels, information regarding the mechanisms modulating CaV3 currents is scarce. In this context, we investigated the sensitivity of CaV3 currents to activation of GHSR, a receptor involved in energy balance and memory, among other central functions. We have previously showed that GHSR decreases CaV1 and CaV2 current in neurons, and that this inhibition impacts neurotransmission in areas where GHSR is physiologically relevant: the hypothalamus and the hippocampus. We performed whole cell patch clamp on hypothalamic neuronal primary cultures and found that ghrelin inhibits CaV3 currents. We next assayed this effect on CaV3 subtypes (CaV3.1-3) isolated in transfected HEK293T cells and found that CaV3.3 is the only CaV3 subtype inhibited by ghrelin in a Gq-dependent and Gβγ-independent manner. For CaV3.3, we observed a 30% reduction in the number of channels available for opening, acceleration of the activation and inactivation kinetics, and no changes in voltage dependency parameters nor in the kinetics of deactivation or recovery from inactivation. Ghrelin application increases V1/2 of steady-state inactivation but does not affect steady-state activation, changing the window current size. Finally, we compile these parameters and run simulations on the program NEURON to model the putative impact of GHSR and CaV3.3 on neuron firing activity.

P82.-Wnt7b is involved in axon differentiation and elongation in hippocampal neurons

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The establishment of neuronal polarity and the development of axon and dendrites are essential for the formation of neuronal circuits. Wnt factors are secreted proteins functioning as neuronal modulators since are involved in neuronal differentiation, maturation and synapses. After Wnts bind to Frizzled (Fz) receptors, different signaling cascades can be activated: Wnt/β-catenin, planar cell polarity (PCP) and Wnt/Calcium pathways. Previously, we demonstrated that Wnt7b, through Fz7 receptor, regulates dendrite development and maturation. Now, we investigated the potential role of Wnt7b during early stages of neuronal development. Our findings showed that neuronal differentiation is altered after Wnt7b stimulation. The presence of Wnt7b stimulated axonal outgrowth and elongation compared to controls. Surprisingly, the function of Wn7b on neuronal differentiation did not seem to be mediated by Fz7 receptor, since the expression of Fz7 did not affect axonal growth. Also, we found that Wnt7b effect was blocked when neurons were cultured in the presence of SFRP1 (the antagonist of Wnt), suggesting the specificity of Wnt effect on axonal growth. To go further, we examined the intracellular cascades triggered by Wnt7b. Pharmacological inhibition revealed that Wnt7b requires JNK activation to modulate the development of axon. More analyses are being performed in order to fully evaluate the Wnt7b function on early neuronal development.

P83.-Regional microgliosis in transgenic mice expressing a mislocalized form of TDP-43: implications for neurodegenerative disease pathogenesis

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Activated microglia is a universal feature of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), two neurodegenerative disorders associated to mislocalization and aggregation of TAR DNA-binding protein 43 (TDP-43); however, its role in pathogenesis is not well understood. We generated and characterized transgenic (TG) mice conditionally overexpressing either nuclear (WT) or cytoplasmic (ΔNLS) forms of human TDP-43 in forebrain neurons. Recently, we showed that hTDP-43-WT mice display higher levels of microglial activation in hippocampal CA1 region and somatosensory cortex (SSC) respect to controls. In this study, we aimed to explore microgliosis in hTDP-43-ΔNLS mice. We analyzed microglial (Iba1+) staining in TG mice after 1 month of post-weaning induction in different brain regions. TG mice showed significant increases in total % Iba1+ area, microglial cell number and Iba+ cells with activated morphology (larger somatic area) in SSC and CA1 region compared to controls. In addition, there was a significant increase in mean Iba+ soma area in SSC, with borderline significance in CA1 region. Prefrontal cortex displayed no significant differences in any of the parameters analyzed. We are currently evaluating microgliosis in additional regions, including motor cortex and dentate gyrus, and also the status of astroglial response using GFAP staining. These results will help elucidate the role of gliosis in ALS, FTD and other TDP-43 proteinopathies.

P84.-INTRACISTERNAL DELIVERY OF IGF-1 MEDIATED BY A RECOMBINANT ADENOVECTOR IS NEUROPROTECTIVE FOR THE RAT SPINAL CORD EXCITOTOXIC DAMAGE INDUCED BY KA

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Insulin-like growth factor-1 (IGF-1) is a potent neurotrophic factor whose neuroprotector effects on the central nervous system have been well documented. The intraparenchymal injection of kainic acid (KA) into the C5 segment of the spinal cord induces functional and histopathological changes. KA-injected animals show several motor and sensitive impairments on their performance, and a reduction in the neuronal counting and gliosis at the injected segment with a relative compromise of neighbor segments (C4 and C6). The aim of the present work was to evaluate whether the intracisternal delivery of IGF-1 mediated by a recombinant adenovector abrogates or at least decreases the structural and behavioral damaged induced by the KA. Male Sprague Dawley rats were injected with 30 µl of recombinant adenovectors (4x1010 pfu/ml RAds) expressing fluorescent protein (DsRed) or rat IGF-1 three days before (day -3) the injection of 1 mM KA (day 0). Motor and sensitive trials were tested on both groups before and after KA injection (days -3, 0, 1, 2, 3 and 7). Animals were euthanized either on day 3 or day 7. RAd-IGF-1-injected rats performed better the trials and showed a higher neuronal counting at the injection segment as compared to RAd-DsRed-injected control. A neuroprotective effect of IGF-1 in this model is thus proposed. Further studies will be focused on analyzing changes in glial cells and in the cytokine profile induced by the therapy.

P85.-CLONAL ANALYSIS OF STEM/PROGENITOR CELLS IN CHICKEN NEURAL RETINA

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Clonal cell analysis defines the potential of single cells, allowing to decode neural heterogeneity of cell lineages and their clonal relationships. We adapted the mouse genetic tracing strategy UbC-StarTrack to a chick model. UbC-StarTrack is based on transfection of genes encoding fluorescent reporter proteins, six in the cytoplasm and six in the nucleus, driven by an ubiquitous promoter in PiggyBac-based vectors. This method produces inheritable marks that enable long-term in vivo cell tracing and attributes a unique color-code to single neural precursors, determining their differentiation potential and degree of dispersion. Once probed the accurate expression of these constructs in neurospheres obtained from dissociated cells of the chick retinal ciliary margin (CM) at 7 days of development (E7), UbC-StarTtrack mixture was co-electroporated into the retinal CM at E3.5. Labeled cell progenies were analyzed at different time points (2, 5 and 8-days postelectroporation). This allowed us to determine both, cell types originated from single cells and their clonal relationships within the retina. In conclusion: 1) UbC-StarTrack is valid in chicken model. 2) Cell clones formed columns extended between the inner and outer limitants of neural retina. 3) Cell clones displayed a large dispersion along the dorso-ventral axis but a limited dispersion by the anterior-posterior axis. 4) Different types f cells presented similar color combinations, revealing multipotency of some clones.

P86.-NKX2.1 controls the differentiation of hypothalamic melanocortin neurons and regulates arcuate Pomc expression and body weight

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Food intake is tightly regulated by brain circuits that receive multiple central and peripheral signals. A group of neurons present in the arcuate nucleus of the hypothalamus activate satiety by releasing Pomc-encoded melanocortins, the absence of which induces marked hyperphagia and early-onset obesity. Little is known about the transcription factors that establish their cellular fate, terminal differentiation and phenotypic maintenance. We report that the neuronal Pomc enhancers nPE1 and nPE2 contain highly conserved canonical binding sites for NKX2.1, a homeodomain transcription factor that plays a key role in the early development of the anterior brain. We have found that Pomc coexpresses with Nkx2.1 since its onset at E10.5 in the future arcuate nucleus and throughout the entire lifespan. NKX2.1 binds in vitro and in vivo to NKX binding sites present in nPE1 and nPE2 and, in addition, transgenic and mutant mouse studies showed that these NKX binding sites are essential for the transcriptional activity of the neuronal Pomc enhancers. The conditional early inactivation of Nkx2.1 in the developing ventral hypothalamus prevented the differentiation of POMC neurons. Furthermore, selective Nkx2.1 ablation from POMC neurons reduced Pomc expression and increased body weight and adiposity. Thus, our results demonstrate that NKX2.1 plays a critical role in the early determination of arcuate melanocortin neurons and the regulation of Pomc expression and body weight in adulthood.

P87.-Intracellular trafficking defects induced by α-synuclein as a pathogenic mechanism for Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons of the substantia nigra. One of the hypotheses regarding the molecular mechanisms involved in the development of this disease postulates that defects in the intracellular protein and/or membrane trafficking is an initial event in the pathogenesis of this disorder. It is well known that increased expression of α-synuclein is associated with a higher incidence of PD. However, the underlying cellular and molecular mechanisms remains to be elucidated. We utilized a state-of-the-art system to synchronize the secretory pathway in order to study if α-synuclein is capable to affect the dynamics of vesicular transport between the endoplasmic reticulum (ER) and the Golgi apparatus, and the vesicle release from the latter. This system is based in fusion proteins that aggregates in the ER and can be synchronously released to the Golgi apparatus by a membrane permeable drug. Interestingly, we found that the expression of α-synuclein induces a delay in the proteins transport between the ER and the Golgi apparatus, and also a delay in the vesicle exit from the Golgi apparatus towards the neuronal processes. These results suggest that the toxicity of α-synuclein may be due, at least in part, to the delay or blockage of the exocytic pathway.

P88.-The physiological role of the GTPase Rab21 in neuronal migration and the development of the cerebral cortex

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The development of the complex structure of the mammalian neocortex requires the proper migration of developing neurons from the ventricular zone containing neural progenitors to the cortical plate. The precise coordination of different cellular processes such as cytoskeleton dynamics, membrane trafficking and cell adhesion during migration is achieved by a variety of signaling pathways. GTPases play a central role in all these processes. In this context, the small GTPase Rab21 has been implicated in the regulation of cell adhesion dynamics by controlling the trafficking of endocytic vesicles containing adhesion molecules. Interestingly, Rab21 has been also implicated in neurite outgrowth. With the following project, we propose to study how Rab21 regulates sorting, traffic and endocytosis of adhesion proteins such as amyloid beta precursor protein (APP) and N-cadherin and elucidating its function in neuronal migration and the development of the cerebral cortex. These studies are important to better understand the mechanism governing the development of the cerebral cortex and the mechanisms that participate in neurodevelopmental pathologies such as autism spectrum disorders and cortical malformations.

P89.-Posttranslational modifications of α-tubulin in Alzheimer's disease: focus on tyrosination/detyrosination cycle

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Alzheimer disease (AD) is a neurodegenerative disease characterized by neurofibrillary tangles (NFTs) and senile plaques (SP) in brain. In early phases of AD, the exact role of SP and NFTs is still unclear and a contribution from other factors is expected to explain the synapse loss underlying the cognitive decline.Dendritic spines are dynamic structures regulating synaptic plasticity and cognitive abilities. Spine plasticity depends on actin and microtubule (MT) dynamics: the entrance of dynamic MTs into spines regulates their activity and morphology. Our team established causal link between MT dynamics and tubulin tyrosination: tyrosinated and detyrosinated tubulin are respectively present in dynamic and stable MTs. In the detyr/tyrosination cycle, the C-terminal tyrosine of α-tubulin is removed by recently identified carboxypeptidases (TCPs) and re added by the ligase (TTL). The role of this cycle on synaptic plasticity modulation is still unknown. We investigated TTL levels and modified tubulins in control and AD brains. TTL level significantly decreases with AD progression and is highly correlated with increased levels of modified tubulins. TTL reduction leads to cognitive impairment in mice and reduced dendritic spine density in cultured neurons. Moreover, TTL over expression rescues spine density and protects spine loss induced by Aβ toxicity. Our results highlight the role of detyr/tyrosination cycle of tubulin in AD and refer TTL as a potential target for drug design.

P90.-ROLES OF KIF5C ON NEURONAL POLARIZATION AND NEOCORTICAL FORMATION

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Three early signals of asymmetry have been described to occur in a single neurite of neurons in culture at stage 2 of differentiation and shown to be essential for neuronal polarization: i) Accumulation of stable microtubules; ii) Enrichment of the plasma membrane with activatable IGF-1r; and iii) Polarized transport of the microtubular motor KIF5C. We have demonstrated that silencing of KIF5C expression prevents the polarized insertion of IGF-1r into the neuronal plasmalemma and neuronal polarization. Syntaxin 6 and VAMP4, necessary for the polarized insertion of the IGF-1r, are associated to vesicles carried by KIF5C and are transported preferentially to the neurite where KIF5C accumulates. We conclude that the enrichment of stable microtubules in the future axon enhances KIF5C mediated vesicular transport of syntaxin 6 and VAMP-4, which in turn mediate the polarized insertion of IGF-1r in the plasmalemma, a key step for neuronal polarization. These results prompted us to study the possible participation of KIF5C on neocortical formation. Using “in utero” electroporation we have demonstrated that KIF5C is essential for early cortical neurons migration and, thus, neocortical formation. Neurons electroporated with a shRNA targeting KIF5C failed to migrate to the upper cortical layers and accumulated at the ventricular/subventricular zones. Further investigation will be necessary to study the regulation of dynamic changes in neuronal polarity during cortical neurons migration.

P91.-Proteolipid Protein as a marker of olfactory bulb granule cell progenitors during adult neurogenesis

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The subventricular zone is a neurogenic niche that produces olfactory bulb interneurons throughout life. Stem cells that express glial fibrilary acidic protein (GFAP) generate transit amplifying progenitors that divide to produce neuroblasts, which in turn migrate to the olfactory bulb via the rostral migratory stream, mature, and integrate to the local circuit as granule and periglomerular neurons. Outside this neurogenic niche, neurogenesis of pyriform cortex pyramidal neurons has been shown to occur in the adult stage and involve progenitors expressing the oligodendrocyte marker proteolipid protein (PLP). Here we ask whether PLP-expressing progenitors can generate new olfactory bulb interneurons. We used a tamoxifen-inducible PLP-Cre mouse line crossed with a Cre-reporter line (LSL-tdTomato) to label PLP-expressing cells and looked for labeled olfactory bulb interneurons at an early (1 week) and late (1 month) time points after induction. We found tdTomato-labeled spiny cells with a morphology compatible with olfactory bulb granule cells at the late but not at the early time point. We will: 1. Test whether tdTomato-labeled cells at the late time point express characteristic markers of olfactory granule cells and 2. Address whether tdTomato-labeled cells at the early time point are found in the subventricular zone and/or rostral migratory stream co-expressing markers characteristic of transit amplifying progenitors and/or neuroblasts of the olfactory bulb neuronal lineage.

P92.-Platelets bioenergetics screening reflects the impact of brain Aβ plaque accumulation in a rat model of Alzheimer

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Alzheimer's disease (AD) is associated to depressed brain energy supply and impaired cortical and hippocampal synaptic function. It was previously reported in McGill-R-Thy1-APP transgenic (Tg(+/+)) rats that Aβ deposition per se is sufficient to cause abnormalities in glucose metabolism and neuronal connectivity. These data support the utility of this animal model as a platform for the search of novel AD biomarkers based on bioenergetic status. Recently, it has been proposed that energy dysfunction can be dynamically tested in platelets (PLTs) of nonhuman primates. PLTs are good candidates to find peripheral biomarkers for AD because they may reflect in periphery the bioenergetics deficits and the inflammatory and oxidative stress processes taking place in AD brain. In the present study, we carried out a PLTs bioenergetic screening in advanced-age (12-14 months old) control (WT) and Tg(+/+) rats and found a significant decrements in the maximal respiration of thrombin-activated PLTs of Tg(+/+) as compared to WT rats. In summary, our results provide original evidence that PLTs bioenergetic profiling may reflect brain bioenergetics dysfunction mediated by Aβ plaque accumulation. Further studies on human PLTs from control and AD patients are required to validate the usefulness of PLTs bioenergetics as a novel blood-based biomarker for AD.

P93.-Regulation of cellular sphingolipid metabolism by lipid-protein adducts and genetic variants associated with age-related macular degeneration

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Age-related macular degeneration (AMD) is a common sight-threatening condition with complex etiology. Genetic, environmental, and diet factors are associated with AMD risk. Oxidative damage is thought to play a key role in the causality of AMD, and by-products of lipid peroxidation, such as malondialdehyde-acetaldehyde (MAA) adducts, were shown to be highly elevated in AMD retinas. We previously reported increased levels of serum ceramides in AMD patients compared to controls, and observed that genetic variant rs1061170 (p.Y402H) in the complement factor H (CFH)/factor H-like protein 1 (FHL-1) gene correlates with Cer d18:1/16:0 levels in AMD. The aim of this study was to evaluate the cellular sphingolipid metabolism under treatment with MAA adducts, and the modulation by FHL-1, an alternative splicing isoform of CFH. For this purpose, we evaluated cell survival, gene expression, and sphingolipid levels in WERI-Rb1 and ARPE-19 cells exposed to MAA-BSA or BSA. In the concentrations evaluated, WERI-Rb1 cells were more affected than ARPE-19 cells, with a decrease in survival, upregulation of ceramide synthesis genes, and higher ceramide levels under MAA treatment. Notably, WERI-Rb1 cells exposed to the non-risk isoform FHL-1:Y402, but not the AMD risk associated isoform FHL-1:H402 or CFH, revealed a downregulation of ceramide synthesis genes. Together, our findings suggest that ceramide levels are influenced by AMD associated risk variants and oxidative stress by-products.

P94.-Light-regulation of ArylalkylamineN-Acyltransferase (AANAT) and a new potential rol in vertebrate retina

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A key regulatory step in melatonin synthesis is that at which serotonin is converted to N-acetyl-serotonin (NAS) by the enzyme Aralkylamine N- Acetyltransferase. AANAT is present in the retina and other regions while NAS can activate the TrkB receptor to generate neuroprotective effects. In photoreceptor cells, AANAT activity peaks during the dark (D) and at subjective night while activity is significantly decreased by light (L). By contrast, melatonin synthesis, AANAT expression and activity are high during the subjective day or L phase in chicken retinal ganglion cells (RGCs). Here we investigated the expression of AANAT and of nonvisual opsins in enriched embryonic RGC cultures exposed to different L conditions. Cultures expressed Opn4 (melanopsin), Opn3 and Opn5 which may confer intrinsic photo sensitivity. Moreover, cultures exhibited blue L (BL) induction of AANAT immunoreactivity and mRNA as compared with D or red L treatedcells. In addition, expression of this enzyme was significantly increased by adenylate cyclase activator forskolin (10 uM) in D. Interestingly, AANAT showed a localization change, from the cytoplasm to nucleus, increasing in BL, and this effect was reversible in darkness condition after L exposure; in addition the nuclear importation of AANAT was blocked with protein synthesis inhibitor cycloheximide (50uM) in BL. Results suggest that AANAT is a blue L-induced enzyme in RGCs controlled by cAMP, likely playing important roles in inner retinal cells.

P95.-Pea3 transcription factors as mediators of nociception

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Sensory neurons of the dorsal root ganglion (DRG) are involved in the correct perception of external stimuli and requires the appropriate peripheral target tissue innervation. The majority of DRG neurons, have a small-diameter soma, express the neurotrophin receptor TrkA during embryonic development, and project unmyelinated fibers to innervate the epidermis, depending on target-derived nerve growth factor (NGF).

In mammals, peripheral neurotrophic signals have been shown to induce the expression of the Pea3 subfamily of ETS transcription factors, which comprise three members: Etv1, Etv4, and Etv5. Previous studies of our group showed that Etv4 and Etv5 are expressed by developing TrkA DRG neurons and are induced by peripheral NGF. Moreover, downregulation of Etv4 or Etv5 reduces DRG axonal growth in response to NGF in vitro. These results lead us to study TrkA sensory neuron population in the DRG in vivo and the target tissue innervation of peptidergic neurons. In the present study, we analyzed the in vivo role of Pea3 on the development of DRG, target innervation and its role in nociception. We investigated the consequence of disturbed Etv4 mediated signaling for pain sensation using different nociception assays such as the hot plate test, tail flick and formalin test. The results obtained by behavioral assays correlate with defects in target innervation observed in mutant mice. Our data indicates that Etv4 has a key role in sensing noxious nociceptive stimuli.

P96.-HDAC3 negatively modulates long-term memory formation at two different levels: histone deacetylation and NF-kB inactivation

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Histone acetylation is a key process for gene expression during long-term memory consolidation. On the contrary, the activity of histone deacetylases (HDACs) diminishes transcriptional activity, thus functioning as negative modulators. Here we study the effect of different HDACs inhibitors in long-term memory formation using the Novel Object Recognition task in mice. We found that RGFP966, an HDAC3 sprcific inhibitor, administered immediately after a waek training session generates a memory that lasts 7 days. In contrast, class I HDAC inhibitor sodium butyrate, and HDAC6 specific inhibitor Tubastatin A failed to facilitate memory consolidation. As one of the target substrates of HDAC3 is the transcription factor NF-kB, we expect that the administration of RGFP966 will also produce an increse in the acetylated form of NF-kB. Acetyl-NF-kB is the active form of this transcription factor, that is a key regulator of gene expression during memory consolidation. Thus the inhibition of HDAC3 would be acting at two different levels: first increasing histone acetylation, that recruits tanscriptional machinery; and second increasing the active form of one of the transcription factors required for gene expression. Ongoing experiments are in course to elucidate this last issue.

P97.-Participation of nuclear receptors PPARγ and RXR in the remyelination process

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Demyelination in the CNS is a pathological process resulting from an insult on oligodendrocytes, while remyelination is a repair process by which oligodendroglial precursor cells restore myelin sheaths. Recent work has proven a significant increase in the mRNA of retinoid X receptor γ (RXRγ) during remyelination. RXRs are nuclear receptors forming complex with peroxisome proliferator activator proteins (PPARs), which regulate OL differentiation and maturation. Our aim is to study the joint activation of RXRγ and PPARγ by specific agonists 9 cis retinoic acid (RA) and pioglitazone (PIO), respectively, and their impact on remyelination through in vitro and in vivo experiments. NPC obtained from the SVZ were treated with RA, PIO, PIO+RA or their vehicle for 4 days. PIO treatment rendered a higher proportion of PDGFRα+/KI67+ cells. In contrast, RA cultures showed a higher proportion of MBP+ cells, with no significant differences in the PIO+RA condition regarding vehicle. For in vivo experiments, cuprizone-demyelinated mice were stereotaxically injected vehicle or PIO+RA, unilaterally into the corpus callosum (CC) and sacrificed 7 days after injection. Immunohistochemical and Western blot analyses of the CC rendered a decrease in the proportion of Iba-1+ and GFAP+ cells as a consequence of PIO+RA treatment, together with an increase in myelin deposition. These preliminary results hint at a pro-myelinating and anti-inflammatory effect of RXRγ and PPARγ activation, respectively.

P98.-Role of cytoplasmic c-Fos as an activator of lipid synthesis during neuronal differentiation

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Cytoplasmic c-Fos activates phospholipid synthesis by associating with particular lipid synthesizing enzymes at the endoplasmic reticulum (ER). This activity of c-Fos supports the high rates of membrane genesis required for neuronal differentiation. In hippocampal cultures, blocking either c-Fos expression or its activity promotes an impairment in differentiation with no observable development of axonal processes. In addition, the expression of N-terminal deletion mutants of c-Fos capable of blocking only its cytoplasmic activity produces a similar effect. Moreover, using an in utero model to evaluate neuronal cortical migration, neurons electroporated with a shRNA targeting c-Fos fail to migrate and are mostly visualized in the ventricular/subventricular zones. Since we found c-Fos strongly co-localizing with ER markers in neuronal processes, we examined if its lipid synthesis activator capacity is exerted in neurons by examining CDP-diacylglycerol synthase (CDS), previously described as one of the enzymes activated by c-Fos, and CTP:phosphocholine cytidylyltransferase-β2 (CCTβ2), that is responsible for CDP-choline formation in the brain. A strong interaction between c-Fos and the enzymes was found by FRET experiments together with a marked increase in CDS enzymatic activity in the presence of recombinant c-Fos. These results support our hypothesis that c-Fos plays a main role in neuronal differentiation and this might be achieved through phospholipid synthesis regulation.

P99.-Analysis of the key functional residues within the C-terminal cytoplasmic tail of Gpm6a critical for filopodium outgrowth

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Gpm6a is a neuronal membrane glycoprotein with four transmembrane domains and the N- and C-terminal ends facing the cytoplasm. It functions in the processes of neuronal development and its overexpression leads to the extensive formation of filopodia. However, the mechanism of action of Gpm6a is not clearly understood. Previously, we mapped the regulatory effect of Gpm6a in filopodium formation to its C- but not the N-terminal cytoplasmic end. Following alanine scanning mutagenesis of the C-terminal cytosolic end identified K250, K255, and E258 as the key functional residues. Subsequent bioinformatic analysis revealed that K250, K255, and E258 are predicted as part of sorting signals of transmembrane proteins. Here, we use flow cytometry analysis to show that total expression levels of truncation mutants do not differ from the wt Gpm6a, but the amount of both truncated proteins on cell surface is lower. Our colocalization assay shows that deletion of the C- but not the N-terminus diminishes the association of Gpm6a with clathrin implying involvement of clathrin-mediated trafficking events. Substitution of K250, K255, and E258 with alanine also diminishes the amount Gpm6a on cell surface and in case of K255 and E258 also leads to the lower amount of total expressed protein. Subsequent subcellular localization studies using confocal microscopy reveal that mutant forms of Gpm6a that fail to induce filopodia formation display preferential localization to Lamp1-positive structures.

P100.-Experimental febrile seizures in young postnatal rats have a long-lasting effect in epileptic threshold and astroglial morphology.

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Retrospective studies in adult epilepsy patients show an initial precipitating injury, usually febrile seizures, during childhood between 6 months and 5 years of age. Using an animal model of hyperthermic seizures (HS), we here investigated the consequences of early HS young rats. Rat pups (10-11 postnatal, PND) were placed in a glass chamber, and their core temperature was raised and hyperthermia (39.5–42.5C) was maintained for 30 min. The seizures onset was monitored behaviorally, and consisted of an acute sudden arrest of hyperthermia-induced tonic freeze postures and occasional oral automatism (biting and chewing) and often body flexion. Rats were then placed on a cool surface, monitored for 5 min before being returned to their mothers. At PND37-39 rats were exposed to repeated pilocarpine subconvulsive doses (10 mg/kg). We observed a significative reduction in the convulsive threshold in HS-exposed animals compared with controls. Another group of animals (PND35) was deeply anesthetized, fixed and brains processed for immunohistochemistry. HS animals showed neuronal alterations with NeuN relocalization to the cystoplasm, moderate reactive gliosis with an atypical astrocytes distribution in the pyriform cortex and other brain structures. Our results suggest that HS exposure early in the postnatal brain development produce long-lasting effects in animals, which could be related to their future susceptibility to develop epilepsy. Supported by grants UBACYT, PICT 2015-1451.

P101.-Ceramide induces the death of retina photoreceptors through activation of parthanatos

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Ceramide (Cer) has been proposed as a messenger in photoreceptor cell death in the retina. Here we explored the pathways induced by C2-acetylsphingosine (C2-Cer), a cell permeable Cer, to elicit photoreceptor death. Treating pure retina neuronal cultures with 10 µM C2-Cer for 6 h selectively induced photoreceptor death, decreasing mitochondrial membrane potential and increasing the formation of reactive oxygen species. Noteworthy, the amount of TUNEL-labeled cells and photoreceptors expressing cleaved-caspase 3 remained constant and pretreatment with a pan-caspase inhibitor did not prevent C2-Cer-induced death. C2-Cer provoked polyADP ribosyl polymerase-1 (PARP-1) overactivation. increased polyADP ribose polymer (PAR) levels and induced the nuclear translocation of apoptosis inducing factor (AIF). Inhibiting PARP-1 decreased C2-Cer induced photoreceptor death and prevented AIF translocation. A calpain inhibitor reduced photoreceptor death whereas selective cathepsin inhibitors granted no protection. Combined pretreatment with a PARP-1 and a calpain inhibitor evidenced the same protection as each inhibitor by itself. Neither autophagy nor necroptosis were involved in C2-Cer-elicited death. These results suggest that C2-Cer induced photoreceptor death by a novel, caspase independent mechanism, involving activation of PARP-1, decline of mitochondrial membrane potential, calpain activation and AIF translocation, which are all biochemical features of parthanatos.

P102.-SARA participation as a negative regulator of the TGFβ signaling pathway in neuronal development

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Several events are necessary for proper neuronal development, such as cytoskeletal dynamics and endosomal trafficking. Smad Anchor for Receptor Activation (SARA) is a protein that binds to early endosomes; carrying out specific functions related to traffic but also participating in signaling such as TGFβ pathway. It has been described that SARA recruits Smad2/3 and, therefore, favors the activation of the pathway in epithelial cells. Moreover, it has been shown that TGFβ signaling specifies axon during neuronal development; however, SARA participation in this signaling pathway during the developmental process remains unknown. For this reason we proposed to analyze the role of SARA in the TGFβ signaling during neuronal development. Preliminary results in hippocampal neurons, through FRET Acceptor Photobleaching showed interaction between SARA and the TGFβ receptor. Also, performing loss and gain of function experiments, SARA supression (through shRNA expression) generates both greater axonal growth and loss of axonal specification since neurons have more than one axon compared with the control. Interestingly, this same phenotype is obtained when we use a mutant form of SARA that prevents its binding to PP1c protein and therefore, the TβRI remains hyperphosphorylated, keeping the pathway activated.These results suggest that SARA participates in TGFβ pathway in neurons through the negative regulation, which seems to be a requirement for the correct neuronal development.

P103.-ROLE OF ELECTRICAL ACTIVITY IN THE ASSEMBLY OF SENSORY CIRCUITS DURING THE DEVELOPMENT OF THE NERVOUS SYSTEM

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Spontaneous electrical activity (SEA) expressed during early stages of development is required for the correct assembly and function of the nervous system. In the developing auditory system, SEA originates in the cochlea and is key for neuronal survival, maturation of auditory neurons, and refinement of tonotopic maps. In order to decipher the role of SEA in the development of sensory circuits, we used the in vivo Zebrafish (Danio rerio) lateral line system (LL). The LL is the sensory system that allows fishes and amphibians to detect water motion. It consists of clusters of mechanosensory hair cells, called neuromasts, which are innervated by afferent and efferent neurons and surrounded by non-sensory supporting cells. LL hair cells share structural, functional and molecular similarities with the hair cells in the vertebrate inner ear. It has been reported that zebrafish LL afferent neurons exhibit SEA between 5 and 7 days post-fertilization. However its role in the assembly of LL sensory circuits is still unknown. To answer this question, we silenced electrical activity by stochastic expression of inward rectifier K+ channels in single LL afferent neurons and analysed the resulting phenotype under a confocal microscope. Suppression of SEA in single LL afferent neurons led to anomalous growth of axon arbors in the developing hindbrain and errors in neuromasts innervation. Our results provide an in vivo demonstration of the role of SEA in the correct assembly of the LL system.

P104.-Trafficking of ASIC1a channels between cellular compartments: role in neuroinflammation

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Interleukin 6 (IL-6) is one of the main neuroinflammatory cytokines in the central nervous system (CNS). CNS IL-6 is upregulated when neuroinflammation occurs, determines changes in metabolic activity and can result in acidosis. Changes in regional pH levels in the brain have been observed in a number of neurological and neurodegenerative disorders. ASIC (Acid sensing Ion) channels are sodium channels activated by tissue acidosis and thus become active in many pathological conditions. ASIC1 is the most abundant ASIC subunit in the mammalian CNS, permeate sodium and slightly calcium ions and could contribute to intracellular calcium levels and neuronal injury in pathological conditions. We decided to analyze the role of IL-6 on ASIC1 channels. We established a method to analyze the presence of the channel in the different cellular compartments. Our preliminary results show that IL-6 determines the redistribution of ASIC1 channels to the plasma membrane of the cells and an increase in calcium currents via ASIC1. Also, we studied dissociated mouse hippocampal cultures. We incubated it with IL-6 and did inmunocytochemistry of the samples to detect ASIC1 and used calcium-sensitive dyes and ASIC1 blockers to detect calcium currents posterior to ASIC activation. These results point at a mechanism by which neuroinflammation could contribute to neurodegeneration and ASIC1 as a potential target in these conditions and a method to analyze proteins in the different cell compartments.

P105.-α-synuclein overexpression triggers a lipid metabolic switch: lipid droplets as an early marker of neurodegeneration

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Pathological accumulation of α-synuclein (α-syn) is a hallmark of Parkinson 's disease. α-syn is highly expressed in the brain and has the intriguing characteristic of interacting with lipids. However, little is known about its biological role. We demonstrated that α-syn overexpression downregulates neurofilament expression (NF) through the modulation of phosphatidic acid signaling (Conde et al, 2018). Here, we studied lipid metabolism in neuroblastoma cells either stably transfected with pcDNA3 vector (as a transfection control) or pcDNA-WT-α-syn (WT α-syn). WT α-syn neurons displayed an increase in triacylglycerides (TAG) and cholesterol content consequently with lipid droplet (LD) accumulation. α-syn overexpression also triggered SREBP-2 nuclear translocation coincidently with this lipid metabolic switch. Enhancers of α-syn aggregation (iron, manganese and bortezomib) increased LD content. WT α-syn overexpression also induced Acyl-CoA synthetase activation which explained, at least in part, the increase in TAG, a rather unusual occurrence in healthy neurons. Pharmacological inhibition of TAG synthesis turned the neurons more vulnerable to the presence of WT α-syn. Additionally, NF recovery increased the expression of cleaved caspase 3. In conclusion, α-syn modulates neuronal lipid biology together with the loss of NF as part of a neuroprotective strategy.

P106.-Spleen alterations and increased brain CD4+ lymphocytes after pilocarpine-induced Status Epilepticus (SE)

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Epilepsy is one of the most frequent neurological diseases worldwide. A high percentage of patients with temporal lobe epilepsy (TLE) refer an initial precipitating event, such as febrile seizures, during childhood, followed by a silent latency period (LP), until the onset of the chronic seizures phase. In an experimental model of TLE, we have previously shown that neurodegeneration, reactive gliosis and macrophages brain infiltration occur during the LP and that early interventions limiting glial and immune activation during the LP increase epileptic threshold during the chronic phase (Rossi et al., 2013; 2017). We here studied the immune cells participation in the LP that follows pilocarpine-induced SE. Male Wistar rats were treated with lithium-pilocarpine (127 mg/kg /30 mg/kg) developing SE that were limited to 20 min by 20 mg/kg i.p. diazepam. After 3DPSE (days post-SE), blood and spleen smears stained with May-Grünwald Giemsa as well as splenocytes cultures of 3DPSE showed an increase in relative abundance of plasmocyte-like cells. Histological analysis of spleen sections showed increased cell density in the spleen white pulp and brain sections presented increased abundance of CD4+ lymphocytes in the choroid plexus as well as CD4+infiltrating cells in brain parenchyma. Our results suggest that peripheral immune system is probably responding to brain-derived clues released by the SE. Supported by PICT 2015-1451; UBACYT; and FONCYT fellowship (PS).

P107.-Impact of early overfeeding on the transcriptional regulation of genes associated with food intake control

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Nutritional environment is critical during perinatal period and could impact in health in adult life. Litter size reduction is a good experimental model for the study of early overfeeding and obesity. Our aim was to analyze the effects of early overfeeding on the brain control of food intake in rats at postnatal day (PND) 21. Male offspring were divided in 2 experimental groups: small litter (SL, n=4) or normal litter (NL, n=10), from PND3 to PND21. On PND21, animals were sacrificed and the body weight and epididymal fat pad (EFP) were measured. Micropunch technique was used to isolate specific nuclei from rat brains. Energy intake control neuropeptides and mesolimbic dopaminergic related genes were measured by RT-PCR and their epigenetic control were analyzed (N=10/group). Our results showed than the SL group had higher body and EFP weights than the NL group. Moreover, SL rats showed changes in the expression of: a) anorexigenic and orexigenic neuropeptides on specific nuclei of the hypothalamus; and b) mesolimbic dopaminergic related genes in ventral tegmental area and nucleus accumbens. Changes in gene expression were related with the methylation status of their promoter regions, suggesting that the SL group developed an anorectic signal in different regions of the brain controlled by methylation-related mechanisms. Overfeeding during lactation triggered an epigenetic control of genes related with food intake, regulating the body energy balance in SL animals at weaning.

P108.-Contribution of neural crest derived cells and GLAST+ pericytes to liver fibrosis

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Background: Little is known regarding the contribution of neural crest-derived cells (NCDCs) to the liver in health and disease. The aim of this work was to analyze the contribution of NCDCs and GLAST+ pericytes to the liver during fibrogenesis. Methodology: Wnt1Cre2;R26RTom and GLASTCreERT (2);R26RTom mice were used. Two models of liver cirrhosis were applied: 1) chronic applications of thioacetamide and 2) bile duct ligation. Contribution of NCDCs to liver was analyzed. Results: Wnt1Cre2;R26RTom animals showed a small number of NCDCs in the liver, corresponding to GFAP+ glia and hepatocyte-like cells (HLCs). GLASTCreERT (2);R26RTom contributed to small numbers of desmin- pericytes as well as HLCs, but not to GFAP+ glia; Tom+ HLCs were only found when tamoxifen (Tx) was injected at postnatal day (P)-2 and not at P60. Fibrogenesis was found to induce a significant increase in the incidence of glia, HLCs in Wnt1Cre2;R26RTom mice. A 2 week-treatment with TAA was found to increase CD44+ GLAST+ Tom+ cell numbers in the peripheral blood of Wnt1Cre2;R26RTom mice and to decrease such stromal population within the bone marrow. Consistently, total and Tom+ CFU-F numbers were also reduced in the bone marrow of those animals. Conclusions: Glia cells numbers increase with fibrogenesis. In addition, stromal NCDCs get likely mobilized from the bone marrow during this process. Finally, NCDCs and/or GLAST+ pericytes likely contribute with myofibroblasts in the fibrotic liver.

P109.-Kainate excitotoxicity in the spinal cord of female young and adult rats

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The understanding of the pathophysiology of the devastating effects of spinal cord injury have been the aim of numerous investigations using different experimental models. Kainic acid (KA) is a glutamate-agonist widely used to induce excitotoxic lesions in the CNS. Neuroprotective effects of estrogens against glutamate-induced excitotoxic assault are well-known. We have previously reported that aged female rats showed higher neuronal counting and serum prolactin levels in comparison to young female rats. In the present work, we aimed to compare the functional and histological changes between young (y) and adult (a) female rats after an intraparenchymal injection of 1 mM KA into the C5 segment of the spinal cord. Animals were grouped as KA-y/KA-a (injected with 1mM KA) and sham-y/sham-a (injected with saline). Histopathology and clinical evaluation using motor and sensitive tests (ladder rung walking test, suspension from wire pole mesh, von Frey nociceptive assay) were analyzed at day 0, 1, 2, 3 and 7 post injection (pi). KA-y/KA-a showed a significant impairment of their performance in the motor and sensitive tests at day 2 and 3 pi in comparison to sham-y/sham-a. Also, a reduced excitotoxic effect was observed in KA-a rats in comparison to KA-y rats. Controversial data are reported in reference to vulnerability to excitotoxicity during aging. Future studies will determine whether sex hormones and prolactin are involved in the reduction of KA neurotoxicity in adult females.

P110.-Inhibition of SIRT-1 reduces brain cholesterol synthesis

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A reduction in the expression/activity of SIRT-1 has been observed during aging in different tissues. While SIRT-1 can regulate many cellular processes including metabolism, the particular role of SIRT-1 in brain cholesterol metabolism remains unknown. In an attempt to emulate SIRT-1 loss of function in the aging brain, we inhibit SIRT-1 in primary cortical cultures and C57BL/6 mice. Cortical cultures treated with 1 µM EX-527, a SIRT-1 cell-permeable specific inhibitor (IC50 = 98 nM), showed a significant reduction in the levels of cholesterol, without noticeable changes in the levels of oxysterols, the main cholesterol-derived metabolites. In order to better understand this effect, the expression of cholesterol-related genes was evaluated using quantitative RT-PCR. SIRT-1 inhibition induced a repression of three key genes related to cholesterol homeostasis: HMGCR (synthesis), CYP46A1 (catabolism) and Apo-E (transport). Furthermore, C57BL/6 mice treated for 5 days with 10 mg/kg of EX-527 exhibited a similar reduction in the cholesterol content within the hippocampus. Lower levels of cholesterol upon treatment with EX-527 were also detected in synapses purified from mouse cortices. The reduced cholesterol levels in vivo were accompanied by repression of the transcription factor SREBP-2 and its target gene HMGCR. Altogether, these results suggest that SIRT-1 sustains cholesterol synthesis in the brain, and influences the synaptic cholesterol content.

P111.-The physiological role of the GTPase Rab21 in neuronal migration and the development of the cerebral cortex

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Abstract. The development of the complex structure of the mammalian neocortex requires the proper migration of developing neurons from the ventricular zone containing neural progenitors to the cortical plate. The precise coordination of different cellular processes such as cytoskeleton dynamics, membrane trafficking, and cell adhesion during migration is achieved by a variety of signaling pathways. GTPases play a central role in all these processes. In this context, the small GTPase Rab21 has been implicated in the regulation of cell adhesion dynamics by controlling the trafficking of endocytic vesicles containing adhesion molecules. Interestingly, Rab21 has been also implicated in neurite outgrowth. With the following project, we propose to study how Rab21 regulates sorting, traffic and endocytosis of adhesion proteins such as amyloid beta precursor protein (APP) and N-cadherin and elucidating its function in neuronal migration and the development of the cerebral cortex. These studies are important to better understand the mechanism governing the development of the cerebral cortex and the mechanisms that participate in neurodevelopmental pathologies such as autism spectrum disorders and cortical malformations.

P112.-Sex differences in gene expression of X-linked histone demethylase Kdm6a in embryonic hypothalamic neurons

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Kdm6a and Kdm5c are histone demethylases that play an important role as epigenetic regulators of gene transcription by removing the di- and tri-methylation of Lys27 or Lys4 on histone H3 (H3K27me2/me3 - H3K4me2/me3). Both demethylases are implicated in regulation of transcription during neuronal growth and differentiation, being possible to hypothesize that they may contribute to generate sex differences in brain since they are encoded by X-linked genes and escape X-chromosome inactivation. Using the Four Core Genotypes (FCG) mouse model, we first analyzed the expression of Kdm6a and Kdm5c genes by RT-qPCR in primary hypothalamic neuron cultures from E15. Only Kdm6a showed differences between genotypes, presenting higher levels of expression in XX than in XY neurons ($p<0.05$), regardless of the embryo sex. Estradiol 10-10 M did not affect such expression pattern in vitro. When we measured Kdm6a mRNA in the ventromedial hypothalamic region of adults, we found only XX males presented higher levels than the other three genotypes. We next evaluated the effect of Kdm6a/b activity inhibitor GSK-J4 on the sexually dimorphic expression of neurogenin 3 (Ngn3), a gene involved in the neuritogenesis of cultured hypothalamic neurons. Our preliminary results showed that GSK-J4 diminishes Ngn3 expression only in male cultures. Further experiments are required to better understand the role of Kdm6a in generation of sex differences in growth and differentiation of hypothalamic neurons.
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P113.-Peripheral nerve regeneration promoted by adipose-derived stem cell (AdSC) magneto targeting

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Wallerian degeneration (WD) is an efficient animal experimental model in mimicking the impact of peripheral nerve lesion to shed light on possible regeneration strategies. AdSC transplant is a useful tool for regenerative therapies, while magneto targeting is a nanotechnological strategy to mobilize magnetic nanoparticle (MNP)-loaded cells to a specific tissue guided by an external magnetic field.

In this context, the aim of the present work was to test whether AdSC-MNP magneto targeting can enhance the regenerative ability of AdSC upon rat sciatic nerve lesion.

To this end, cultured AdSC were characterized for multipotent cell marker expression. MNP internalization was evaluated through transmission electron microscopy and vibrating sample magnetometry (VSM) experiments. Likewise, epifluorescence microscopy and VSM analyses were performed to evaluate the arrival of AdSC-MNP at the injured nerve. Finally, AdSC-MNP transplantation effects on nerve morphology and conduction were evaluated through immunofluorescence, Western blot and electrophysiological experiments.

Our results show that AdSC express CD105, CD90 and CD34, and can internalize 2 to 4 pg MNP/cell. We demonstrate AdSC-MNP to supersede AdSC arrival exclusively at the lesion site, exerting beneficial effects on nerve morphology and conduction.

In short, our results prove that AdSC-MNP magneto targeting constitutes a valuable tool to enhance AdSC arrival at the lesion site and consequent nerve regeneration.

P114.-Mechanisms of neuronal degeneration induced by β-N-methylamino-L-alanine (BMAA)

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The non-proteic aminoacid BMAA is released by many cyanobacteria present in most dams and water resources around the world. Human chronic intake of this toxin has been linked with the development of Amyotrophic Lateral Sclerosis, Parkinson and Alzheimer Disease. We here investigated its effects on pure neuronal and mixed neuro-glial cells cultures, obtained from newborn rat retinas. Cultures were incubated with BMAA (400 nM) for 5 days. Apoptosis and cell death were evaluated by DAPI and Propidium Iodide (PI) staining; mitochondrial activity by Mitotracker labelling and cytoskeleton integrity and axonal outgrowth by immunocytochemical methods. In pure neuronal cultures BMAA increased the percentage of apoptotic amacrine and photoreceptor neurons, from 22% to 45% and from 33% to 49%, in controls and BMAA-treated cultures, respectively. Noteworthy, functional mitochondria decreased significantly in amacrine neurons, and only slightly in photoreceptors. In addition, BMAA disrupted the organized assembly of tubulin in axons. In neuro-glial cultures, BMAA induced lamellipodia retraction and loss of mitochondrial membrane potential in glial cells, without increasing glial cell death. Noteworthy, glial cells partially prevented BMAA-induced neuronal death. This suggest that BMAA induces subcellular changes in both neurons and glial cells, and markedly affects the viability of retinal neurons, confirming its threat to human health as a potential inducer of neurodegenerative damages.

P115.-EphA3 ectodomain and GDNF regulate axon growth and guidance of retinal ganglion cells

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The Eph/ephrin system participates in the chicken retinotectal mapping. We showed that: Tectal EphA3 stimulates axon growth of nasal retinal ganglion cells (RGC) toward the caudal tectum preventing them from branching in the rostral tectum. Ephrin-A-mediated EphA4 forward signaling decreases axon growth of RGC whereas the tectal EphA3 produces the opposite effects by decreasing the EphA4 signaling by competing with EphA4 for ephrin-As binding. GDNF stimulates motor neurons axon growth binding to GFRalfa, RET functions as correceptor of GFRalfa and binds to ephrin-A5. Thus, RET integrates the effects of GDNF on GFRalfa and of EphA4 through ephrin-A5.

Our purpose was to study the individual and combinatorial effects of EphA3 and GDNF on axon growth and guidance.

We cultured chicken embryo retinal explants exposed to control conditions, to EphA3 ectodomain (EphA3-Fc), to GDNF or to EphA3-Fc plus GDNF to evaluate their effects on axon growth and guidance using stripe assay.

The results showed that: Decreased ephrin-A-mediated EphA4 forward signaling by EphA3-Fc increases nasal RGC axon growth and has an axon guidance effect. GDNF increases RGC axon growth and decreases EphA4-ephrin-A2 colocalization as EphA3-Fc does. EphA3-Fc plus GDNF increase axon growth more than EphA3-Fc and GDNF alone. This suggests that EphA3 and GDNF potentiate nasal RGC axon growth and that decrease of ephrin-A-mediated EphA4 signaling could participate in the effects of both of them.

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P116.-Extracellular Galectin-3 induces accelerated oligodendroglial differentiation through changes in actin dynamics and Akt - mTOR signalling pathway

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Galectin-3 (Gal-3) is a chimeric protein structurally composed of unusual tandem repeats of proline and short glycine-rich segments fused onto a carbohydrate recognition domain. Our studies have previously shown that Gal-3 drives oligodendrocyte (OLG) differentiation. Cytoskeleton plays a key role in OLG maturation: early OLG process extension requires dynamic actin filament assembly, while subsequent myelin wrapping concurs with actin disassembly protein upregulation dependent on MBP expression. In this context, the present work aimed to elucidate the mechanism underlying recombinant Gal-3 (rGal-3)-mediated effect on OLG maturation, focusing on the actin cytoskeleton and Akt-mTOR signaling pathways. Our results showed rGal-3 to induce early actin filament assembly, accelerating the shift from polymerized to depolymerized actin between treatment day (TD) 3 and TD5. Significant increases in MBP, gelsolin, rac1, rac1-GTP, and β-catenin expression at TD5 were observed. Furthermore, western blot studies revealed Akt signaling activation at TD1 and TD3, mTOR and mTOR substrates 4EBP1 and p70SK6x phosphorylation, and Erk 1⁄2 deactivation at all times evaluated. These results were strongly supported by assays using Erk 1⁄2, Akt and mTOR inhibitors, which shows these pathways' key role in rGal-3-mediated effects. Altogether, these results indicate that rGal-3 accelerates OLG maturation by modulating signaling pathways and protein expression involved in actin cytoskeleton dynamics.

P117.-ASSESSING THE NEURONAL ROLE IN HIPPOCAMPAL HYPOCONNECTIVITY IN THE VPA MODEL OF AUTISM

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Autism spectrum disorders are characterized by impairments in social interaction and repetitive-stereotyped behaviours. Applying the VPA model, we reported in the hippocampus of juvenile VPA rats: a decrease in synaptophysin (SYN) along with an increased expression of the neural cell adhesion molecule (NCAM) and a decrease in its polysialylated form (PSA-NCAM). The aim of this study was to evaluate synapse formation and remodeling of primary hippocampal neurons from VPA or control male pups. Cytoskeletal and synaptic markers were evaluated by immunocytochemistry and WB. Neurons from VPA animals displayed a reduced dendritic tree (reduced MAP2 area), a reduced number of glutamatergic synapses (decreased vGLUT and PSD-95 puncta number) and NMDA receptor clusters (decreased NR1 puncta number and individual puncta area). These neurons exhibited reduced number of functional synapses (FM4-64 labelling) which contained smaller vesicular pools; total NCAM expression increased while PSA-NCAM decreased. While in neurons from control animals glutamate (5µM-3min) induced an NMDA-dependent dendritic retraction and SYN puncta number reduction, neurons from VPA animals were only capable of dendritic retraction without any change in synapse number. Our results indicate that neurons from VPA animals form fewer glutamatergic synapses that exhibit a more adhesive and resistant profile to synaptic remodeling what would contribute to hippocampal hypoconnectivity and reduced synaptic plasticity.

P118.-Yerba mate tea and Parkinson's disease. Neuroprotective effect on dopaminergic neurons in an animal model

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Parkinson's disease (PD) is the second neurodegenerative disease with a wide range of prevalence worldwide. The neurodegenerative process primarily affects the dopaminergic neurons of the substantia nigra. Since the mechanisms that underlie this neuronal degeneration have not been fully clarified, currently there is no preventive therapy for PD. However, a case-control study in Argentina revealed that consumption of yerba mate (YM) has an inverse association with the risk of developing PD. YM consumption is widely popular in the countries of the Río de la Plata. It has been shown to provide numerous health benefits, strongly related to its variety of bioactive phytochemicals. We propose to characterize the extract of YM and to evaluate if the consumption of YM provides a benefit on the survival of dopaminergic neurons in a mouse model of PD. The extract of YM was obtained by 'cebada simulada' and the concentrations of the main bioactive components were quantified by HPLC. Wild type mice received water or 'mate' as their only source of fluid for 4 months before receiving an intrastriatal injection of 6-OHDA, and continue 1 month with treatment. It was found that mice treated with YM have a density of dopaminergic remaining fibers in the striatum 12% higher than the control mice. Our results suggest that this neuroprotective effect could be beneficial to slow the evolution of the neurodegenerative process experienced by dopaminergic neurons in people suffering PD.

P119.-High plasticity of new granule cells in the aging hippocampus

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The aging brain displays a generalized decline in cognitive capacity and circuit plasticity, including a marked decrease in production of adult-born hippocampal neurons. In previous studies we have shown that morphological development of new dentate granule cells (GCs) is affected by age. However, their functional properties and integration to the circuit along maturation remains unclear. We performed whole-cell recordings in 8-month old Ascl1(CreERT2);CAG(floxStopTom) mice to measure intrinsic properties, firing behavior and afferent excitatory connectivity in adult-born GCs labeled with Tomato. We found that the functional properties and connectivity of these neurons also develop in a slow manner.

Despite the delayed maturation, new GCs in aging mice display a remarkable potential for structural plasticity. Retrovirally labeled 3-week-old GCs in middle-aged mice are small, underdeveloped and disconnected. Notably, enriched environment and voluntary exercise induced substantial dendritic growth and spine formation. To investigate whether these physiological stimuli could also modulate output connectivity, we analyzed axonal branching in the hilus and CA3-boutons morphology. We found that mice exposed to the running wheel for 21 days presented a higher number of axonal ramifications in the hilus and a 2-fold increase in the number of filopodia of CA3 boutons. This results indicate that not only does running accelerate input integration but also boosts output connectivity.

P120.-GABAergic proopiomelanocortin neurons regulate energy balance through an arcuate - dorsomedial hypothalamic circuit

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The arcuate nucleus is a key regulator of energy homeostasis where different neuronal populations integrate peripheral signals of energy status, and project to the hypothalamus and other brain areas. In particular, arcuate proopiomelanocortin (POMC) neurons inhibit food intake and promote energy expenditure. POMC neurons co-secrete either glutamate (7%) or GABA (40%). Considering the antagonic responses these neurotransmitters elicit, we hypothesize that both subpopulations have different physiological roles. In order to elucidate the role of GABAergic POMC neurons, we intercrossed hyperphagic and obese mice bearing a reversible mutation that prevents arcuate POMC expression, with another line expressing a GABA-specific Cre driver. We found that Pomc rescue restricted to GABAergic neurons leads to food intake and metabolic efficiency normalization. Surprisingly, these physiological improvements were achieved with the recovery of Pomc expression in only 25% of total hypothalamic POMC neurons. Immunohistochemical analysis showed that GABAergic POMC neurons preferentially project to the dorsomedial hypothalamus (DMH), a nucleus that induces food intake by releasing NPY. Interestingly, we found NPY expression in the DMH of POMC deficient but not of WT mice. Finally, NPY expression is highly reduced after POMC recovery. Altogether, these results show that GABAergic POMC neurons have a major role in the regulation of energy balance, probably by regulating NPY expression in the DMH.

P121.-Rol of Retinoid X Receptors on survival and modulation of inflammatory response in a mouse model of Retinitis Pigmentosa

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Retinal neurodegenerative diseases, which have no effective treatments, share as a final common step the photoreceptor cells (PhR) death. Also inflammation has a role in these pathologies. Retinoid X receptors (RXR) have the capacity of modulate and integrate multiple cell functions; and their activation has shown beneficial clinical effects in animal models of chronic inflammatory diseases. In this work we assessed whether this receptors might prevent PhR death and/or inflammation.

Using rd1 mice, we analyze in vivo and in vitro the roles of RXR in retina degeneration. Here, we show, by qRT-PCR analysis, that the alpha isoform levels are decreased in rd1 mice retina respect to their wt counterparts, in concordance with our previous data obtained by immunohistochemistry from retina slices. Noteworthy, RXR activation modulated the mRNA levels of all three RXR isoforms in mixed neuroglial cultures from rd1 retina. Moreover, it also delayed the onset of PhR apoptosis, analyzed by TUNEL assay,and decreased Bax mRNA levels; also decreased GFAP expression of both mRNA and protein level, in Müller glial cells (MGC). Therefore we evaluate whether RXR could regulate anti-inflammatory response in the retina. Our preliminary results suggest that RXR activation increased the transcription of IL-10 in rd1 mixed neuroglial cultures.

As a whole, the activation of RXR could promote survival of PhR eith.er by direct action on them, or indirectly by modulating the inflammatory response of MGC.

P122.-INTER-HEMISPHERIC HYPO-CONNECTIVITY AND REGIONAL METABOLIC HYPER-ACTIVITY IN AN EXPERIMENTAL MODEL OF AUTISM

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Autism spectrum disorders (ASD) are a group of neurodevelopmental disabilities characterized by alterations in brain connectivity and neuroinflammation. In accordance with the long-distance hypo-connectivity and local hyper-connectivity hypothesis, previous studies in our laboratory with the valproic acid (VPA) model demonstrate connectivity alterations and reactive gliosis in the prefrontal cortex and hippocampus of VPA rats. The aim of this work was to evaluate the brain metabolic activity and the structure of the corpus callosum (CC) in VPA animals. For this purpose, glial cells in the CC were studied at PND 36 by CC1, PDGFαR, GFAP and tomato lectin staining. Also, CC ultrastructure was assessed by electron microscopy (EM). Evaluated by positron emission tomography, glucose uptake was increased in local areas along the brain of VPA rats, while it was decreased when considered the whole forebrain. In the CC of VPA rats, the number of CC1+ cells diminished and number of PDGF+ cells increased, in the absence of astrogliosis or microgliosis. Concomitantly, EM showed less myelinated axons and aberrant myelin in the CC of VPA rats. To sum up, VPA animals exhibit hyper-metabolism in circumscribed brain areas along with global hypo-metabolism. Concurrently, CC myelination in VPA animals is disrupted, accompanied by an altered balance in the oligodendroglia lineage. Taking together, our findings support the local hyper-activity and long-distance hypo-connectivity hypothesis in ASD.

P123.-Neurorestorative and protective effects of palmitoylethanolamide in perinatal asphyxia: an analysis of the rat striatum

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Perinatal asphyxia (PA) caused by low O2 availability during birth is associated with brain damage, been the striatum one of the most affected areas. Palmitoylethanolamide (PEA) is a neuroprotective amide in brain injury models, including PA. However, its effects against PA requires deeper study in the striatum. Using Bjelke' model, full-term pregnant rats were rapidly decapitated, and uterus horns placed in a water bath (37C,19 min). One hour after, rats were treated with PEA (10 mg/kg,s.c.) and later given to surrogate mothers. Thirty day animals were perfused and striatum was analysed either for immunohistochemistry (n=3) and blotting (n=3). Phosphorylated high/medium molecular weight neurofilaments (pNF-H/M), Microtubule-Associated Protein 2 (MAP2), and Glial fibrillary acidic protein (GFAP) were analysed. 2-way ANOVA followed by Tukey analysis revealed a reduction in: pNF-H/M and MAP2 reactive areas (45% and 70%), GFAP+ cells (20%) and reduced MAP2 and pNF-H/M protein levels in PA-rat striatum respectively to the control value. PEA totally restored GFAP+ cells and MAP2 immunoreaction and partially prevented the decreased pNF-H/M reactive area (78%) induced by PA. PEA also reversed the MAP2 reduction and partially prevented the decrease of pNF-H/M protein levels induced by PA. No alteration in the GFAP protein levels was detected. PEA treatment attenuated the striatum damage induced by PA, demonstrating its therapeutic potential against PA.

P124.-A defective crosstalk between neurons and Müller glial cells impairs glial stem cell regenerative capacity in the rd retina

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Müller glial cells (MGCs) are stem cells in the retina. Their regenerative capacity is high in lower vertebrates, but it is very low in mammals and cannot restore photoreceptor losses during retina degeneration, such as in retinitis pigmentosa or its animal model, the rd mice. Since rd retinas show no evidence of neuronal renewal, we hypothesize that, in addition to the low regenerative capacity of MGCs and the molecular abnormalities of rd photoreceptors, the rd MGCs may have alterations affecting even more deeply their stemness potential. We here investigated whether MGCs in rd retinas present abnormalities altering their regenerative capacity. We analyzed MGC in mixed neuro-glial cultures and in slices obtained from newborn “rd” and normal (wt) retinas. We demonstrated that rd MGCs had alterations in stem cell markers compared to wt MGCs, showing reductions in Nestin and Sox2 expression and significantly decreasing their cell cycle. They also evidenced significant morphological changes in their nuclei. We evaluated whether neuro-glial crosstalk might be responsible of these changes. Noteworthy, when we co-cultured rd MGCs with wt neurons, Nestin expression was restored in rd MGCs. Conversely, in co-cultures of wt MGCs with rd neurons, Nestin expression in MGCs decreased. These results suggest that the mutations in rd photoreceptors lead to a disruption in neuro-glial crosstalk, affecting the proliferative and regenerative capacities of rd MGCs.

P125.-Dynamics of GABABR and associated proteins in the postnatal rat cerebellum

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Before glutamatergic synapses are formed, GABA-mediated signaling is considered to drive cell differentiation in the developing central nervous system (CNS). GABA, a classical inhibitory neurotransmitter, can also depolarize immature cells. Although this shift is mediated by the ionotropic GABA A receptor (GABAAR), recent evidence suggests that the electrical properties of GABAARs can be modulated by the metabotropic GABA B receptor (GABABR). GABABRs are macromolecular complexes, formed by a G protein-coupled receptor and a large number of constituents that interact together and ultimately influence cell identity and behavior. The composition of these complexes exhibits wide spatiotemporal variations; however, the implications of such dynamism during development of the CNS are far from being understood. We have determined total protein expression of some constituents of GABABRs (GABABR1a; GABABR1b, GABABR2; KCTD12) in the developing cerebellum of postnatal rats at 5, 15 and 90 days after birth, by performing Western Blots. Our findings suggest that the expression levels of the core and auxiliary subunits of GABABRs vary ontogenetically. This dynamism was also observed at the mRNA levels by RT-PCR. In addition, multiple immunolabeling followed by confocal microscopy of cerebellar sections showed Purkinje cells as the most dynamic cell type in terms of subcellular localization of the different molecules studied here. Our data support a cell lineage-dependent GABABR regulation.

P126.-Neuron-specific expression of Drd2 is directed by multiple transcriptional enhancers in the mammalian brain

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The dopamine D2 receptor (D2R) is expressed in several brain areas where it plays essential roles in motor, emotional and cognitive functions. To identify the transcriptional mechanisms controlling cell-specific expression of the D2R gene (Drd2), we tested the ability of genomic regions carrying potential enhancers to activate the expression of the fluorescent protein Tdimer2 in the brain of transgenic mice. We have detected an intronic region containing four evolutionary conserved elements which can act as transcriptional enhancers in the striatum or in midbrain dopaminergic neurons. To investigate the in vivo importance of these enhancers we generated mice carrying deletions of the conserved elements located in the first intron of Drd2 using CRISPR/Cas9 genetic editing. We found that deletion of individual enhancers fails to ablate Drd2 expression in the striatum, in agreement with results obtained in transgenic mice showing that Drd2 expression in this area is directed by several elements. In addition, elimination of an enhancer identified to drive Drd2 expression to the midbrain is not sufficient to prevent transcription in these neurons, evidencing that Drd2 expression in midbrain neurons is also activated by at least two different elements. Our results indicate that neuron-specific expression of Drd2 in the striatum and midbrain is driven by the concerted interaction of multiple partially redundant enhancers some of which are located within the first intron of the gene.

P127.-Inhibition of colony-stimulating factor 1 receptor through BLZ945: impact on remyelination, neurodegeneration and behavior

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Cuprizone (CPZ)-induced demyelination is frequently used to study the de/remyelination processes as a multiple sclerosis (MS) model. Chronic CPZ induces oligodendrocyte loss, neuronal death, astrocytosis and microgliosis. Microglia (MG) participate in demyelination and neurodegeneration processes and are physiologically dependent on colony-stimulating factor 1 receptor (CSF-1R) signaling. The aim of this study is to evaluate the effects of BLZ945 –a CSF-1R inhibitor which significantly reduces the number of MG– on remyelination and behavior in mice submitted to a chronic CPZ model. Mice were fed either control or CPZ (0.2% p/p) chow for twelve weeks, administered BLZ945 (200 mg/kg/day, oral gavage) or vehicle during ten weeks (C, BLZ945, CPZ and CPZ+BLZ945, respectively), and evaluated in the twelfth week of CPZ treatment. Although other authors reported CPZ-induced changes in locomotion and working memory, our preliminary results showed no significant differences across groups in open field, accelerated rotarod and locomotor activity behavior. In contrast, assays on MBP immunoreactivity and NeuN+, AβPP+ and Neurotrace+ cell number showed significant demyelination upon CPZ. In addition, a significant decrease was observed in neurodegeneration in CPZ+BLZ945 regarding CPZ mice. Positive results from these experiments could be transferred to the treatment of progressive forms of MS, an urgent and still unmet medical need.

P128.-Post-translational incorporation of L-Dopa into the C-terminus of α-tubulin in living cells affects microtubule dynamics and mitochondrial traffic

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The C-terminal tyrosine (Tyr) of the α-tubulin is post-translationally removed and re-added in a process termed detyrosination/tyrosination cycle. We showed previously, using soluble rat brain extracts, that L-Dopa is incorporated into the same site as Tyr. We now demonstrate that L-Dopa incorporation into tubulin also occurs in living cells. We detected such incorporation by determining the "tyrosination state" of tubulin before and after incubation of cells in the presence of L-Dopa. The presence of a tubulin isospecies following L-Dopa incubation that was not recognized by abs specific to Tyr- and Glu-tubulin was presumed to reflect formation of Dopa-tubulin. L-Dopa was identified by HPLC as the C-terminal compound of the α-tubulin. L-Dopa incorporation into tubulin was observed in several cell lines and did not alter cell viability, morphology, or proliferation rate. CAD cells were cultured under differentiating conditions and treated with L-Dopa, resulting in a reduction of microtubule dynamics in neurites, most likely due to L-Dopa incorporation into tubulin. Rat hippocampal neurons treated with L-Dopa showed a reduced mitochondrial traffic along axonal microtubules, may be due to an abnormal interaction between L-Dopa-microtubules and molecular motors which participate in organelles transport. We hypothesized that these alterations could be associated with movement disorders sometimes observed in patients treated with L- Dopa for prolonged periods.

P129.-It's time to be motivated: circadian modulation of motivation for food rewards

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In mammals, the circadian clock is mainly synchronized by the light-dark (LD) cycle, and regulates several physiological, behavioral and molecular rhythms like activity-rest, feeding, and gene expression.

Food intake is regulated by a homeostatic and a hedonic mechanism. Hedonic food consumption has strong effects in the central reward system stimulating striatal dopaminergic signaling pathways. In addition, evidence suggests that the dopamine D2 receptor (DRD2) plays an especially important role in this regulation.

In this work, we present evidence that motivation for food reward (normal pellets) varies dramatically with the LD cycle in young (4-months old) but not in old-aged (over 1.5 years old) C57BL/6 mice. This variation is consistent with a daily oscillation in the striatal DRD2 content, both at mRNA and protein level, in young mice under LD but not constant light (LL) conditions. This variation in motivational behavior was also assayed under constant dark (DD) conditions, in order to evaluate the possibility of an endogenous rhythmicity. Finally, the effect of the circadian clock on motivation was also studied by using a palatable reward (chocolate) under a protocol without food restriction.

Taken together, our results of daily rhythms in motivation and dopamine signaling may contribute to improve treatment related to psychiatric disorders or drugs of abuse. This knowledge would also be of great importance in order to plan behavioral experiments in animal models.

P130.-Dietary restriction promotes tissue-specific reprogramming of circadian gene expression

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Caloric restriction (CR) extends lifespan in many species, yet the mechanisms are unclear. Our previous studies showed that CR protocols involve a 2h-temporal restricted (TR) feeding followed by 22h of fasting, all of which impact on health. Thus, it is unclear whether the timing, frequency or amount of food intake is the critical factor that improves metabolic fitness. Here, we investigated how feeding conditions modulate the circadian (24h) profile of gene expression in the hypothalamus and 3 major metabolic tissues: liver, white and brown adipose tissues. We developed an automated feeders to fed mice either during the day or the night, with or without 30%CR.

We found complex tissue-specific circadian changes in mRNA expression induced by both timing and amount of food intake. While feeding time determined the circadian profile of core clock genes in the liver and WAT, it did not affect expression in the BAT and hypothalamus. Remarkably, despite the core clock machinery remaining unchanged; the profile of metabolic genes such as leptin followed feeding time in BAT. Thus, revealing misalignment within the BAT. Altogether, these results show that metabolic tissues integrate environmental (feeding and day/night cycles) and systemic signals in a tissue-specific manner.

Integrating these tissue-specific signatures with metabolic outcomes may help elucidate the mechanism by which dietary restriction extends longevity, revealing a link between circadian clocks and healthy aging.

P131.-Deregulation of cell cycle and immune response in a mice model of tumor development under circadian desynchronization

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Circadian disruption by shift work and jet-lag has been established as a health hazard both in humans and animal models. The aim of this study was to analyze the tumor growth in mice under chronic jet lag (CJL, 6 hours advances of the LD cycle every two days), using a melanoma model induced by a subcutaneous injection of the murine B16 cell line. We found an increased tumor growth rate and a decreased latency in comparison with mice maintained in a LD12:12 cycles. We also observed that circadian disruption induced the loss of clock genes Bmal1 and Cry1 rhythmic expression as well as the cell-cycle genes Cyclin E and B1 in liver, together with about 6-h delay of their maximum levels. In the tumor, both clock genes and cyclins did not show a rhythmic expression pattern, but the mean levels of clock genes were decreased while Cyclin A2 levels were increased under the CJL conditions. Circadian disruption also abolished the rhythmic pattern of the cell-cycle inhibitor p21 both in liver and in tumor. Finally, we analyzed the immune response in spleen and tumor, and found that the daily pattern in the percentage of M1 (anti-tumoral) and M2 (pro-tumoral) macrophages and in the levels of proinflammatory cytokine were modified under the CJL conditions. In summary, we observed an increased tumoral growth rate together with a circadian deregulation in the mRNA levels of the cell cycle related molecules and in the immune response both in the tumor and in the peripheral tissue.

P132.-Differential thermoregulatory and inflammatory patterns in the circadian response to LPS-induced septic shock

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Septic shock is a lethal condition caused by a pathogen-induced chain of events. The same dose of lipopolysaccharide (LPS) inducing septic shock in mice generates survival at the night (ZT19), while it is lethal at the end of the day (ZT11). A similar effect was observed with cytokine Tumor Necrosis Factor-α (TNF-α) administration. In this study, we aim to characterize the circadian response to high doses of LPS in mice. We found higher hypothermia in mice treated with LPS at ZT11, than those at ZT19. Both hypothalamic preoptic and paraventricular nucleus activation was significantly higher after LPS administration at ZT11 (vs. ZT19). When we injected naïve animals at ZT11 or ZT19, with the serum of animals inoculated with LPS at ZT11, we observed the same daily pattern in thermal response. Increased serum levels of TNF-α were found in mice injected at ZT11, whereas Tnf-α mRNA expression was higher in the liver of animals treated at ZT19. Moreover, mice that lack the receptor 1 for TNF-α showed a greater survival and a lower hypothermia compared to WT mice injected at ZT11. The same thermal response appeared in mice subjected to circadian desynchronization, but the survival percentage of both groups was similar to that challenged at ZT11 in standard light conditions. These results suggest a circadian dependency of the central thermoregulatory and peripheral inflammatory response to septic-shock, being TNF-α signaling likely related to this circadian response.

P133.-Circadian study of antioxidant defense system in the hippocampus of aged rats subjected to caloric restriction

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Oxidative stress plays a critical role in brain aging. Caloric restriction (CR) is the most accepted approach to slow the aging process and delay many age-related diseases. Previously, we showed circadian rhythms in the expression and activity of antioxidant enzymes in the hippocampus of young rats, that were abolished in the old animals. In the present work, we investigated temporal patterns of catalase (CAT) and glutathione peroxidase (GPx) expression and activity, as well as Nrf2 mRNA levels, in the hippocampus of aged rats under CR. Holtzman male rats were fed with a diet reduced by 40% in calories during the last 3 months prior to the 22 months of age. The mRNA levels were determined by RT-PCR and the enzymatic activity were evaluated by kinetics assays in hippocampi isolated every 4 h during a 24h-period. Interestingly, we observed CR restored the circadian rhythmicity of all the studied parameters (Chronosfit: $p<0.05$). In addition, CR accentuated the rhythms of the amplitudes and the mesor of both CAT and GPx (t-Test: $p<0,05$ and $p<0,05$, respectively), and the Nrf2 mesor (t-Test: $p<0,05$). CR restores the 24h-patterns of antioxidant defenses in aged animals. Restoration of temporal coordination could be one of the basis of CR efficiency and provide promising prospects against neurodegenerative diseases and cognitive decline.

This work was supported by PICT 2010-1139-ANPCyT and PROICO 2-0314-UNSL, Argentina.

P134.-DAILY RHYTHMS OF Aβ-DEGRADING ENZYMES IN THE RAT HIPPOCAMPUS. EFFECT OF AN I.C.V. INJECTION OF AMYLOID BETA PEPTIDE (1-42) AGGREGATES

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One of the main pathological features in the Alzheimer disease (AD) is the presence of senile plaques, primarily composed of Aβ peptide aggregates, in cortex and hippocampus. AD late onset, which constitutes 90% of cases, could be mainly attributable to deficiencies in the clearance of the Aß peptide. The objective of this work was to investigate the effects of an i.c.v. injection of Aβ (1-42) aggregates on the 24h rhythms of Aβ-degrading enzymes as well as Aβ, BMAL1 and RORα protein levels, in the rat hippocampus. Four-month-old male Holtzman rats were divided into two groups defined as: control (CO) and Aβ-injected (Aβ). Rats were maintained under12h-light:12h-dark conditions and received water and food ad libitum. Tissues samples were isolated every 6 h during a 24h period. NEP, ECE and IDE mRNA levels were determined by RT-PCR and Aβ, BMAL1 and RORα protein levels were analyzed by immunoblotting. Interestingly, we found that expression of Aβ-degrading enzymes varies on a daily basis in the hippocampus and that an i.c.v. injection of Aβ aggregates phase shifted daily NEP and IDE expression and increased the mesor of ECE rhythms, as well as clock proteins (BMAL1 and RORα) daily rhythms. According to these results, we could suggest that the changes in the temporal patterns of enzymes involved in the clearance of Aβ, would precede the increase in the Aβ peptide levels and the deterioration of the endogenous clock function, observed in the Alzheimer's disease.

P135.-COMBINATION TREATMENT WITH PPARγ AGONIST PIOGLITAZONE AND RETINOIC ACID MODIFIES DAILY PATTERNS OF APO E IN THE TEMPORAL CORTEX OF AN EXPERIMENTAL MODEL OF ALZHEIMER DISEASE

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Numerous studies has shown that an imbalance between the production and clearance of amyloid-β (Aβ) peptides in the brain results in accumulation of Aβ. The removal of Aβ deposits is a process facilitated by apolipoprotein E (ApoE). ApoE expression is transcriptionally induced by PPARγ in coordination with RXRs. On the other hand, absence of ApoE has been correlated with diminished antioxidant capacity. Previously, we found that an i.c.v. injection of Aβ(1-42) modified the daily rhythms of lipid peroxidation and protein carbonyls in the rat cortex. Taking into account those observations, the objectives of this study were: first, to analyze the effect of an i.c.v. injection of Aβ(1-42) on the 24h rhythms of Aβ, BMAL1 and ApoE protein levels in the rat temporal cortex; second, to evaluate the effect of pioglitazone-retinoic acid (Pio-RA) on those temporal patterns. Four-month-old male Holtzman rats were divided into three groups defined as:1)control 2)Aβ-injected 3)Aβ-injected treated with Pio-RA. Aβ, BMAL1 and ApoE proteins levels were analyzed by immunoblotting. Lipid peroxidation and protein carbonyls levels by colorimetric assays and ELISA, respectively. We found that injection of Aβ(1-42) phase shifted Aβ, BMAL1 and ApoE rhythms. Noteworthy, Pio-RA reestablished rhythmicity of those temporal patterns indicating PPARg-RXR heterodimer might be a transcription factor involved in circadian regulation and a potential target for restoration of daily rhythmicity of Apo E in AD.

P136.-Exploring the contribution of Evening -cells to the circadian pacemaker of Drosophila

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The circadian clock of Drosophila is composed of 150 cells, which can be divided into 7 clusters. Under laboratory conditions, rhythmic locomotor activity is condensed in morning and evening bouts. Each activity peak has been linked to a specific group of neurons: the PDF-positive small ventral lateral neurons (sLNv) control the morning component (M-cells), and the dorsal lateral neurons plus the 5th sLNv control the evening component (E-cells). While M-cells have long been considered as the main pacekeepers of the circadian clock, there is increasing evidence pointing to the contribution of E-cells in sustaining a coherent rhythmic output, although the mechanisms underlying their role are not fully described yet. Our aim was to characterize the neurotransmitters secreted by E-cells, as well as their impact in the generation of a robust behavioral rhythm. To do so, we genetically manipulated the expression of the different neurotransmitter transporters in a subset of E-cells using an array of RNAi lines, and monitored locomotor activity rhythms, particularly, the period and deconsolidation of the activity rhythms. This strategy proved successful to identify glycine as one of the neurotransmitters released by the LNvs (Frenkel et al., Cell Rep 2017). Thus, our results confirmed the E cells are cholinergic (Johard et al., JCN 2009) and likely glutamatergic, and that these fast neurotransmitters contribute to provide coherence to the circadian network.

P137.-A GABAA receptor in circadian and arousal neurons regulates sleep in Drosophila melanogaster

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Sleep is a complex and vital behavior regulated by both homeostatic and circadian mechanisms. The neural circuits involved in sleep homeostasis are not well described yet. However, it has been previously proposed that GABAergic inputs to the large lateral ventral neurons (lLNvs) of Drosophila may be responsible of informing those highly integrative arousal neurons about the sleep homeostat status. On the other hand, the current paradigm proposes that the main circadian pacemaker of the Drosophila brain, the small lateral ventral neurons (sLNvs) have only minor influence in the control of sleep behavior. Starting from this point, our aim is to describe the mechanisms of GABAergic inhibition in both sLNvs and lLNvs, their influence on sleep behavior and their role on the sleep homeostat. For this we have performed specific genetic manipulations and quantified sleep behavior under basal and sleep deprivation conditions. Moreover, we have collected preliminary electrophysiological recordings to identify the extent of the role of the neurotransmitter GABA in the neuronal circuit studied, given that our final goal is to describe this network in detail. Our findings confirm that the lLNvs receive information about the sleep homeostat status via the GABAA receptor Rdl through a complex neuronal circuit. They also suggest that the sLNvs are involved not only in the control of the circadian sleep timing but also, through GABAergic inputs, can regulate the quantity and quality of sleep.

P138.-EFFECTS OF PIOGLITAZONE-RETINOIC ACID ON DAILY RHYTHMS OF OXIDATIVE STRESS PARAMETERS IN AN EXPERIMENTAL MODEL OF ALZHEIMER DISEASE

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Alzheimer's disease (AD) is the main cause of dementia in the elderly. The pathological hallmarks of AD include senile plaques of amyloid-β (Aβ) aggregates and neurofibrillary tangles in brain. Elevated levels of Aβ causes an increase in intracellular reactive oxygen species associated to a deficient antioxidant defense system. The objectives of this study were: first, to analyze the effect of an i.c.v. injection of Aβ(1-42) on the 24h rhythms of oxidative stress parameters in the rat prefrontal cortex(PC); second, to evaluate the effect of pioglitazone-retinoic acid (Pio-RA) on those temporal patterns. Four-month old males Holtzman rats were used in this study. Groups were defined as: 1) control 2) Aβ-injected 3) Aβ-injected treated with Pio-RA. PC samples were isolated every 4 h during a 24h period. Lipid peroxidation and protein carbonyls levels were determined by colorimetric assays and ELISA, respectively. CAT and GPx enzymatic activities were determined by kinetic assays and Aβ, BMAL1 proteins levels by immunoblotting. We found that injection of Aβ(1-42) modified the daily rhythms of lipid peroxidation, protein carbonyls, CAT and GPx enzymatic activities, Aβ and BMAL1 protein levels in the rat PC. The treatment of Pio-RA reestablished rhythmicity of those temporal patterns. These findings might constitute, at least in part, molecular and biochemical basis of restoration of circadian rhythmicity by the administration of Pio-AR in neurodegenerative disorders.

P139.-CIRCADIAN CONTROL OF LIPID AND REDOX METABOLISMS IN PROLIFERATIVE CANCER CELLS

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The circadian system comprising oscillators present in organs, tissues and even in individual cells temporally controls the body physiology. Circadian rhythm disruption may cause higher cancer risk, but little is known about clock function in tumor cells. For this, we evaluated the circadian, redox and metabolic state in glioblastoma T98G cell cultures under different proliferating conditions. In arrested cells we observed functional and rhythmic clock oscillations in mRNAs for clock- (CGs) and glycerophospholipid (GPL) enzyme genes, and redox state/peroxiredoxin oxidation cycles. By contrast, in proliferating cells, circadian rhythms of gene expression were affected whereas metabolic rhythms persisted; moreover, rhythms in ROS levels were altered when Bmal1 expression was knocked down. Thus, the metabolic clock operates in proliferative tumor cells regardless the molecular clock. Here, we extended these studies to the human hepatoma cell line HepG2, to evaluate if this is a general phenomenon. We assessed the molecular clock work and its link with the lipid metabolism in HepG2 cells under proliferation. We analyzed the expression and protein content of CGs, clock controlled genes (CCGs) and enzymes involved in the GPL biosynthesis. We also studied the endogenous content and individual level of GPLs and lipid droplet content (number, size and variation over time) and we found an active time-dependent control of gene expression and metabolism in proliferating HepG2 cells.

P140.-Synchronization of the circadian network: a new role for the BMP signaling pathway

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Circadian behavior is controlled by an endogenous clock. In Drosophila, this clock resides in about 150 neurons; among them, the sLNvs are relevant to set the free-running period. Synchronization among the different clusters of circadian neurons has to be very accurate to achieve a coherent output but it also has to be flexible to respond to environmental challenges. We tested the hypothesis that the BMP pathway is recruited by the LNvs to modulate circadian locomotor activity. To investigate the role of specific ligands, we overexpressed and downregulated DPP and GBB specifically in the sLNvs, lLNvs or LNvs. Overexpression of both ligands in the LNvs gave rise to a long period while their downregulation triggered loss of rhythmicity. Since this pathway is recruited at the neuromuscular junction, we hypothesized that its activation could affect the morphology of the sLNv projections. Interestingly, ligands overexpression in the LNvs for one day correlated with decreased complexity of the sLNv arborization pattern that did not change along the day, with no effect on PDF levels. Our results suggest that communication among LNvs through the BMP pathway fine tunes locomotor activity patterns perhaps through changes in the morphology of the sLNv projections. The lLNvs would contribute to the network activating the BMP pathway in the sLNvs, opening the possibility that this pathway provides a means to adjust the circadian behavior to changing environmental conditions.

P141.-Studying the selective vulnerability of Drosophila melanogaster clock neurons to huntingtin polyQ elongation

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One of the hallmarks of polyglutamine (polyQ) diseases is the selective vulnerability of different neurons, in spite of ubiquitous expression of the pathogenic protein. The reasons behind this specificity underlying neurodegeneration is still an unsolved mistery.

It has been reported that the two circadian clusters of lateral ventral neurons (LNv) of Drosophila melanogaster respond differently to the elongation of the polyQ tract of the huntingtin (Htt) protein. It has been shown that while HttpolyQ protein functionally ablates the small LNvs (sLNvs) subgroup, the large LNvs (lLNV) remain unaltered.

Our goal is to explore this differential response of LNvs to the HttpolyQ. In order to do this, we are studying morphological phenotypes and the consequences over the behaviors these neurons command. Our preliminary results regarding the morphology of the LNvs under the expression of HttpolyQ in young flies fit well with the published literature. We have found that, in spite of being expressed in both neuronal types, sLNvs present protein accumulations of HttpolyQ and lLNvs do not. However, in aged flies lLNvs also show HttpolyQ protein aggregation, both in the somas and on their projections. These results suggest that, although the reported differential sensibility between the two neuronal groups exists, lLNvs are not immune to HttpolyQ protein aggregation. We will also show preliminary data regarding the effects of HttpolyQ expression in LNvs on the control of sleep behavior.

P142.-A methodological advance in the study of the circadian behavior of oviposition in Drosophila melanogaster

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Biological clocks allow organisms to anticipate changes in the environment to achieve adequate adaptation. In Drosophila spp., the periodic behavior of egg-laying or oviposition is one of several physiological processes regulated in circadian fashion. However, this rhythmic behavior is one of the less studied rhythms, perhaps due to the difficulties involved in monitoring and recording it. For example, the collection and counting of eggs is usually done manually, making the experiments particularly demanding and labor-intensive. This motivates us to develop an automated device for monitoring oviposition behavior in Drosophila melanogaster. Our device allows the simultaneous analysis of 21 flies individually, and can be operated by a single person. In addition, since the sampling interval is controlled automatically, it is possible to test different time intervals to determine which is the most suitable to measure this rhythmic behavior. With this device we can detect rhythmic and arrhythmic phenotypes, with percentages of rhythmicity and periods similar to those obtained with the previous methodologies used to monitor this behavior. In addition, the number of rhythmic flies over the total (for genotypes considered rhythmic) is similar between manual vs. semiautomatic methodologies, which supports the fact that the differences between the methodologies do not affect the results. Therefore, we developed a novel device for the study of oviposition behavior.

P143.-Chronopharmacological study of the novel drug 1A for glioblastoma treatment

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Glioblastoma has a 90% mortality rate and had have no therapeutical improvements in the last 30 years, so research for novel drugs becomes critical. The efficacy of several drugs is modulated by the circadian system leading us to hypothesize that a chronopharmacological approach would improve the efficacy of glioma treatment. Our purpose was to study the effects of the drugs 1A (a Rac1 inhibitor), and Temozolomide (TMZ)(current treatment of choice) when applied at different circadian times to LN229 glioblastoma cells.

Because two of the main roles of Rac1 are related to cell proliferation and migration, we studied the effects of 1A and TMZ over these processes when applied at different circadian times. We found that the effectivity of 1A is rhythmic, showing a minimum inhibition of proliferation and migration when applied at CT3 after a serum shock; and a maximum of inhibition of both processes when applied at CT19. In primary murine astrocytes, 1A was not toxic in neither of the circadian times.

The preliminary in vivo studies consisted on treating nude mice with 1A or control at ZT3 or 12. We found that the median survival of the mice treated at ZT3 was 82 days and at ZT12 was 78 days, whereas animals treated with control had a median survival of 58 days.

Our in vitro results suggest that effects of this drugs are modulated by the circadian system. The novel drug 1A could be a viable candidate for chronomodulated therapies in the future.

P144.-Temporal control of tumor formation and growth in nocturnal mammals: impact of the circadian system

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Circadian rhythm disruption as a modern life consequence (shiftwork, jetlag, etc.) may lead to metabolic disorders or higher cancer risk. Cancer cells display aberrant proliferation with a very active metabolism to facilitate tumor growth and metastasis. However, little is known about the circadian clock function on tumor growth regulation. Here we investigate the day/night differences in the growth of peripheral tumors of sciatic nerve after the inoculation of A530 glioma cells isolated from NPcis (Trp53+/-; Nf1 +/-) heterozygous mice, a human neurofibromatosis type I model. In A530 cultures, mRNA of clock and clock-controlled genes, levels of ROS and susceptibility to Bortezomib chemotherapy exhibited temporal fluctuations. When A530 cells were injected into the sciatic nerve of C57BL/6 mice during the morning or the night of a 12:12 h L/D cycle, tumors growing on animals injected during the night showed a higher rate of growth as compared with those injected at day. Day/night differences were also found after subcutaneous inoculation of melanoma B16 cells in mice at day or night with higher values observed in males of night group. Lastly, when we examined the role of the molecular clock activator Bmal1 in tumor growth, a higher rate of tumor growth was found when Bmal1 expression was diminished by CRISPR/Cas9 in A530 cells compared with controls. Our observations strongly suggest that the tumor growth is subject to temporal control and mainly dependent on the host state.

P145.-Low nutritional state impairs novel object recognition memory in Drosophila

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Specific behaviors are driven by specific motivational states, which in turn depend on a computation relating the internal state, the specific contexts and previous experiences. To examine how the brain processes environmental information in distinct internal states and its effects on learning, we adapted to Drosophila the novel object recognition (NOR) test, in which novelty, but not adverse stimuli, drives the behavior. The NOR test, widely used to study recognition memory in rodents, consists of three stages: habituation to the context, training and testing, across which different behavioral variables can be quantified. For this, we developed a device in which freely behaving flies can be recorded and subjected to thermo and optogenetics. First, we found that fruit flies habituate better to contexts with visual cues. The habituation response became a habituation memory only if flies were removed from the context. Then, we found that the behavior in well fed flies was normally driven by novelty and were capable of forming NOR memory. However, mild fasting eliminates recognition memory, but did not affect habituation or aversive olfactory conditioning memory. The effect of fasting on NOR memory was mimic by classic mutants with reduced insulin-like signaling. In addition to constitutive genetic manipulations, in this study we examined by acute thermogenetic manipulations the contribution of mushroom body neurons and neuromodulation to NOR memory.

P146.-Ethanol-related breathing disruptions in rat pups during the brain growth spurt period

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Rat pups during postnatal days (PDs) 3-9 are sensitive to ethanol´s (EtOH) disruptive effects upon respiratory neuroplasticity. This stage in development is analogous to the 3rd human gestational trimester in terms of brain development. In this study, during PDs 3, 5 and 7, pups received an i.g. administration of vehicle or EtOH (2.0 g/kg). Respiratory frequencies and apneas were recorded via whole body plethysmography. At PD9, pups representative of each prior treatment were administered with vehicle or different EtOH doses (0.75, 1.37 or 2.0 g/kg) and evaluated in terms of breathing patterns under 3 sequential phases defined by differential levels of ambient oxygen (normoxia, hypoxia and recovery normoxia). During PDs 3-7, breathing frequencies progressively increased as a function of age. EtOH consistently exerted a depressant effect upon respiration. Pups treated with EtOH also showed a progressive sensitization effect relative to the depressant effects of the drug and lesser levels of apneas. At PD9 dose-dependent respiratory depressions were observed when pups were defied with a hypoxic event. Independently of drug treatment at test, prior experience with EtOH significantly disrupted respiratory frequencies particularly during the hypoxic and the recovery normoxia phases. These results show that breathing plasticity is disrupted during a critical stage where respiratory alterations may lead to hypoxia-associated syndromes that endanger the development of the brain.

P147.-Unidirectional optomotor responses in two distant families of estuarine crabs

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When a rotational movement of the visual panorama occurs, animals, from invertebrates to humans, tend to stabilize the movement through compensatory movements of the eyes, head or the whole body. This is known as optomotor response. In particular, unidirectional optomotor responses occur when animals stimulated monocularly with a horizontal optic flow show a unique effective direction of motion. This phenomenon has been reported in various species from mammals to birds, reptiles, amphibious and flies. In all vertebrate reported cases the preferred direction is always from the uncovered eye towards the covered eye (back-to-front direction (BTF) of movement in the ipsilateral receptive field). In contrast, the few reports in invertebrates (flies) show that the progressive (front-to-back, FTB) direction of motion induces a stronger optomotor response than the regressive direction. Here we present the results of behavioral experiments aimed at exploring optomotor responses in two semiterrestrial crab species belonging to distant families: the varunid crab Neohelice granulata and the fiddler crab (Ocypodidae) Uca uruguayensis. We used different conditions of stimulation (binocular, monocular) and directions of stimulation (FTB, BTF) to shade light on the underlying circuit commanding this behavior. Results indicate that the circuitry underlying OR in crabs is very similarly organized to the one present in flies.

P148.-Differential activity of striatal cholinergic interneurons in context that propitiate decision making/ strategy selection

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Assimilation of novel strategies into a consolidated action repertoire is critical for behavioral adaptation. This includes processes like decision making, planning actions and selection of strategies that require complex cortico-basal ganglia processing. The striatum is the main input nucleus to this subcortical loop and its activity is tightly controlled by local interneurons. In this regard, striatum cholinergic interneurons (SCIN) play a causal role in regulating behavioral flexibility, including reversal learning and goal-directed versus habitual response selection. We have previously shown that SCIN are necessary to switch between solving-problem strategies in order to optimize cost benefit ratios. However, it has not been studied whether a differential activation of SCIN exists when animals are required to select between competitive spatial strategies. Here, we aimed to study activity levels of SCIN under different degrees of spatial novelty and decision making demands. For that, we subjected C57BL/6 wt mice to two mazes with increasing decision-making requirements (Y maze and dual solution cross maze) and evaluated SCIN activation, measured as rpS6 expression levels by IHC. Mice exposed to contexts that require decision making situations present lower levels of SCIN activation compared to control littermates exposed to non-decision conditions. This result suggests that SCIN modify their activity patterns in contexts that propitiate decision making/ strategy selection.

P149.-Stress-induced fear memory generalization: c-fos analysis in amygdala and hippocampus.

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We have previously demonstrated that stress prior to fear conditioning favor the generalization of fear in a non-paired context (cxt-B) which is different to the conditioning context (cxt-A). The aim of this work was to analyze the c-fos cell expression in amygdala and hippocampus, with the aim to detect some differential activation pattern that could underlie the stress-induced fear memory generalization.

The restraint stress session was performed one day before the fear conditioning. The memory test (cxt-A) or generalization test (cxt-B) were performed 24 after conditioning and one hour later their brains were fixed. Then, c-fos immunohistochemistry were performed and the number of c-fos positive cells was counted in different regions of hippocampus (CA1, CA3, DG) and amygdala (LA, BLA, CeA).

We observed an increase of c-fos positive cells in LA and BLA of conditioned rats (with or without prior stress) exposed to the training context, indicating an increase of the activity in basolateral amygdala complex during the retrieval of fear memories. Surprisingly, no differential activation was observed in the hippocampus in any of the groups tested. Animals that were exposed to the generalization context did not show any difference either in amygdala or hippocampus.

In conclusion, the current results indicate that under our experimental parameters no differential pattern of c-fos activation in amygdala or hippocampus is associated with the generalization of fear memories.

P150.-Everyday metaphors- Functional Anatomy

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Metaphors are omnipresent in everyday language as idiomatic expressions (IE). These are specific to the country or region they originate. There are hundreds of IE in a widely spoken language as Spanish. Neural correlates for literal and non-literal language differ between each other, however there are not studies using stimuli in Spanish. Aim: to investigate the functional anatomy of Spanish IE in healthy participants. Methods: 20 normal subjects, right-handed, (10 women), underwent a paradigm-related fMRI session in a 3T scanner. Literal sentences or IE were displayed every 4 secs. in an event-related design. Participants had to pick one of 4 possible meanings via a key press. 213 whole brain volumes were acquired and analyzed using SPM12, computing a BOLD contrast image for each subject and comparing, by t tests, IE vs figurative language, as well as female vs male processing. Results: Extensive clusters were activated in left F3/ F2, bilateral T1/T2, supramarginal gyrus, left insula, and pars triangularis bilaterally. Brain activation in males was lateralized leftwards, while women activated similar areas in both hemispheres. Discussion: Spanish IE processing requires simultaneous activation of several areas in both hemispheres, as other forms of non-literal language. These findings agree with previous reports about the functional anatomy of pragmatic language. Biological differences in IE processing between sexes were found.

P151.-ASYMMETRY AND GRAY MATTER CONTENT OF FRONTOPARIETAL OPERCULUM IN ADULTS

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Anatomical structures with bilateral symmetry are characterized by the repetition of characters on both sides of the sagittal plane. They usually exhibit morphological differences between left and right sides. The causes of these asymmetries and include genetic, functional and developmental factors. In the human brain, numerous asymmetries have been described, mainly in size, although other morphological aspects have been less studied. The aim of this study is to identify anatomical asymmetries, in relation to the number and presence of accessory sulci, of the frontoparietal operculum. This region is formed by the portions of the frontal and parietal lobes and contains various areas related to language. We analyze a sample of 47 T1 magnetic resonance images of the brain of healthy individuals of both sexes between 18 and 41 years old. The frontoparietal operculum was identified in parasagittal sections in each hemisphere and the following variables were registered: number of furrows in the anterior and posterior portions of the lateral sulcus; presence of accessory sulci (triangular and diagonal); continuous or discontinuous pattern of the precentral inferior and inferior frontal sulci; and the shape of the tip of the lateral sulcus (oblique up / down or horizontal). These variables were correlated with the content of gray matter of the gyri surrounding the lateral sulcus. The results obtained will allow us to characterize the normal asymmetry of the frontoparietal operculum.

P152.-Withdrawn abstract

P153.-Dopamine D2 receptors of the central amygdala regulate unconditioned fear in mice

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The central nucleus of the amygdala (CeA) plays a key role in the execution of stress-induced and emotional-driven behaviors. Although the CeA is densely innervated by A10dc dopaminergic neurons and expresses dopamine D2 receptors (D2R), the behavioral role of this pathway is still poorly understood because previous pharmacological attempts to block or stimulate D2R in this nucleus led to controversial results.

In this study we combined the use of conditional mutant mice and stereotaxic injections of viral vectors to specifically eliminate D2R from CeA neurons of adult mice while maintaining other D2-like receptors and D2-autoreceptors intact. We found that mice lacking D2R from the CeA increased the avoidance of potentially dangerous environments without altering fear conditioning responses. We have also found that the systemic administration of cocaine activated PKCδ positive neurons of the CeA, a population previously associated to anxiolytic effects. Finally, using in vivo optogenetic stimulation, molecular tracing and anatomical analysis of gene expression, we demonstrated that there are a least two different dopaminergic pathways that innervate the CeA, with distinct localization of the neuronal somas, axons distribution and dopamine transporter expression levels.

These results constitute, in our opinion, an important advance in the understanding of the dopaminergic regulation of emotional and cognitive behaviors.

P154.-Effect of IGF-1 gene therapy on the formation of a contextual fear memory trace

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Basolateral amygdala complex plays an essential role in the generation of an emotional state caused by an aversive experience. Insulin growth factor like I (IGF-I) could modulate hippocampal circuits modifying cognitive functions, and possibly, the molecular mechanisms involved in some psychopathologies related to traumatic memories. Objectives: 1)To promote and evaluate the expression of a memory trace through IGF-I gene therapy; 2)To evaluate if structural plastic changes in dorsal hippocampus, are responsible for the expression of this memory trace. M&M: Adult male Wistar rats were bilaterally infused into BLA with RAd-DS-Red, as a control virus and RAd-IGF-I, as therapeutic virus. 7 days later we performed a weak fear conditioning protocol (WFCP). Freezing behavior (FB) was assessed as a measure of retrieval and memory retention. At day 15 we performed hot plate test to evaluate sensitivity damage. Rats were perfused and the brain fixed for dendritic spine analysis. Results: A significantly increase in FB in the RAd-IGF-1 group was observed after 7 days and maintained for 14 days post injection. There was not sensitivity damage in both groups. Preliminary results for dendritic spine analysis indicate no significant differences in spine density. Conclusions: IGF-I gene therapy induces a significant expression of FB in a WFCP, with a possible promotor effect on the formation of a fear memory trace which prompt us to further studies under this experimental model.

P155.-The probiotic Bacillus subtilis ameliorates the progression of Alzheimer`s disease in the model organism Caenorhabditis elegans

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Alzheimer´s disease (AD) is one of the most common neurodegenerative pathologies and is strongly related to microbial dysbiosis. One indicator of AD is the accumulation of amyloid-β (Aβ) in the brain. Currently, no treatment is available for preventing or slowing the progression of AD. Bacillus subtilis is a spore-forming bacterium and is worldwide used as a probiotic for human consume. The aim of this work was to investigate the effect of B. subtilis as a potential treatment of AD in the animal model Caenorhabditis elegans. C. elegans strains (CL2006 and CL2120), which express the human Aβ in muscle, fed on the probiotic B. subtilis (DG101) increased their healthy longevity significantly compared with worms fed on the non-probiotic Escherichia coli OP50 strain. The C elegans CL2120 strain fed on DG101 spores shown no paralysis throughout the experiment compared with worms fed on OP50 cells. In behavioral experiments, the CL2355 (neuronal expression of human Aβ) strain fed on DG101 spores shown better behavioral proficiency, evaluated as efficiency to arrive at the location of the chemoattractant diacetyl (0.5 %), than CL2355 worms fed on OP50 cells. Interestingly, all the AD models strains of C. elegans fed on DG101 behaved and lived like the wild-type C. elegans strain N2, indicating a complete prevention of AD development in the transgenic worms. In conclusion, B. subtilis DG101 represents a promising food additive for the treatment of AD in human beings.

P156.-Behavioral changes induced by striatal interneurons ablation

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Corticostriatal dysfunction is involved in Parkinson's disease and Tourette syndrome(TS), among other neuropsychiatric disorders. There are studies showing a reduced number of multiple striatal interneurons (SIs) types in the brain of TS patients. In a previous study where we induced a selective ablation of striatal cholinergic interneurons in the mouse, we observed perseverative behaviors reminiscent of those observed in TSand related disorders, but we did not observe tics. In order to reproduce more closely the striatal changes observed in TS, we aimed to perform a combined ablation of striatal cholinergic and GABAergic interneurons by directing the expression of the human diphtheria toxin receptor to neurons that express Nkx2.1 before differentiating into different types of SIs. By administering diphtheria toxin (DT) into the striatum we obtained a selective ablation of Nkx2.1 positive interneurons. Mice treated with extensive SIs ablations developed unwilling and abnormal movements, alterations oflocomotion and posture, and usually died during the first week after DT injection. Mice with restricted SIs ablations showed unwilling movements that did not progress and are being studied with a battery of behavioral tests. Altogether our data suggest a putative mechanism for the involuntary movements observed in patients with “benign hereditary chorea” caused by mutations of the Nkx2.1 gene and that tics in TS may be caused by combined dysfunction of multiple SIs types.

P157.-Temporal dynamic of the hippocampal structural plasticity associated to contextual fear memory: influence of the destabilization/reconsolidation process

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Increasing experimental evidence indicates that fear memory reactivation induces a transient plastic state that presumably activates the neuronal circuit involved in the encoding of the long term fear memory. Under certain circumstances, such reactivation allows the incorporation and integration of new information to the original memory trace.

Here, we evaluated whether fear memory reactivation impacts on the dendritic spines remodeling in CA1 region of the dorsal hippocampus associated with the formation of the contextual fear memory. In the same way, we tested whether stress exposure affects such dendritic spine remodeling. Thus, stressed and control animals were fear conditioned and sacrificed 24hs post conditioning (pre retrieval), 60min post retrieval or 24hs post retrieval.

A higher dendritic spines density, particularly mature ones, were observed after fear encoding and later reduced to basal levels 60min after fear reactivation, returning to higher levels 24hs post retrieval. This temporal dynamic structural plasticity was prevented by pharmacologically blocking the destabilization/reconsolidation process in the basolateral amygdala complex or by a single stress exposure just before fear memory conditioning.

Thus, the destabilization/reconsolidation process was evidenced by a change in the hippocampal structural plasticity immediately following reactivation, a plausible necessary step for the integration of new information.

P158.-Central Hypothermic Effects of Ethanol and Acetaldehyde in Newborn Rats Regulated through Associative Learning Processes

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Different effects of ethanol (EtOH) during early ontogeny are modulated by the central accumulation of acetaldehyde (ACD). Newborns are sensitive to the reinforcing effects of ACD as well as to its depressant effects upon respiration. Both phenomena, studied in older organisms, have been linked with thermoregulatory disruptions caused by ACD. In this study, EtOH (100 mg%) or ACD (0.52 µM) were intracisternally administered during postnatal days (PDs) 2 and 4. Control pups received no explicit treatment (Untreated, UT) or were centrally administered with buffer (PB). Pups experienced the drug effects when exposed to EtOH odor. At PD6 pups were administered with PB with the sole exception of the UT group. Body temperatures and ultrasound emissions (USVs) under the presence of EtOH odor were recorded. In newborns USVs are elicited by stress-related events. During PD2, significant levels of hypothermia were observed in PB, EtOH and ACD groups. At PD4, only ACD pups showed heightened hypothermia. At test, pups pre-exposed to ACD again showed hypothermia despite being administered with buffer; an effect suggestive of a conditioned thermal response elicited by stimuli previously associated with ACD. USVs were not affected by prior treatments. Yet, temperature decrements were negatively correlated with USVs. The results show that central ACD recruits poikilothermic alterations in newborns which are associated with stimuli that later elicit isodirectional conditioned responses.

P159.-Use of c-Fos for neuronal activity detection in amphibian medial pallium during an extra-maze cue spatial navigation task

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Spatial navigation is a skill conserved between vertebrates, suggesting that it is important for survival. We are interested in the evolution of neural mechanisms that rule this ability, looking for learning patterns potentially present in a common ancestor. We use the terrestrial toad, Rhinella arenarum, as a model of ancient vertebrate. Amphibians have a homologous area to the hippocampal formation (brain structure involved in spatial learning) called medial pallium, which functions are not yet fully described. We trained toads in a water finding orientation task using a transparent open field (with access to extra maze cues). After acquisition, brains were analyzed using c-Fos immunohistochemistry technique. Expression of c-fos is an indirect marker of neuronal activity because it is often expressed when neurons fire action potentials. c-Fos is an immediate early gene (IEG) that codes for a transcription factor that is thought to mediate long-term changes in neural functioning. Thus, c-Fos staining in a neuron indicates recent activity and it is believed that increased c-Fos expression is induced by a novel experience, such as learning spatial task in a maze. Our results revealed increased c-Fos + neurons in the medial pallium region, suggesting that this structure is involved in spatial navigation strategies in amphibians. Hippocampus and medial pallium seems to be partially functional equivalents, telling us that this ability is evolutionary conserved.

P160.-Systemic administrations of Naloxone before reward downshift or reward omission

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Opioid circuit is part of the mechanisms of physical pain regulation but it could also be implicated in the regulation of psychological pain, the emotional state observed after surprising reward devaluation (successive negative contrast, SNC paradigm) or omission (extinction paradigm). Two experiments are presented using intraperitoneal administration of Naloxone (2mg/kg), an opioid antagonist. In experiment 1, Long Evans rats were trained in an instrumental SNC. Animals received 12 runway preshift sessions reinforced with 32 micropellets, and 10 post shift sessions reinforced with 4 pellets. Their runway performance was compared with animals that always received 4 micropellets. Animals could be assigned to a 32-4 or 4-4 condition and a Saline or Naloxone condition. Injections took place before postshift sessions 1 and 2. Downshifted animals in the saline condition exhibited a runway performance impairment in postshift sessions 5 and 6, and a quick recovery. Animals in the Naloxone condition also exhibited performance impairment but did not showed recovery. In experiment 2, two groups of animals received 12 runway acquisition trials and 10 extinction trials. In extinction trials 1 and 2 a Saline or Naloxone injection was administrated. Both groups differed only in extinction trial 3, where Naloxone group exhibited an increase in runway latency. Both experiments suggest that blocking opioid receptors increases the effect of surprising reward devaluation and omission.

P161.-Withdrawn abstract

P162.-Interoceptive associations in addiction to smoked cocaine

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Contemporary neurocognitive models of drug addiction underscored the role of interoception. In these models, interoception is defined as the sensing and processing of body signals to serve a homeostatic function related to the onset and maintenance of addictive-behavior. In this work we assess the relation between interoception and smoked cocaine dependence with a multimodal and multi-dimensional approach. We use the Hearbeat-detection (HBD) task and related Heart Evoked Potential (HEP) recordings at baseline (interoceptive accuracy) and during learning. We combined this behavioral and electrophysiological data with structural and functional connectivity analysis of the main interoceptive hubs. Smoked cocaine dependent subjects presented ongoing psychophysiological measures of enhanced interoception accuracy (HBD & HEP); accompanied by structural and FC tuning of interoceptive networks. Our findings support both specialized effects of smoked cocaine on interoception, and also provide direct empirical evidence for drug models suggesting that hyper-interoception processing is a key aspect in addictions. Thus, multimodal assessment of interoception could serve as a potential domain to asses clinical and neurocognitive characterization of psychophysiological and underlaying neurophysiological adaptations in addiction.

P163.-Role of the lateral habenula in a rewarded contextual dependent task

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The lateral habénula (LHb) is a diencephalic nucleus that plays critical functions in cognitive process. Increased activity of LHb neurons correlates with aversive stimuli presentation, whereas stimulation of LHb promotes avoidance behaviors. Concordantly, LHb projects to areas that control motivation, such as the ventral tegmental area and the rostromedial tegmental nucleus. Rewards, either negative or positive, are always given in a context. Increasing evidence supports a functional relation between the the LHb and the hippocampus, a brain structure relevant for coding contextual information. In this scenario, our main goal is to study how the LHb processes information, and ultimately, how it functionally interacts with the hippocampus when animals perform a rewarded contextual dependent task. We implemented an arduino/Bonsai based system to analyze the behavior of rats as they look for a reward in our heart shaped-maze task. This system allow us to optogenetically stimulate in a specific part of the maze. . Our preliminary results indicate that stimulation of the LHb makes the animal avoid the place where stimulation has occurred, either evaluated in a real time preference task or in our maze.

P164.-Retrosplenial cortex integrity is required during acquisition for its participation in an object-recognition memory

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Several studies demonstrated that the retrosplenial cortex (RSC) is involved in navigation and contextual memory. Recently, we found that the RSC is also required for the processing of an object-recognition memory. We inactivated this structure with muscimol infusions performed at different time points of that task and found that memory was impaired when the RSC was inactivated during consolidation or retrieval. In this case, animals did not explore preferentially the novel object. In contrast, inactivating the RSC during acquisition did not interfere with recognition memory and animals explored preferentially the novel object. Taking into account these results, we evaluated whether inactivating the RSC during acquisition interferes with its recruitment in memory processing. Animals were subjected to a double-inactivation of the RSC, in order to affect both acquisition and consolidation or both acquisition and retrieval. We predicted that the first injection would disengage the RSC from memory processing, thus leaving consolidation and retrieval intact, despite the second injection targeting them. Our results showed that this was indeed the case as double-injected animals exhibited intact recognition memory. We thus propose that the RSC is recruited to process the object-recognition memory, only if it is active during the acquisition of that memory. On the contrary, when the RSC is not active during acquisition, other brain structures may take control of memory processing.

P165.-Dissociating reconsolidation and extinction of contextual aversive memory in female rats using midazolam treatment and reinstatement paradigm: influence of reactivation time span

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Females (FEM) have particularities in contextual aversive memory (CAC). Reactivated aversive memories may follow alternative outcomes which are dependent on duration of reactivation session. Although the time course of a CAC after retrieval has been well characterized in male rats, this temporal pattern is still unexplored in FEM. We aimed to investigate the passage from reconsolidation to extinction of memory combining CAC, different reactivation time span, midazolam and a reinstatement procedure in FEM. Rats were trained and, on the following day, rats were exposed to different re-exposure times (1, 2, 5, 7, 10 or 30 min) that were followed by MDZ administration. Given that FEM showed a decrease in freezing expression with the increase in the number of re-exposures to the CAC, we used a reinstatement strategy that allowed dissociating the effect of MDZ on memory. Our findings showed that when the reactivation session lasted 2-5 min, memory returned to a labile state sensitive to disruption by MDZ and memory showed no reinstatement. When 30-min reactivation session was performed, memory was directed to extinction and MDZ was able to disrupt the retention of this process and memory showed reinstatement, but, memory was insensitive to MDZ effect when reactivation session lasted 7-10 min. In summary, combining post-reactivation MDZ treatment with a reinstatement protocol, we managed to dissociate the mutually exclusive processes of reconsolidation and extinction in FEM rats.

P166.-Injection with Kainic Acid in mice decrease the performance in Novel Object Recognition and Patter Separation task

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The mechanism underlying epileptogenesis has been largely studied with the Kainic Acid (KA)-injection model. In this model the epileptiform activity begins at the injection site, in our case the amygdala, and spreads to the hippocampus and surrounding cortex in less than 60 minutes and seizures are perceivable in less than 6 hours. A recurrent symptom reported in patients suffering temporal lobe epilepsy is the difficulty to distinguish between past events. Assessing the performance on the described murine model could help to discover a palliative treatment for this symptom.

One group of mice was unilaterally injected with KA in the amygdaloid complex (KA group), whereas another group was injected with saline solution (control group). Performance was assessed for both groups in two behavioural tests that asses Novel Object Recognition and spatial Pattern Separation.

The control group spent more time exploring the new object in comparison to the KA group. This suggests that KA-injected mice could not discriminate between a familiar and novel position of the objects tested. Furthermore, electrophysiological recordings showed prominent epileptiform activity, ipsilaterally, and sometimes bilaterally in KA-injected mice.

In conclusion these results show control group with a better performance in episodic memory task, suggesting that the treatment should be focus in dentate gyrus, the hippocampus area which is responsible of this type of memory.

P167.-Dopamine modulation of mPFC activity in the control of retrieval induced forgetting

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There's been a growing human literature on a phenomenon called retrieval-induced forgetting (RIF). RIF has pointed to inhibitory control processes that resolve retrieval competition as a cause of adaptive forgetting. Using spontaneous recognition memory in rats, we have developed a rodent paradigm for RIF that recapitulate the characteristics and conditions observed in humans. Since imaging studies in humans suggested a role of mPFC dopamine in the resolution of memory interference we decided to analyzed if dopamine signaling was a requirement for RIF in rats. We used local pharmacological inactivation to show that the Ventral Tegmental Area (VTA) is necessary for the forgetting to occur and that the infusion of a D1/5 agonist in the mPFC is sufficient to rescue the expression of the RIF phenomenon impelled by the inactivation of the VTA. Correspondingly, infusion of a D1/5 antagonist into the mPFC was sufficient to prevent forgetting. In a variant of the protocol, in which the RIF phenomenon is not observed, the infusion of the D1/5 agonist in the mPFC allowed the forgetting of the competing trace. With these results, we bring new evidence supporting the role of dopamine acting in the mPFC through the D1/5 receptors in the resolution of interference between competing memories.

P168.- Withdrawn abstract

P169.-Long-term spatial memory consolidation during sleep along developmental neuronal circuits maturation

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Sleep following encoding favors the formation of episodic long-term memory (Rasch and Born, 2013). In particular, slow wave sleep appears to support hippocampus-dependent declarative memory consolidation (Inostroza and Born, 2013). It has been proposed that this process is supported by the phase-locking of three cortical rhythms: neocortical slow oscillations, thalamic spindles, and hippocampal sharp wave-ripples sustaining hippocampal-neocortical long-term storage (Staresina et al, 2015).

During postnatal development oscillations emerge in the network along with allocentric spatial abilities and sensorimotor repertoire (Altman J, et al., 1975; Tan H. 2017). We are interested in the study of oscillation phase-locking related to memory consolidation during sleep, coupled with allocentric spatial emergence during development. To address this, Long Evans rats were repeatedly trained in a spatial memory task (OPR) during several postnatal days. Our data suggest that animals acquire the task at around P32, after several repetitions. Moreover, we predict that interregional connectivity will be enhanced during that period, reflected in enhanced synchrony in thalamocortical networks during sleep. According to this, we will implant multichannel electrodes in the cortex, thalamus, and hippocampus (CA1) for LFP recording during sleep. We hypothesize that early spatial memory reinforcement following sleep may improve the oscillation phase-locking and in consequence long-term storage.

P170.-Analysis of hippocampal-prefrontal cortex interaction during spatial exploratory behavior

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The ventral hippocampus (vHP) is connected to medial prefrontal cortex (mPFC) by a monosynaptic unidirectional projection that is known to be altered in psychiatric disorders such as schizophrenia. The vHP-mPFC connection is thought to provide contextual information to the mPFC, and it plays a key role in the modulation of emotional behaviors such as fear and anxiety. However, it is still unknown how the interaction between the vHP and mPFC may allow the acquisition of relevant contextual information and regulate exploratory behaviors. It is well established that prominent theta oscillations emerge in the hippocampus during environmental exploration, and this rhythm impacts on mPFC activity. Our ongoing project focuses to understand the role of the vHP-mPFC interaction in mice performing exploratory behaviors. We aim to record simultaneously from the mPFC and vHP in mice performing a battery of exploratory tasks with different degrees of cognitive loads. We will analyze the correlation between vHP and mPFC activity and the phase locking of mPFC spikes to the hippocampal theta rhythm. We expect to find an increase in the vHP-mPFC interaction during stages of exploratory tasks where a high level of contextual information integration is required. This augmented vHP-mPFC interaction will be evidenced as an increase in the number of synchronized prefrontal units to the hippocampal theta rhythm and in the strength of this synchronization.

P171.-Hide if you can't fly? Behavioral plasticity and action selection in Drosophila

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Phototaxis is an iconic example for behaviors dominated by innate components or preferences. Such preferences likely reflect evolutionary adaptations to predictable situations, and the behaviors dominated by them have traditionally been conceptualized as hard-wired stimulus-response links. Perhaps therefore, the century-old discovery of plasticity in Drosophila phototaxis has received little attention. Experiments performed by McEwen demonstrated that wing defects, caused by mutation or damage, profoundly affect phototaxis in walking Drosophila1. The fact that manipulating an unrelated organ, such as wings, affects phototaxis contradicts the assumed hard-wired organization of this behavior, suggesting that it may not be a simple stereotypic and automatic response, but that it contains at least a certain element of flexibility. To explore this hypothesis in our laboratory, walking flies were tested for their light/dark preference in several different behavioral tests. Interestingly, light/dark preference tested in walking flies is dependent on various aspects of flight. If flying ability is temporarily compromise, photopreference reverses concomitantly. Neuronal activity in circuits expressing dopamine and octopamine, respectively, plays a differential role in photopreference, suggesting a potential involvement of these biogenic amines in this case of behavioral plasticity.

We conclude that flies monitor their ability to fly, and that flying ability exerts a fundamental effect on action selection in Drosophila. This work suggests that even behaviors which appear simple and hard-wired comprise a value-driven decision-making stage, negotiating the external situation with the animal's internal state before an action is selected.

P172.-Sexual dimorphism in aging mice: effect of IGF-1 gene therapy on motor and cognitive performance

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Previously we reported some therapeutic benefits of IGF-1 gene therapy administered in aging female rats. Here we assessed the effects of gene therapy in the quantification of frailty through a clinical assessment of aging mice. The concept of frailty, which is a state of increased vulnerability to adverse health outcomes for people of the same age, was developed to explain the heterogeneity in clinical outcomes for older patients, so in this study we compared the relationship between frailty index scores, treatment and sexes. We performed Clinical Frailty Index (© Susan E. Howlett, 2013) and a set of behavioral tests in C57BL/6 mice of 74 weeks. We divided the animals in 3 experimental groups for each sex and administered i.m. PBS, RAd-DS-Red or RAd-IGF-1. After 21 days, we re-quantify FIs scores and measured locomotor activity, strength and cognitive performance. We observed a reduction of FIs in both sexes in the group administered with IGF-1 compared with the PBS group. However, there were no significant differences in the scores between sexes. Moreover, IGF-I gene therapy induced a significant improvement in strength performance in males compared with PBS group and in females compared with RAd-DS-Red group. These preliminary results have important implications in the design of therapeutic approaches geared to identify basic mechanisms of cellular dysfunction in aging into meaningful treatment.

P173.-Effect of short and long term high-fat diet on contextual fear memory

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High-fat diet (HFD) consumption is associated not only with an increased risk of metabolic and cardiovascular diseases, but also with cognitive deficit, depression and anxiety disorders. The HFD effects on the central nervous system could be related to neuroinflammation, being the hippocampus one of the most vulnerable brain regions to HFD-induced alterations. We explored whether short-term (5 days) or long term (6 weeks) HFD consumption would serve as a neuroinflammatory trigger, leading to cognitive deficits. HFD impaired fear contextual (hippocampal dependent) memory if it is consumed during a long time, but not after 5 days. Interestingly, it has been described that in the hippocampus, HFD (during a short period), even as little as 3 days, is not directly inflammatory and only sensitizes cells to over-respond to future inflammatory stimuli. Accordingly, the intraperitoneal injection of LPS in rats that received HFD during 5 days impaired memory consolidation.
The treatment with α-MSH (0,1ug/0.25ul) in dorsal hippocampus could not reverse the effect of long term HFD in contextual fear memory. Considering that α-MSH is a potent anti-inflammatory peptide and that previous results indicated that α-MSH could reverse the effect of IL-1β on memory consolidation and reconsolidation, we will continue studying a possible α-MSH effect, with different doses and treatment protocols.

P174.- Dopaminergic Neurodegeneration and Neuroinflammation: Modulation by IGF-I gene therapy

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Insulin-like growth factor 1 (IGF-1) is emerging as a powerful neuroprotective molecule since most brain disorders are accompanied by IGF-1 deficiency and/or resistance. IGF-1 has a wide variety of functions and its study could provide the basis to prevent the deleterious effects of neurodegeneration. The aim of this study is to explore the effects of IGF-1 gene therapy on different experimental models of neurodegeneration and neuroinflammation. Under an experimental model of Parkinson´s disease, hippocampal IGF-1 gene therapy has important effects on neuronal activity that could explain, in part, the improvement in working memory dysfunction that we observed after 20 days of neurodegeneration in rats injected with 6-OHDA. ICV IGF-1 gene therapy induced a restorative effect in the hypothalamus of senile rats with DA dysfunction, and a significant improvement in motor performance in aged rats. Besides, in a clinical assessment of frailty in female and male mice we observed cognitive and motor improvements in the groups injected with IGF-I. Neuroinflammation comprises glial cells activation and the release of pro-inflammatory molecules, which is a normal response oriented to protect neural tissue. With regard to this, IGF-1 gene delivery to astrocytes in vitro reduces their inflammatory response to lipopolysaccharide. Besides, IGF-1 exerts neuroprotective actions in a traumatic brain injury, which triggers the activation of glial cells in the cortex. Our results provide a support to develop new therapeutic approaches.

P175.-Lateral Habenula and formation of fear conditioning memory

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The Lateral Habenula (LHb) is a small brain structure that forms part of the epithalamus, which codifies negative motivational value and has been related to major depression. We have previously shown that LHb activity determines temporal stability of aversive memories. Fear Conditioning (FC) is a well established paradigm of associative learning mediated by well described neuronal circuits. In order to get an insight of the mechanisms by which LHb modulates temporal stability of aversive memories, we decided to test its function in FC.
In our experiment, we inactivated LHb by local infusion of muscimol before training rats in FC. One week later we tested fear memory to context or tone. We found LHb inactivation disrupts both context and tone FC memory. Our results suggest LHb plays a general role in aversive and fear learning.

P176.-Mood disorders in animal models of neuropathic pain

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Chronic pain is a debilitating neurological condition of high clinical relevance. The treatments currently available show limited efficacy. The transition to chronic pain fundamentally remodels neuronal circuits in the brain regions that mediate pain perception. In particular, in the long term it is associated with exaggerated activation of the limbic system and a highly prevalent occurrence of mood disorders such as anxiety and depression. Although this brain plasticity was initially considered to be an epiphenomenon secondary to altered nociceptive signaling in the spinal cord, studies in both patients and animals suggest that it may actively contribute to the development of chronic pain symptoms.

In order to seek for a suitable animal model to study long-term pathological mechanisms in the limbic system during pain chronicity, we addressed the behavioral profiles of two mice models of neuropathic pain: chronic constriction injury and spared-nerve injury. We established a timeline of the persistence of nociceptive sensitization and the emergence of mood-disorders associated symptoms. We tested the mechanical allodynia of the injured paw (Von Frey test) and the expression of anxiety (open field, elevated plus maze), depression (grooming behavior, sucrose preference) and cognitive-related (y-maze) impairments. Our preliminary results show that nerve injury induces a late onset (~4 weeks) of mood disorders that persist even after the nociceptive sensitization is reverted.

P177.-Does a short nap reinforce reactivated memories in humans?

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Consolidated memories may be reactivated by a reminder of the original memory; followed by a process of re-stabilization known as reconsolidation. We have previously observed that the presentation of two consecutive reminders reinforces memory re-stabilization. On the other hand, a preliminary study of our Lab showed that a 90-min nap after memory reactivation shortened the time window of reconsolidation being NREM sleep EEG slow-wave activity involved in this process. However, it is not clear whether it stabilizes the trace protecting the memory against interferences or if it strengthens the labilized memory making it more difficult for it to be disrupted. Here, we are going to discuss preliminary data disentangling this matter. For that, participants learned a list of 5 syllable pairs on Day 1, they receive one or two consecutive reminders on Day 2 or one reminder followed by a 90-min nap and they were tested on Day 3.

P178.-Familiar face recognition in the primate brain

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We have known for some time that there is a network of brain regions for face recognition. However, attempts at finding how and where face familiarity is encoded in the brain have proven inconclusive. We used functional magnetic resonance imaging (fMRI) in macaque monkeys to measure brain activity as they looked at pictures of other monkeys' faces that were familiar and unfamiliar to them. Activity in the entire face-processing system increased in response to the faces of long-term acquaintances. Additionally, these faces prompted the activation of two previously unknown face-selective areas. One is located in the perirhinal cortex (PR), a region that has been associated with declarative memory and the other one is embedded in a region involved in audio-visual integration and social knowledge: the temporal pole (TP). These two areas showed a nonlinear response as blurred faces became gradually visible, becoming abruptly active when the faces of familiar monkeys became recognizable. We are now exploring the electrophysiological properties of single-cell and neural populations in these areas. Preliminary results confirm our fMRI study: we found a high fraction of face-selective cells tuned to familiarity. Individual cells encoded specific familiar faces, and unfamiliar faces that were similar in shape or appearance failed to elicit the same neural responses. TP and PR emerge thus as special regions within the macaque face processing system that encode individual familiar faces.

P179.-The lack of c-Abl improve behavioral performance in an animal model of Alzheimer's disease

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c-Abl is a non-receptor tyrosine kinase that plays a role in neuronal development, neurogenesis and synaptic plasticity. Increasing evidence suggests that the c-Abl play a role in the pathogenesis of Alzheimer's disease (AD). Our laboratory has shown that c-Abl is activated in both in vitro and in vivo AD models, and its activation is involved in synaptic loss and long-term potentiation inhibition induced by Aβ oligomers. Also, treatment with Imatinib, a c-Abl inhibitor, reduces neuronal loss, Aβ deposition and cognitive impairments in a AD mouse models.
In the present study, we assess the effect of the genetic ablation of c-Abl in a transgenic AD mouse (APP/PSEN1) on behavioral performance and functional connectivity. Here, we use a new transgenic strain of AD that has a brain-specific genetic deletion of c-Abl (APP/PSEN1/Abl-KO). We evaluated the cognitive performance through two different behavioral tests: Novel Object Recognition (NOR) and Object-Location Memory (OLM). Also, we evaluated the functional connectivity in the hippocampal-prefrontal cortex axis, to establish a relationship between behavior and neuronal activity.
We found that APP/PSEN1/Abl-KO mice recovered the ability to discriminate in the OLM test. However, NOR test didn't show differences between groups. Also, our data suggest that functional connectivity might be recovered in APP/PSEN1/Abl-KO mice.
The present study contributes to the understanding of how c-Abl is involved in the pathogenesis of AD.

P180.-Novel spatiotemporal perturbations in a finger-tapping task

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Finger tapping is a paradigmatic task to study sensorimotor synchronization. In this task, the subject must tap with his finger in synchrony with a periodic sequence of brief tones, as in keeping pace with the music. Temporal differences (asynchronies) between each response and the corresponding stimulus are recorded. A usual experimental manipulation is the unexpected shortening or lengthening of the sequence's period (tempo change). In model interpretation, this is a limitation because this type of perturbation generates a change in the parameter (period of the sequence), but also in the variable (asynchrony) as a forced error occurs. In this study, we make a novel perturbation: we generate a temporal perturbation without changing the tempo. To achieve this we use a servo to shift the contact point either upwards or downwards, leading to an earlier- or later-than-intended finger tap, respectively. In this way, we uncouple the effects of the traditional temporal perturbations as the variable of interest (asynchrony) is manipulated without changing the parameter (tempo).

Our results reproduce nonlinear effects already reported and suggest that the origin of the asynchrony (forced by tempo change or by contact point shift) does not influence the subsequent resynchronization. Both types of asynchronies are processed by the same error mechanism.

P181.- “Limbo” state of memory: identification and characterisation of a new retrieval-dependent memory process in the crab Neohelice granulata

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In aversive Pavlovian conditioning, contingent presentation of a neutral stimulus (conditioned stimulus, CS) and a negative outcome (unconditioned stimulus, US) results in the formation of a CS-US fear memory. Thus, the presentation of the CS alone triggers a conditioned response (CR). Fear memory persistence could be differentially affected by retrieval. Brief CS exposures trigger memory reconsolidation and CR maintenance, whereas exposure to a high number of CSs triggers extinction and CR inhibition. Both reconsolidation and extinction have been characterised at the molecular level, presenting specific mechanisms for each process in vertebrates and invertebrates. Here we tested the hypothesis that intermediate CS exposure sessions fail to engage either fear memory reconsolidation or extinction in crabs. Our results show that, whereas 1 or 40 CS presentations rendered the fear memory sensitive to the amnestic agent cycloheximide, 80 CSs failed to do so and were insufficient to trigger memory extinction. These results indicate that intermediate CS presentations leave the original memory in an insensitive or "limbo" state, characterised by the absence of behavioural effect of the amnestic agent cycloheximide. Considering that “limbo” has been also reported in rodents and humans, our results strongly suggest that it is an evolutionary conserved retrieval-dependent mechanism whose fundamental condition is the arrest of the memory labilisation process initiated by the first CSs.

P182.-Cholinergic-prediction error signaling in aversive learning: towards a better understanding of prediction error on memory reconsolidation processes

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A consolidated memory would remain in an "inactive" state, insensitive to different interfering modulators. However, if one could access the stored internal representation of a memory (memory labilization) it would return that memory to an "active" state allowing its "update" (adding details or modifications to elements of the stored information). The passage from an "inactive" to an "active" state constitutes what is commonly called memory reactivation. Several factors are said to play an important role on the reactivation/reconsolidation processes leading to memory labilization, including: the training strength, the age of memory, the structure of the reminder (duration), the incongruence between what is expected and what actually occurs and, recently, prediction error (PE) was postulated. Recently published works carried out in our lab, emphasize not only PE as a determinant factor for memory labilization; but their importance in the different memory processes. Both works propose a novel alternative to the function of memory reconsolidation processes at physiological level in "normal" conditions and in dysfunctional memories. In the present work, we study the importance of PE as a necessary condition for a memory to labilize and reconsolidate. Furthermore, we study, for the first time, the participation of the central cholinergic system in this process by using a pharmacological approach on the inhibitory avoidance (IA) task in mice.

P183.-The interplay between behavioral pattern completion and pattern separation for retrieval in a cue-degraded context

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Because our environment is permanently evolving, it is crucial for episodic memory to remember our previous experiences despite environmental changes. Computational models have suggested the existence of a pattern completion process by which networks could retrieve entire memories from partial or degraded cues. The CA3 region of the hippocampus was proposed to mediate this computation by the plastic enhancement of the recurrent collateral connections of CA3 neurons that were active during learning. In this work, we manipulated the amount of cues available during retrieval (test phase) in a spontaneous object recognition task to investigate the function of CA3 NMDA-receptors (NMDAR) for pattern completion. We show that pharmacological intervention of hippocampal CA3 NMDAR receptors impairs retrieval of the object location memory only when cues are degraded, while similar manipulations in the dentate gyrus have no effect. Moreover, while the context alone is enough o guide retrieval of the object memory under partial cues, antagonists of NMDAR in the test phase prevent this retrieval. These findings suggest that NMDAR in CA3 are necessary for the retrieval of spatial memories when the amount of environmental information is reduced, and that plastic changes in the dentate gyrus and CA3 are important to define if behavioral pattern separation or pattern completion occurs when exposed to a modified context.

P184.-Enriched environment as an effective strategy to reverse hippocampal-related behavioral and molecular changes after an early chronic noise exposure

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Noise exposure can induce hippocampal (HC)-related behavioral and molecular alterations that could be prevented by housing rats in enriched environment (EE). As the effects of EE housing during longer periods were not explored, the aim was to test behavioral and HC oxidative markers after exposure to noise at 7 and 15 days (N7 and N15) and the possible reversal after 2 weeks of EE housing.

Male N7 and N15 Wistar rats were exposed to noise for 2 h for 5 days. After weaning, rats were transferred to an EE, while others were placed in standard cages (S). After 1 or 2 weeks, different behaviors as well as HC levels of Trx1 and Trx2 were evaluated.

Results showed that N7-S1 had an increase in associative memory and anxiety-like behaviors (AB), whereas N7-EE1 showed a full prevention. In contrast, no behavioral changes were observed in N7-S2. On the other hand, N15-S1 showed an increase in exploratory behavior and EE was unable to restore it. N15-S2 presented a decrease in AB that was reversed by EE housing. Finally, whereas N7 and N15-S1 showed an increase in Trx1 levels that were reversed in EE1, no changes were observed after an additional week. On the other hand, HC Trx2 levels were increased in N7-S1 and S2.

These findings suggest that rats exposed to noise at different developmental ages might differentially affect behavioral and molecular parameters. Furthermore, EE might be an effective strategy to reverse most alterations that seems not to depend on the housing length.

P185.-Novelty improves or impairs LTM acting on the behavioral tagging process during reconsolidation

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Prevailing theories propose that upon retrieval memories may be updated through a reconsolidation process. However, despite that daily-life remembering rarely occurs disassociated of other experiences, little is known about the rules that bound the fate of memory reconsolidation under these conditions. During the last years, we contributed to this problem by showing that the reconsolidation of different memories is achieved through a behavioral tagging (BT) process.

Now, using the spatial object recognition (SOR) task in rats, we show when and how experiences occurring close to memory reactivation positively or negatively affect the reconsolidation. We demonstrate that a 2 min reactivation session is able to add new information to the trace through a BT process specifically during memory reconsolidation. We also show that the exploration of a novel OF close to the reactivation can improve the original memory, and the memory of the newly incorporated information, by providing further PRPs. Interestingly, the same experience occurring immediately after memory reactivation, interferes with the tag inducing retrograde and anterograde amnesia. In addition, we provide evidence of specific mechanisms associated to the setting of the tag and the synthesis of PRPs.

In summary, our results show how experiences associated to a reconsolidation process improve or impair memories and their update, depending on their effect over the reconsolidation tag and the availability of PRPs.

P186.-Somatostatin containing interneurons of dentate gyrus participate in discrimination of similar contexts pattern separation mechanism

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Pattern separation is the process that ensures that similar memories will be stored in different way. For this process is important to keep a low excitability of granule cells, a principal neuron of dentate gyrus (DG). To understand the mechanism of pattern separation, we studied in transgenics mice the physiological and behavioural effect of optogenetic inhibition of somatostatin containing interneurons of dentate gyrus (SOM).

In electrophysiological experiments we found that inhibition of SOM produces an increase in the firing rate of units that have longer duration and higher burst index, two characteristics of excitatory neurons of DG, within which are the granule cells. In behavioral experiments, we found that inhibition of SOM in encoding phase of the test affect the discrimination of two similar contextual configurations.

According with our results, we propose that pattern separation mechanism involve activation of SOM, while memories are being encoded, ensuring low excitability of granule cell. For other hand, loss of SOM (which happens in epileptic and aged mice) would implicate problems in pattern separation mechanism.

P187.-Prefrontal cortex serotonin type 2a receptor activity mediates retroactive interference during consolidation phase

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Retroactive interference (RI) could be defined as the prosses by which the consolidation of a memory trace (memory A) is interrupted by the occurrence of a second consolidation process (memory B). The serotoninergic modulation of the prefrontal cortex (PFC) has been related to the correct execution of executive functions and attentional processes. Using an object recognition task calls object-in-context (OIC) we demonstrated that the PFC serotonin type 2a receptor (5-HT2AR) participates in the resolution of interference during the retrieval phase. However, little is known about the relationship between PFC 5-HT2AR activity and the RI resolution during the consolidation phase. The OIC training consists of two training session (TR) in which two different object-context associations (TR1 and TR2) are acquired. So, depending on the strength of the trainings or the delayed between TR1 and TR2, a RI process could occur. We observed that if the animals were exposed to a weak training consisting of only 3 min, they were unable to form a long-term OIC memory. Moreover, we observed a decrease in the memory expression of memory A in contrast to memory B when we used the WTP. This suggest that the consolidation of memory B interfere with the consolidation of memory A. Besides that, if we infused DOI (5-HT2AR agonist) in the PFC post-TR2 the expression of memory A increase, suggesting that PFC 5-HT2AR activity is required for the RI resolution when the WTP was used.

P188.-The role of NREM sleep in Memory Reconsolidation

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Consolidated memories can be reactivated by the presentation of a memory-cue (reminder) returning to a labile state followed by a process of re-stabilization known as reconsolidation. Thus, if amnesic agents are presented inside the reconsolidation time window (when the memory is still labile) the memory is impaired. However, if they are presented outside (~6 hours after reminder presentation), it has no effect on re-stabilization. Sleep is known to support the consolidation of newly encoded memories and it is also suggested that sleep has a beneficial effect on reconsolidation. Here we ask whether sleep accelerates re-stabilization of consolidated memories protecting reactivated memories from interferences. Participants learned a list of non-sense syllable (L1) pairs on Day 1. On Day 2, they received a reminder and they were allowed to sleep a 90 min diurnal-nap or they stayed awake for the same period of time or for 10 hours. After that, they received an interference task (L2). We found that the memory performance was impaired at testing (Day 3) only when the interference task was given 90 min after the reminder (inside the time window of reconsolidation). There was no impairment when it was given after 90 min sleep or 10 hours after the reminder presentation. Finally, a short-nap after reactivation accelerates memory re-stabilization being NREM sleep EEG slow-wave activity (SWA, power density between 0.5–4 Hz) involved in this process.

P189.-Mossy fiber plasticity of adult born dentate granule cells take weeks to mature in vivo

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New granule cells (GCs) of the hippocampus are constantly incorporated during mammalian adulthood. Ex vivo studies showed that four-week-old GCs (young) are transiently hyper-plastic, excitable and poorly coupled to feedback inhibitory loops. In agreement with this notion, young cells show enhanced synaptic plasticity on their main output, pyramidal cells in the CA3 region, visualized upon induction of long term potentiation in anesthetized mice. Our aim is to investigate output properties of developing adult-born GCs under physiological conditions on free-moving mice. We hypothesized that young GCs would be more likely to activate CA3 network than old GCs. We implanted arrays of optotrodes in transgenic adult mice and stimulated new GCs expressing channelrhodopsin-2 at different frequencies and variable laser intensities to stimulate GC cohorts trough their development, while simultaneously recording CA3 activity. We found that young GC activation evoke scarce spiking events in single cell recordings and small local field potential responses in CA3. Both spiking and field potentials increase substantially as GCs become mature. Interestingly, frequency facilitation of the postsynaptic response appeared by the fifth week and increased consistently until reaching neuronal maturation. This prolonged process of mossy fiber maturation may offer critical windows of network plasticity, which might be a crucial network property contributed by adult neurogenesis.

P190.-Thalamo-cortical information transfer during memory expression

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In addition to bottom-up signalling, auditory cortex (ACx) receives top-down input involved in cognitive processes like memory and attention. Afferents carrying such feed-back information from higher-order areas preferentially target neocortical layer 1 (L1) where they may provide depolarization to the distal dendrites of lower layer pyramidal neurons or recruit local interneurons. One strong projection derives from higher-order thalamic nuclei (MGm/PIN). However its function as well as how it affects cortical processing remains unexplored. Using Calretinin (CR) as a marker for MGm/PIN combined with in vivo 2-photon calcium imaging, electrophysiology, optogenetics and auditory fear conditioning, we find that thalamic input to ACx contributes to encoding of stimuli that acquire behavioral relevance through associative learning. Associative learning induces plasticity of sound responses in the majority of individual thalamic synaptic boutons in L1 of ACx, which correlates with the strength of the memory trace. These signals are received by excitatory and inhibitory neurons across cortical layers and can in turn be locally modulated by presynaptic inhibition from defined L1 interneurons. Our results thus reveal that MGm/PIN afferents convey information on behavioural relevance to ACx, which can recruit dendritic signalling as well as inhibitory and disinhibitory circuits.

P191.-THE IMPACT OF EARLY LIFE FAMILY STRUCTURE ON PARENTAL CARE BEHAVIOR AND OFFSPRING ANXIETY RESPONSE IN C57BL/6 MICE

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Social attachment plays an important role in progeny development. Different social experiences during lactation and throughout life can affect offspring behavior. We aimed to analyze if mono- or biparental parenting, in C57BL/6 mice, may have a differential impact on adolescent behavior and on the parental care behavior during lactation. Mice were reared in a monoparental (MP, only mother) or biparental (BP, cohabitation of father-mother since copulation) condition until weaning (postnatal day, PD, 21). Litters from both parenting conditions were filmed during PDs 6, 9 and 12 and an ethogram was made taking into account the nest occupancy and the activity of the parents. At PDs 34-37 adolescent animals were evaluated in a modified version of the concentric square field. This test allows simultaneous measurement of different behavioral patterns. The observation of parental care behavior during lactation indicated that mothers MP spent less time in the nest, left the nest alone more time and displayed more self-directed behaviors than mothers BP. BP condition displayed more pup-directed behavior than MP. Analysis of adolescent behavior, indicated that MP subjects displayed more anxiogenic-like behaviors than BP mice. In conclusion, it seems that parenting by mother only implies that pups are more time unattended that, in turn increases anxiety responses during adolescence. Further research is being conducted aimed to analyze the neurobiology corresponding of this phenomenon.

P192.-Inhibition of alpha 7 nicotinic receptors in the prefrontal cortex impairs cocaine-induced conditioned place preference

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Nicotinic acetylcholine receptors (nAChRs) in the prefrontal cortex (PFC) have critical roles in cognitive function including attention and memory and are key players in plasticity processes. Cocaine administration has been shown to induce plastic changes in PFC. However, whether nAChRs in the PFC are required for cocaine-associated memories and the underlying molecular mechanisms are still unknown. Conditioning place preference (CPP) is an animal model in which rats learn to associate the rewarding effects of a drug of abuse with the environmental context in which it is received. Here, we used behavioral pharmacology to assess the effect of intra-PFC methyllycaconitine, a specific antagonist of the α7 subtype of nAChRs, on the acquisition of cocaine-induced CPP in adult rats. We found that pharmacologic inhibition of α7 nAChRs in the PFC before conditioning impaired a 4-trial cocaine-induced CPP without altering acute locomotor response. We are now exploring the expression of molecular substrates for cocaine-associated memory on the mesolimbic circuit to shed light on signaling pathways related to our behavioral findings. In conclusion, our results suggest that α7 nAChRs in the PFC participate in the acquisition of cocaine CPP. Considering that drug seeking often depends on the association between drug-paired cues and the rewarding effects of the drug, α7 nAChRs in PFC could be considered as potential targets for the prevention of addictive behaviors.

P193.- Memory retrieval at the crossroads of mTORC1 pathway and AMPA receptors

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Recently we found that mTORC1 activity close in time to memory retrieval is required for normal expression of aversive and non-aversive long-term memories. Here we used inhibitory-avoidance task to evaluate the potential mechanisms by which mTORC1 signaling pathway participates in memory retrieval. As mTORC1 is necessary during consolidation to increase levels of GluA1-containing AMPA receptors (AMPAR) at the synapse, we assessed if a similar mechanism accounts for memory retrieval. Intrahippocampal infusion of GluA1 antisense but not GluA1 missense oligonucleotides 3 hours before testing impaired memory retention. The same result was observed upon delivery of GluA2 antisense oligonucleotides 3 hours before test, thus showing the necessity of GluA1 and GluA2 AMPAR subunits for memory retrieval. We next studied the role of GluA-subunit trafficking during memory recall and its relationship with mTORC1 pathway. We performed intrahippocampal infusion of GluA23ɣ, a peptide that selectively interferes with the endocytosis of GluA2-containing AMPAR, 30 minutes before rapamycin infusion, which inhibits mTORC1 signaling pathway. We found that GluA23ɣ prevented memory impairment caused by mTORC1 inactivation. Our work indicates that de novo GluA1 and GluA2 AMPAR subunits are required for memory retrieval and suggests that mTORC1 regulates AMPAR trafficking during retrieval.

P194.-Memory reconsolidation interference of an implicit aversive memory in humans

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The process that allows the labile trace of a memory in the short term to become stable and lasting is known as consolidation, memories can be later reactivated by the presentation of a reminder. This reactivation (labilization) of memory is followed by a process of re-stabilization known as reconsolidation, the role of this process is to update the memory both in force and content.

Anxiety manifest as a persistent and generalized defensive system, activated when predicted aversive events are perceived as a threat and uncertain. In laboratory, Pavlovian threat (fear) conditioning has been taken as the paradigm for assessing fear memories and anxiety disorders. In the framework of the reconsolidation the idea that this process would allow to modify this type of memories has been frequently cited. In most of reconsolidation works, a second task, with similar characteristics to those of the target memory, is used as an amnesic agent.

Here we aim to interfere with the process of reconsolidation of an implicit aversive memory with a task associated with another memory system. To reach such goal, we design a 3 day protocol, and compared a trained threat conditioning group, that have or not a reminder 24 hs. later and both group underwent an interference task; 48hs after, they perform an extinction follow by a reisteitment and different valanced and cognitive systems tasks. Preliminary results revealed that the memory reconsolidation interference is effective.

P195.-Positive Emotional Induction Interferes with the Reconsolidation of Negative Sad Autobiographical Memories, in women only.

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After reactivation, a previously consolidated memory can enter into a labile state followed by a re-stabilization process defined as reconsolidation. In a recent work we demonstrated that autobiographical negative angry memories can be modified by the presentation of a positive audiovisual presentation, in women only. The aim of this study was to explore whether an existing negative sad autobiographical memory can be modified using the same technic. Participants 'memories were reactivated on day 1 (retrieval) by means of the Autobiographical Memory Test (AMT) by the presentation of the negative adjective "sad" and they were instructed to remember one specific event from their own past and to write down the event in 4min. Ten min later half of the subjects were shown the positive audiovisual inductor and the other half was shown an equivalent neutral audiovisual inductor. The memories were tested 7 and 30 days later by means of the presentation of the title of the event and they had again 4 min to write down the event. The results shown that only in women the presentation of a positive inductor reduced significantly the negative emotional content 7 and 30 days later (post hoc, $p < 0.05$). In sum, we found that a positive emotional experience after a negative autobiographical memory reactivation may lead to a change in the emotional information of the original trace and that such effect can be mediated by the reconsolidation process.

P196.-Analysis of striatal neural activity during an exploration/exploitation task in a virtual environment

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The correct balance between exploration of new territories and exploitation of known resources is key for an organism's survival. Studies suggest that the dorsomedial striatum is involved in decision making and action selection. Our aim is to analyze the activity of striatal single units while head-fixed mice perform a virtual exploration/exploitation task. The task consists of a virtual linear track with short rewarded zones followed by longer unrewarded corridors. Mice are implanted with tetrodes and a metal plaque that is used for atraumatic head restraint. Mice run on a cylinder and the virtual environment is presented on two monitors in front of them. Running speed is detected using an optical mouse, and is used to control the speed at which animals navigate the virtual environment. Upon arrival to a rewarded zone, mice need to lick a spout a certain number of times to obtain a drop of water. Our results reveal that mice are able to learn the task in hand by running through the corridors towards the rewarded area and licking there to obtain a reward. As sessions progress, the animals' behavior becomes more organized restricting their licks to the rewarded zones. Our results also reveal a change in neuronal activity -by increases or decreases of firing rate- related to relevant events of the task such as entrance and exit from the rewarded areas or reward delivery. We also found a correlation between striatal firing rate and animals' speed.

P197.-Neuropeptide F and mushroom body neurons acutely control Food-seeking behavior in adult fruit flies

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How motivational drives shift from novelty-seeking behavior (NSB) to food-seeking behavior (FSB) is unclear. We recently have adapted the novel object recognition behavioral test to fruit flies. In this assay we found that fed flies show preference for novelty, whereas fasting impaired recognition memory, but not habituation or olfactory conditioning memory. We hypothesized that in hungry flies, hunger but not novelty drives the behavior. To analyze the relationship between NSB and FSB we began by developing a behavioral assay to examine and quantify FSB in the context of object recognition. Here we show that neuropeptide F and mushroom body (MB) neurons, but not insulin-like peptide release, acutely control FSB in adult fruit flies. First, we set the conditions where fasted flies strongly prefer an object loaded with food compared with an empty object. Then we examined the requirement of different neuronal components in FSB. Acute thermogenetic inhibition of the synaptic output of NPF neurons by Shits1 completely abolishes FSB in fasted flies, in agreement with previous reports. In addition, acute thermogenetic inhibition of the synaptic output of all MB neurons also abolished FSB in fasted flies. More interesting, the inhibition of the synaptic output of all MB neurons in flies fed ad libitum promotes FSB, indicating that MB neurons constitutively inhibit FSB in fed flies. Ongoing experiments explore the role of NPF and MB neurons in NSB in fasted flies.

P198.-Acute physical activity could improve spatial pattern separation in humans

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To allow similar episodes to be distinguished in memory, the brain must form distinct representations of events. This process is called “pattern separation” and recently our group has shown that the brain-derived neurotrophic factor (BDNF) could be part of an essential mechanism underlying the consolidation of pattern-separated memories. Likewise, under conditions of physical activity, high levels of this factor have been reported, both in rodents and in humans. We specifically designed a task to assess spatial pattern separation in humans in a virtual reality environment, which consisted on testing the long-term memory of the position of two flags separated by different angles. The preliminary results of this study show that acute physical activity (25 minutes of fixed bicycle) could improve performance in this task using a small angle. It is a translational proposal that can certainly have an impact on the knowledge of the biological bases of human cognition and mental health.

P199.-Social Interaction and Memory are affected by Chronic Administration of Fluoxetine in 5-HT2AR Knockout Mic

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Fluoxetine (FLX) is a selective serotonin reuptake inhibitor (SSRI), well known for its antidepressant effects and for being widely prescribed in the treatment of different psychiatric disorders. Since the SSRI blockades the serotonin (5-HT) reuptake, the final effect of this drug is to increase the 5-HT permanence in the synaptic space. The Serotonin type 2A receptor (5-HT2AR) is one of the most expressed receptors in the post-synapses of the serotoninergic system. This receptor has been linked with the cognitive symptoms presented in some psychiatric disorders. Then, we intended to analyze if chronic administration of FLX presented cognitive effects and the possible role of 5-HT2AR in those effects. For this purpose, we administrated a chronic oral dose of fluoxetine (10mg/kg) to Wild Type (WT) and 5-HT2AR knockout mice (KO). After 4 weeks of FLX administration, we performed a novel object recognition task and a social interaction test. The results showed that a 3 min training session is not enough to generate a long term NOR memory (24 h delayed) independently of the genotype. Interestingly, FLX treatment allowed WT mice to solve the NOR test. However, we didn't see this effect in KO mice. Regarding social interaction, FLX improved the performance of the WT mice but not the KO. These results suggest that 5HT2A signaling might be involve in the effects of fluoxetine in memory and social interaction in mice.

P200.-Memory deficits in Transgenic McGill-R-Thy1-APP hemizygous rats

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McGill-R-Thy1-APP Wistar transgenic (Tg) rats, with human APP under the Thy1.2 promoter, bearing the Swedish and Indiana mutations corresponding to familial AD in homozygous condition, had been reported to show significant cognition deficits at 3 months of age. On the other hand, hemizygous Tg rats show a more subtle phenotype. In this work, 6 and 13 month old hemizygous Tg males and their WT litter mates rats were individually left to freely explore an open field (OF) for 5 min and tested at 24 h; the numbers of crosses in the floor were recorded. There were no differences between WT and Tg groups during the training and the number of crosses significantly decreased in the test compared with training. Rats were then trained in an inhibitory avoidance task (IA) of a mild electric foot shock and tested at 24 h to evaluate long-term memory (LTM). Latency to go accross a door to get into a dark compartment where the rat will get the shock, was recorded. There were no significant differences in training latencies between animal groups. 24 h later, test latencies were significantly higher than training latencies for WT rats, while there were no significant differences for Tg rats. Therefore, both Tg and WT rats are able to habituate to the OF, keeping LTM; on the other hand, WT animals learned and remembered the IA at 24 h, while the Tg were not able to remember it, evidencing deficits in these sort of associative memory involving aversive and spatial components.

P201.-Reinforcing what is good: Appetitive memory strengthening through reconsolidation in the crab Neohelice granulata

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Information stored in the memories allows organisms to predict future events based on previous experiences. Thus it must persist even in the absence of the indicators used at the time of acquisition, and might be susceptible to changes in the environment. In this sense, the reconsolidation process opens the possibility to update memory in both strength and content. A recent work performed in rats has shown that brief memory reactivations events lead to memory enhancement as a result of reconsolidation, suggesting memory strengthening. However, this function has not been demonstrated in appetitive paradigms. In this study we were interested in addressing if an appetitive memory could be strengthened by this process in the crab Neohelice granulata. Animals received an appetitive training and were re-exposed to the training context 24 hours later. Given the assumption that reconsolidation processes strengthen the original trace, the resulting memory should be more robust and less sensitive to the amnesic agent cicloheximide when administered minutes before reactivation. Preliminary results revealed that a single re-exposure to the training context triggers the reconsolidation process, and as a result, we observe memory enhancement. Future experiments will allow us to address the mechanisms of this modulation, such as if this strengthening as a consequence of reconsolidation implies plastic changes on the trace which can be revealed through neural correlates or epigenetic change.

P202.-Effect of postnatal mynocicline treatment on a two-hit model of autism in female mice

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Autism spectrum disorders (ASD) are characterized by reduced sociability, diminished communicative skills and repetitive behaviors. Notably, the proportion between boys and girls diagnosed with ASD is 4:1 approx. This suggests a higher susceptibility in boys to develop ASD, or resilience in girls. To identify the biological mechanisms underlying this bias, we used a mouse model of ASD: the prenatal exposure to valproic acid (VPA). Remarkably, this model also presents a different phenotype in males and females, as females do not show the reduction in sociability observed in adult males.

One important risk factor in ASD is immune system dysregulation. In fact, we found that prenatal exposure to VPA leads to alterations in microglia and astrocytes in females between postnatal day (PD) 21 and 35. Using a two-hit model, which consists in prenatal VPA exposure and a chronic treatment with LPS between PD 21 and 35, we found that female mice express a reduction in sociability. This evidence suggests that immune alterations during this postnatal period are critical to develop social alterations and may overcome the sex-dependent resilience. Minocycline is an antibiotic that crosses the blood–brain barrier and acts by reducing the microgliosis. We hypothesized that Minocycline administration during the critical period mentioned above can revert the behavioral alterations observed in our two-hit model.

P203.-Layer IV and V pyramidal neurons of A29 are required for disambiguate emotionally relevant contexts

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Retrosplenial cortex (RSC) is divided in two anatomically distinct subregions: A29 and A30, but the functional role of each subunit in cognitive processing remains elusive. Systemic application of MK801 causes elimination of pyramidal neurons in layers IV and Va of A29 (A29MK801 neurons), without affecting A30 or other brain areas. Previously, we showed that selective loss of A29MK801 neurons did not affect freezing behavior but significantly impairs A30-activation and the retrieval of contextual fear memory (CFM). To dissect the functional role of A29MK801 neurons in CFM first we used open field and elevated plus maze tests and found that loss of A29MK801 neurons have no anxiolytic effect, suggesting these neurons are not required for risk assessment during CFM. Elimination of A29MK801 neurons did not impair contextual recognition as assessed by object in place tests or by an A-B-A design of contextual fear test. However, elimination of A29MK801 neurons completely abolishes retrieval of fear memory associated to pre-conditioned stimuli in higher-order conditioning. However, in a higher-order conditioning paradigm elimination of A29MK801neurons completely abolishes retrieval of fear memory associated to pre-conditioned stimuli. Altogether, our data suggest that A29MK801 neurons are critically required for the retrieval of complex contextual association memories with emotional relevance likely by impairing the activation of A30.

P204.-Role of hippocampal remapping in contextual memory

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The Hippocampus (HP) plays a central role in the encoding, consolidation and retrieval of episodic memories. Some hippocampal neurons, called place cells (PC), fire whenever an animal is at a certain location in the environment; however, only a subset of the PC fire in any given environment. When the environment changes, PC can change their activity (remapping). Accumulating evidence has suggested that the functions of PC, extend well beyond a specific role in mapping the physical space. It has been suggested that the hippocampal ability of storing and distinguishing between different situations and contexts, can be related with place cell's remapping.

Several studies have shown how the CA3, a hippocampal region, can either remap or not as consequence of the changes in contextual clues. Still, there is no study showing how this change in neural activity correlates with the behavioural response. In other words, It's still unknown whether when an animal recognizes a certain context as new, there is remapping in the activity of CA3 or not. The ongoing project takes advantage of a behavioral test that allowed us to discriminate if an animal recognizes a context as new, or as one they already knows. We carried out electrophysiological recordings in CA3 region of the HP while they were performing the task in order to correlate the remapping and the evocation of different contexts.

P205.-ETHANOL-INDUCED LOCOMOTION AND INTAKE AFTER ENVIROMENTAL ENRICHMENT IN THE OFFSPRING OF RATS SELECTED FOR HIGH OR LOW ETHANOL INTAKE AT ADOLESCENCE

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Animal models of genetic risk for alcohol use disorders include rat lines selected for high or low-ethanol consumption during adulthood or, as developed in our lab, during adolescence. The latter is the developmental stage in which the onset and escalation of ethanol intake takes place. Recent work suggested that environmental enrichment (EE) could reduce the problematic use of ethanol and other substances of abuse, although others indicated that EE could exacerbate ethanol intake when applied during adolescence. We assessed the effect of environmental enrichment rearing during adolescence upon ethanol-induced locomotion and intake, in two lines of rats, derived from mating “HIGH” or “LOW” ethanol-drinking F2 parents. From postnatal day 21 (DP 21) to 42, the animals – males and females – were reared under EE or standard conditions (SC). Ethanol-induced locomotion was evaluated acutely and after 9 administrations of ethanol (Experiment 1), and voluntary ethanol intake was measured across 3 weeks (Experiment 2). Ethanol-induced locomotion was lower in EE than in SC rats, regardless line (HIGH or LOW). After repeated administrations of the drug, this effect was observed only in male HIGH rats. In experiment 2, ethanol intake was significantly greater in HIGH vs. LOW rats and, within females, in EE vs. SC rats. These results are consistent with previous studies indicating that EE may have deleterious effects upon ethanol intake, when applied during adolescence.

P206.-Vocal effort modulates the motor planning

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Speech requires programming the sequence of vocal gestures that produce the sounds of words. Here we explored the timing of this program by asking our participants to pronounce, as quickly as possible, a sequence of consonant-consonant-vowel (CCV) structures appearing on screen. We measured the delay between visual presentation and voice onset. In the case of plosive consonants, produced by sharp and well defined movements of the vocal tract, we found that delays are positively correlated with the duration of the transition between consonants. We then used a battery of statistical tests and mathematical vocal models to show that delays reflect the motor planning of CCVs and transitions are proxy indicators of the vocal effort needed to produce them. These results support that the effort required to produce the sequence of movements of a vocal gesture modulates the onset of the motor plan.

P207.-Improvement of declarative memories in older adults through the reconsolidation process

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After learning, memories go through a period of lability, to then stabilize (consolidation). However, once consolidated, they are not static. On the contrary, they can return to a labile state after the presentation of a reminder followed by a period of re-stabilization (reconsolidation). Thus, this process represents a unique opportunity to modify stored information: impair, incorporate or improve memories. Here, we will show preliminary results concerning the conditions that can improve declarative memories in older adults trough reconsolidation process.

P208.-Spaced learning and the mechanisms that optimize memory formation

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The superiority of spaced learning over the massed one is a fundamental fact in the formation of long-term memories (LTM). We studied the cellular processes and the temporal demands of this phenomenon, using weak spatial object recognition (wSOR) and weak inhibitory avoidance (wIA) learning tasks. We observed SOR-LTM promotion when two identical wSOR, which individually induced short-term memories but did not form LTM, were spaced by an inter trial interval (ITI) ranged between 15 min to 4 hr. The promoting effect was dependent on hippocampal protein synthesis and MAPKs activity. Also, two identical wIA training sessions spaced by 4 hr, promoted IA-LTM. In contrast, when we combined one wIA with a wSOR, neither of the two tasks formed LTMs.

We discuss these results under the "behavioral tagging" hypothesis which postulate the existence of a tag induced by learning that utilize proteins to form LTM. We suggest that the neural contacts stimulated by the first training session are re-tagged by retraining. Moreover, after retraining, the intracellular mechanisms triggered by both sessions could be added, reaching the threshold for protein synthesis required for memory consolidation. On the other hand, when animals are trained in two different and weak tasks, the processes triggered by them would not meet the spatial requirements necessary to form LTM.

P209.-Early ethanol intoxication alters enzymatic catalase activity and generates associative respiratory learning

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Ethanol (EtOH) during early ontogeny severely affects brain development, learning, memory and breathing platicity. The catalase (CAT) system is the main metabolic pathway of EtOH oxidation to acetaldehyde in the brain; a metabolite that regulates different EtOH effects. We assessed whether EtOH experience may induce a differential activation of CAT while also evaluating respiratory plasticity. At postnatal days (PDs) 3, 5 & 7 Wistar rats were administrated via cisterna magna with EtOH (300mg%) or phosphate buffer (PB) in association (Paired) or not (Unpaired) with EtOH odor (conditioned stimulus, CS). At PD9 all pups were administrated with PB and breathing frequencies were recorded by plethysmography under normoxia and hypoxia conditions with or without the CS. Pups later consumed a 5.5% EtOH solution and their brains were removed for determination of CAT activity. The intake test also provides exposure to the odor of the drug. When exposed to the CS, Paired-pups failed to hyperventilate during hypoxia; an effect that suggests a negative outcome of prior learning processes. A significant increase of CAT activity was observed in pups pre-exposed to central EtOH and this activation was more pronounced in Paired-pups. It appears that EtOH-related associative learning interferes with the capability of the organism to cope with the respiratory demands of a hypoxic event. Prior EtOH exposure was also found to cause an enzymatic induction of CAT modulated by a new toxic episode.

P210.-Effect of systemic administration of mGlu3R agonist in a model of cerebral ischemia

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Chronic cerebral hypoperfusion (CCH) resembles central changes in aging-related vascular dementias and Alzheimer´s disease (AD). Our group has demonstrated, in vitro, that astroglial subtype 3 metabotropic glutamate receptors (mGlu3R) present protective actions against neurotoxic agents including Aβ. However, contradictory results were reported when mGlu3R ligands were administered in vivo

We examined the effect of the mGlu3R agonist, LY376298 (LY) 1mg/kg i.p., in middle aged rats with CCH. Memory retention was evaluated using the aversive radial maze and NeuN and GFAP expression were determined by immunohistochemistry.

All groups showed increased latency and number of reference memory after surgery ($p<0.05$), while CCH+LY treatment aggravated it. We observed a decrease, although not significant, in NeuN expression in the hippocampus of the CCH+LY group compared to CCH. Moreover, GFAP expression showed an increase in CCH+LY hippocampus compared to CCH and sham groups.

To conclude, our results suggest that the in vivo administration of a mGlu3R agonist potentiates the cognitive deficit in the CCH model, probably by inducing the activation of astrocytes and, consequently, decreasing neuronal survival.

P211.-Role of sleep in the organization of the spatial map during episodic memory formation

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The development in the study of place cells discovered by O'Keefe (1971) has put the focus on the study of spatial representation of the environment in the processes and functions lead by the hippocampus. Among these functions, the hippocampus plays a preponderant role in the establishment of spatial memory, in which sleep is fundamental, suggesting a possible relationship between sleep and the establishment of spatial representations by place cells. In this line, there is a query if sleep participates in the consolidation and configuration of spatial representations. In this study we will evaluate the influence of sleep on the variations in the configuration of a spatial map given by changes in spatial context. Specifically, we will analyze the features of place cells recorded in hippocampal CA1 in terms of firing rate, place field location and spatial information during object in place recognition (OPR) test in conditions of Sleep or Sleep deprivation in the post learning phase. Here we will present our preliminary results showing that post-learning sleep enhances performance in the OPR task and that this effect is related to specific changes in the patterns of configurations of the spatial representation leaded by place cells. The study of sleep`s influence on spatial representations given by place cells in the hippocampus will allow us to understand the importance of this process in the performance of a cognitive function such as memory.

P212.-Dorsal hippocampal κ2 opioid receptors activation negatively modulates contextual fear memory consolidation in rats

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The κ opioid receptors (κORs) subtypes (κ1ORs and κ2ORs) are expressed in brain regions involved in fear memory consolidation, including the dorsal hippocampus (DH). The present study sought to investigate the contribution of DH κORs subtypes to contextual fear memory consolidation. Male Wistar rats were fear conditioned to context A (3 shocks 1.0 mA, 3s) and then received an intra-DH bilateral infusion of vehicle (VEH), a κ1OR agonist U-69593 (0.1, 0.3, 1.0 or 30.0 nmol) or a κ2OR agonist GR 89696 (0.1, 0.3 or 1.0 nmol/hemisphere). Tests sessions were performed on days 1 and 8 after conditioning session (Tests A1 and A2, respectively). Freezing behavior was measured as an index of memory retention. Finally, animals had the DH dissected 90 min after fear conditioning and drugs infusion to BDNF analyzes by ELISA. In experiment 1, infusion of GR 89696 0.3 and 1.0 nmol immediately after conditioning session decreased the freezing time in both Tests A1 and A2 when compared with respective VEH groups (Test A1: VEH = 80 ± 4, GR 89696 0.3 = 51 ± 6 and GR 89696 1.0 = 50 ± 4%; Test A2: VEH = 74 ± 3, GR 89696 0.3 = 40 ± 7 and GR 89696 1.0 = 38 ± 3%). In experiment 2, U-69593 infusion had no effect on freezing time. Finally, in experiment 3, GR 89696 0.3 nmol decreased BDNF levels in DH (VEH = 116 ± 13 vs GR 89696 0.3 = 65 ± 11 pg/mg of protein). Present results suggest that DH κ2ORs activation negatively modulates contextual fear memory consolidation, possibly via BDNF reduction.

P213.- Calrretinin+ neurons partially compensate the loss of calbindin+ neurons caused by perinatal asphyxia in the rat's striatum

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The striatum is particularly vulnerable to perinatal asphyxia (PA). The main neuronal populations of the striatum are GABAergic median spiny neurons. A high portion of them also co-express calbindin (CB).

At delivery time GABA has excitatory properties and excitotoxicity process could be mediated via GABAergic networks in case of pathological events.

In previews works we found that PA generate a loss of calbindin neurons (around 50%) followed by an increase in other GABAergic subpopulations.

The aim of the present work is to analyze the effect of PA over subpopulations of GABAergic neurons in the striatum and to assess the deep hypothermia therapeutic outcome.

The uterus was removed by caesarean section and the fetuses were exposed to hypoxia by immersion in water (19 min) at 37 C˚ (PA). The hypothermic group was exposed to 10 C˚ during 30 min after PA. Four experimental groups of 3-4 rats were formed. The immunolabeling of CB, Calretinin, Neun, and reelin was measured in adult rats by a skilled observer blind to treatment.

Reelin+ cells that usually co-express Calretinin, showed no stain in the striatum besides subventricular zone. The PA group showed a significant decrease in CB+ neurons and a paradoxical increase in neurons estimated by Neun stain. Moreover, a specific subpopulation of GABaergic Calretinin + cells showed an increase caused by PA. Deep hypothermia reversed most of these alterations most likely by protecting calbindin neurons.

The mechanism involved in this compensation is not clear. It is possible that Neun and Calretinin + cells filled the space left by Calbindin neurons. As well, an active mechanism to keep the homeostasis at excitation-inhibition balance is also plausible. Deep hypothermia could be a superlative option to reduce severe disability generated by the PA.

P214.-Effect of attention on the synchronization in a paced finger tapping task

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In the present work we investigate the effects of attention and sensory feedback on synchronization to an auditory metronome where the subject must resynchronize after a tempo change. In most of these experiments subjects do not receive any specific indication about what to focus their attention to. We believe that this constitutes a source of uncontrolled variability that significantly affects performance in the task. Here, a group of subjects performs a paced finger tapping task without receiving any specific instruction about what they should focus their attention to (non-forced attention). A second, different group of subjects performs the task that forces them to focus their attention to the tempo change (forced attention). Both groups, in addition, perform the task in two conditions: with and without auditory feedback. We found that the group that tapped in the forced-attention condition showed a lower average asynchrony and a higher autocorrelation of the inter-tap intervals with respect to the group that tapped in the non-forced attention condition. Furthermore, the addition of feedback decreased the average asynchrony regardless of the attention condition. No significant effects of feedback or attention on resynchronization speed were found. These results suggest that the attentional factor has an effect on synchronization at least in the isochronous phase and that it must be taken into account in the experimental design.

P215.-An optimized method to acquire single cell activity for online analysis of screening sessions in humans

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The first requirement for the study of concept cells in the human medial temporal lobe is the finding of the stimuli eliciting responses from the neurons being recorded. To this end, a screening procedure is used, where a large set of stimuli is presented, and the recorded data is analyzed offline. During the analysis time, neurons might disappear from the recording, resulting in the loss of the responses that would be used in the upcoming experimental paradigms. Using the cbMEX interface of Blackrock Microsystems we are able to employ the computational power of the acquisition system for a coarse spike detection and clustering, which is enough to determine whether or not a stimulus can elicit a response from a certain neuron. The strength of the response for each stimulus is automatically quantified, so the best ones can be selected for further tasks. In addition, this procedure allows us to initially present a larger number of stimuli in the same period of time (improving the chances of finding those related to a concept cell) and the possibility of stopping the screening after a few minutes once a certain amount of responses has been clearly found.

P216.-Robotic vehicles as a tool to study the neural basis of locomotor activity

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We used a robotic vehicle to study the neural basis of locomotor activity in the nematode C. elegans. Using a robot has a specific advantage over a biological model, since it is possible to access and have control over all the ingredients that governs its behavior. At the same time it also allows for the implementation of a complex system that is subject in a natural way to the laws of physics in its interaction with a real environment. In particular, we implemented a numerical simulation of the neural system of the nematode C. elegans in a robotic vehicle. The environmental information is obtained by using a distance sensor that transmits information directly to sensory neurons, and locomotor activity is controled by electric motors that are connected and receive information from the corresponding muscle output. We found that, as was observed experimentally in the C. elegans brain by Kato et al. (Cell 163, 656–669 2015), a large proportion of the simulated neurons across the brain share information by engaging in coordinated, dynamical network activity. Also, as in the experiments by Kato et al., the simulation evolves on a smooth cyclical dynamics, where different segments, that correspond to the activities of different neuronal sub-populations, can be mapped to represent action sequences of the robot. Our results show the robustness of the brain dynamics of C. elegans, and also how robotics can contribute to the understanding of the neural basis of locomotor activity.

P217.-Mindfull learning: meditative state classifier using random forest

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The use of EEG signals provides a promising analysis to assess the meditative state in an objective fashion. The changes in brain activity during the meditative state are well documented, however models that build classifiers in a way that enables them to distinguish the meditative state are scare. This analysis was performed in 3 groups of meditators: Himalayan Yoga (HT), Vipassana (VIP) and Isha Shonnya Yoga (SNY). Briefly, the random forest method is based on a decision tree concept where each node represents one characteristic and classes are divided aiming for the maximum purity of the data until 100% purity is reached, hence that group of data becomes classified. To analize the similarities between the different meditative states in a multivariated way, random forest classifiers were generated in order to differentiate the cerebral states of each from the power potential of each spectral band. Throughout all the spectrum studied the trained classifiers with HT data were able to distinguish correctly the SNY data and for all the bands except one the optimized classifiers to distinguish VIP generalized the data of SNY. We observe a similarity between the states along all the bands, being δ, low γ and high γ the ones that present a higher classification inter-state. These results suggest that there is common ground in the cerebral states reached through different meditative traditions, represented by the EEG data, which manifest throughout the studied frequency spectrum.

P218.-Commonalities in whole-brain functional connectivity associated with the psychedelic state determined using machine learning techniques applied to fMRI experiments

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Classic psychedelics (5-HT2A agonists) elicit profound transient modifications in the consciousness of the self and the environment. Other substances that modulate the level and quality of conscious content and are of potential therapeutic value are entactogen psychedelics such as MDMA and the dissociative ketamine (NMDA antagonist). Despite variability in the elicited subjective effects, these drugs share as a common motif the induction of a non-ordinary or altered state of consciousness. We search for the commonalities and divergences between the changes in whole-brain activity elicited by two classic psychedelics: LSD & psilocybin; MDMA, ketamine and a control non-psychedelic drug: Modafinil (dopaminergic stimulant). fMRI data acquired from different scanners was processed according to a unified standard. Then we computed the functional connectivity between all pairs of 90 neuroanatomical regions and trained a random forest classifier to identify them from their associated placebo condition. We investigated whether a classifier trained using data from one drug could generalize to detect the changes in brain activity associated with all other drugs, and mapped in anatomical space the network of functional connections associated with the successful generalization. Our results suggest that the shared effects of psychedelics can be quantitatively measured using fMRI, bringing us closer to dissect the varieties of the psychedelic state and their associated neural correlates.

P219.-Metabolites restriction and connectivity performance of astrocytes networks

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Within brain tissue, astrocytes (AST) represent by far the most abundant cell lineage. It has become widely accepted that AST are anything but the glue of the Central Nervous System and are associated, among others, with cognitive functions, information flow and processing, metabolic regulation and even the pathogenesis of certain neurodegenerative diseases. AST establish a very interesting cellular arrangement through specific and narrow junctions, GAP junctions, allowing a coordinated and dynamic function as a network.
The present work explores how metabolite availability modulates connectivity levels of AST network combining a physiological approach with a biophysical one.
Network connectivity was assessed in AST primary cultures by measuring fluorescence recovery after bleaching (FRAP technique) either in a medium with high glucose or a non-glucose one. In addition, we have designed a numerical model that mimics various dynamic aspects of AST networks. The model is a bidimensional cellular automaton where the first and second neighbor interaction has been set up in such a way that different hypotheses regarding the flow of information could be tested.

P220.-Testing the usability of a cognitive training software for measuring executive functions in unsupervised educational interventions

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Mate Marote is an open source cognitive-training software aimed at children between 4 and 8 years old. It consists of a set of computerized games specifically tailored to train executive functions (EF): a class of processes critical for purposeful, goal-directed behavior, including working memory, planning, flexibility, and cognitive control.

In previous studies we showed that (1) less than 7 hours of training elicited transfer to some (but not all) facets of EF, (2) the academic performance of children living at risk was boosted by the intervention, and (3) the quality of play and behavioural patterns during the training phase in unsupervised interventions are comparable to the data collected in one-to-one supervised designs.

In the present study we assessed whether the software can be used for measuring EF in unsupervised interventions. We show that children performance in the EF tests obtained in unsupervised, but controlled, school environments with their own teacher are comparable to the data collected in the testing phase of supervised designs, as expected. In this unsupervised experiment, the gameflow, the instructions and the feedback were entirely provided by the software and their own teachers only had to ensure the correct login of each children. Our study suggests that testing the results of large scale educational interventions could be simple, under minimal, but appropriate, controlled conditions.

P221.-Testing neural models for birdsong production and perception

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Songbirds are a well established animal model to study the biomechanics and the neural circuits involved in vocal learning and production. The telencephalic nucleus HVC (proper name) is characterized by having selective neurons to the song of each bird. When the bird is asleep or anesthetized and a recording of its own song is reproduced, the neurons respond with a specific firing pattern, similar to the one generated during song production. Currently there is a controversy over the neuronal coding of HVC. One view suggests that HVC encodes every detail of the song. It is proposed that the behavior is encoded by a firing chain in HVC. An alternative model suggests that song production occurs in a distributed manner along several nuclei of the song system and that HVC activity is related to specific motor instances. In this work we developed an extracellular neuronal registration system that allows the simultaneous acquisition of up to 64 recording channels, using commercial multi-electrodes (Neuronexus Tech. Inc). With this system we performed selectivity experiments in zebra finches (Taeniopygia guttata) to study the neural coding of HVC and, in particular, the scope of the two proposed models.

P222.-Effect of GABAergic receptor activity on glutamate release during excitotoxic damage in mouse spinal cord injury model

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Acute spinal cord injury induces loss of motor, sensory and autonomic functions through a process involving a primary injury and a secondary phase during which massive glutamate release occurs. This phenomenon implies dysregulation of the excitatory and inhibitory network balance. The present study on mouse organotypic spinal slices analyzed how pharmacological manipulation of GABA receptors might affect real-time glutamate release following 1 h kainate application. We used a glutamate biosensor placed in the ventral horn area and monitored neuronal survival later. Furthermore, we studied if L-amino-4-phosphonobutyrate (L-AP4; 1 µM) could inhibit glutamate release. Glutamate release evoked by kainate was significantly reduced by the allosteric GABA modulator midazolam (10 nM) or the agonist THIP (10 µM), leading to neuroprotection. On the contrary, higher release was induced by bicuculline (20 µM), while no effect was observed with gabazine (20 µM). L-AP4, an agonist of group III mGluRs, largely depressed glutamate release and protected neurons. These findings indicate that pharmacological depression of glutamate release via enhancement of GABA receptor activity or inhibition of presynaptic release with mGluR activation were effective tools to counteract excitotoxic death in spinal networks. In view of the THIP activity, the present data imply a significant role for extrasynaptic GABA receptors in sparing spinal cord neurons from injury. Supported by ICTP and CONICET.

P223.-Integration of visual and auditory information in a decision-making neuron

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One fundamental task of the nervous system is to make adaptive behavioral decisions based on multiple sources of sensory information. In this context, multimodal integration is the process by which different sensory components of an event are combined to form a single percept. Multimodal integration increases the probability of detecting a relevant event, especially when individual cues are weak or ambiguous.

In fish, the circuit responsible for initiating the escape response is centered on the paired Mauthner cells (M-cell). These neurons are sensory integrators that receive both visual and auditory inputs and upon reaching firing threshold trigger the escape response. This relatively simple circuit provides a unique opportunity to dissect the mechanisms of multimodal integration at neuronal level.

We performed in vivo intracellular recordings in M-cells of goldfish while the animals were stimulated with auditory or visual signals. Auditory signals were produced by a loudspeaker while visual signals consisted on trains of electrical stimulation of the optic tectum. We recorded M-cell responses to either unimodal stimuli or multimodal combinations of auditory and visual stimuli. Our results show that multimodal stimuli produce an enhancement of the M-cell response partly dependent of the delay between the auditory and visual stimuli. This underlines the importance of the temporal coherence of individual components of a multimodal signal to be effectively integrated.

P224.-Subcellular localization of Kv1.3 and Kv1.1 potassium channel subunits in striatal cholinergic interneurons of mouse models of experimental parkinsonism and L-DOPA-induced dyskinesia

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Parkinson's disease (PD) characterizes by a degeneration of mesencephalic dopaminergic neurons that innervate the striatum, a key nucleus for the selection of motor programs. In advanced stages of the disease only L-DOPA as a dopamine-replacement strategy allows an adequate performance in daily activities. However, the effectiveness of L-DOPA decreases and abnormal movements emerge (dyskinesia). Striatal cholinergic interneurons (SCIN) are key modulators of striatal circuits and are hyperexcitable in animal models of PD, owing to dysfunction of voltage-dependent potassium channels containing Kv1.3 and Kv1.1 subunits which is not due to a decrease in Kv1.3 protein expression. Enhanced SCIN activity was also linked to L-DOPA-induced dyskinesia (LID). Here we address whether SCIN dysfunction in mouse models of PD (unilateral lesion of the medial forebrain bundle with 6-OHDA) and LID is associated with an impaired trafficking of Kv1 channel subunits to the plasma membrane. We use genetically modified mice that express a fluorescent membrane marker (channelrhodopsin-EYFP fusion protein) in SCIN (ChAT-Cre;LSL-ChR2-EYFP) and analyze the distribution of the Kv1.3 and Kv1.1 subunits in the plasma membrane and intracellular compartments of SCIN, using immunohistochemistry. Preliminary results show that the fraction of Kv1.3 and Kv1.1 immunolabeling localized to the plasma membrane of SCIN in parkinsonian and dyskinetic mice did not differ from what was observed in unlesioned mice.

P225.-Effects of static magnetic fields on cortical activity in a rat model of epilepsy

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Epilepsy is one of the most common chronic neurological disorder. It is characterized by recurrent and spontaneous epileptic seizures caused by neuronal hyperexcitability. Currently, there is a demand for new clinical approaches to treat this disorder that do not respond to available pharmacological treatments. In that sense, Static Magnetic Field (SMF) reduces cortical activity in both, human and animal models. The aim of this work was to study the effect of SMF on epileptic cortical excitability. EEG was continuously recorded in 8 anaesthetized rats, in which epilepsy was induced by the lithium-pilocarpine model. Rats were anaesthetized to get a stable slow wave activity showing up and down states. Animals were classified as “magnetic” (a NdFeB magnet was placed over the skull before pilocarpine injection), or “control” (a replica without magnetic properties was used). Between 15-30 minutes after a second injection of pilocarpine, EEG changes compatibles with epileptic seizures were clearly observable in the control animals: Down states duration was reduced and the power at 1-4 and 4-8Hz band was increased. Similar effects were visible in those animals with the real magnet but 1-2 hour later, indicating that SMF was able to slow down the appearance of abnormal cortical activity. These results reinforce the view that SMF is able to modulate cortical activity and open the door to future therapeutic use of SMF in epilepsy as a complement to current pharmacological treatments.

P226.-Temporal mapping of adult-born granule cells integration in two major local inhibitory populations of the hippocampus

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Adult neurogenesis provides a continuous pool of new granule cells (GCs) that participate in information processing in the dentate gyrus of the hippocampus. We studied how GCs become integrated toward maturation into the preexisting circuit of the adult mouse dentate gyrus. We chose two major population of GABAergic interneurons (INs) of the hippocampus: Parvalbumin expressing cells (PV) and Somatostatin expressing cells (SST). We combined optogenetics and acute slice electrophysiology to activate PV or SST and GCs, retrovirally labeled, at different stages of maturation and studied their connectivity in both directions, interneuron to GCs and viceversa. We built a temporal map of synaptogenesis for each IN population and observed that connectivity between PV and GCs (input and output) reached maturation when GCs were >6 weeks old. For SST, the inhibitory postsynaptic current increased gradually with GCs development, while the GC output connectivity developed much later (>11 weeks) compared to PV. We found that PV synapses onto GCs were located perisomatically and contributed to both feedforward and feedback inhibitory loops within the granule cell layer. In contrast, SST contacted GCs in proximal and distal dendrites and contributed only to feedback inhibition. These data demonstrates that integration of new GCs within the preexistent dentate GABAergic network is specific of each IN population and that adult neurogenesis promotes a long-term plasticity for circuit remodeling.

P227.-Network dynamics of nociceptive and aversive processing in the anterior cingulate cortex

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The Anterior Cingulate Cortex (ACC) plays a central role in the evaluation of the affective aspects of pain and accumulating evidence indicates that the hyperactivity of the ACC is involved in the manifestation of the emotional distress that characterizes chronic pain (CP) conditions. However, little is known on how the functional organization of ACC microcircuits is affected during CP. Here we addressed how neuronal ensembles of the ACC process nociceptive information and how this microcircuit organization is affected in a mice model of neuropathic pain (NP). Using in vivo recording of spiking activity we have identified a subpopulation of neurons that are activated in response to noxious stimuli and show a preferential increase in spontaneous activity during NP. To gain insight on the organization of ACC "nociceptive" neuronal ensembles, we have monitored the activity of the same network of neurons on subsequent days during the transition to NP with two-photon calcium imaging. Our preliminary results show that noxious stimuli are codified by the activity of a discrete and partially stable assembly of ACC neurons. Interestingly, these neurons are also activated by other aversive but not noxious stimuli, suggesting that the representation of aversive events in ACC neuronal ensembles is not specific for nociception. Finally, we observed that this fine-tuned representation is degraded during NP resulting in a wide-spread neuronal representation of noxious events.

P228.-What happens in the brain during epileptogenesis?: Analysis of single-unit activity during Rapid Kindling

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Epilepsy is the fourth most common neurological disorder affecting people of all ages. This is why knowing what changes in the brain during epileptogenesis is of great importance. The most widely accepted experimental model for mesial temporal lobe epilepsy is Kindling. Hippocampal Rapid Kindling (hRK) is a faster model that provides fully klindled animals in a shorter period of time, which is useful to get stable recordings of single-unit activity (SUA).

Male Wistar rats were implanted with a bipolar macroelectrode in the CA1 region of right ventral hippocampus, through which they were kindled, and eight microwires were placed in the CA1 region of right dorsal hippocampus (rdH). SUA was recorded continuously during hRK protocol and analyzed during basal and ictal activity of rdH.

Quantifying the neuron firing rate (FR) we found different patterns of SUA during epileptic seizures. Some neurons increase (nI) and others decrease (nD) their FR regarding their basal period, while many units did not change it (nNC). A tendency to increase ($p=0.14$) and decrease ($p=0.09$) the FR during the progression of hRK has been seen in nI and nD groups, respectively. Moreover, the nNC group did not show any tendency but a marked stability during the progression of hRK ($p=0.93$). We also found an increase in the duration of seizures through the epileptogenesis progress ($p<0.05$).

Further SUA analysis may lead us to understand how these patterns are involved in epileptogenic networks.

P229.-Neuronal activity of the dorsal striatum involved in the timely execution of actions

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Corticostriatal circuits are involved in the selection and execution of sequences of movements in order to maximize the profit derived from them. With the aim of studying how actions are triggered at the right time in a self-initiated rewarded task, we used tetrodes to record the striatal activity. Briefly, after a minimum inter-trial interval (ITI), water-deprived rats must enter a nosepoke and, following a visual cue, emit an eight-licks sequence onto a tube to receive water. First, we found a modulation of the striatal activity that peaks right before the beginning of the trials. This activity is related to the waiting time and it differs between timely and premature nosepoke entries. Interestingly, such activity profile was also observed when the ITI was duplicated. In a third series of experiments, subjects had to enter the nosepoke in a restricted time window: if they entered prematurely or late, they received no reward. In this version of the task we found that the anticipatory activity was maximum when the animal entered the nosepoke within the rewarded time window. Considering that subjects must estimate the right time to perform a sequence of actions to obtain the reward, we hypothesize that this anticipatory neuronal activity codes for the reward expectancy associated to the time chosen for the initiation of the learned action and it is involved in its timely execution.

P230.-Cholinergic modulation reorganizes dentate gyrus microcircuits

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Neurogenesis in the adulthood continuously provides the dentate gyrus (DG) of the mouse hippocampus with pools of new granule cells (GC) that integrate into the network. When afferent inputs arrive to the DG, immature neurons (4 weeks old-4wpiGC) respond with higher excitability, lower specificity and a different ability to decode temporal information than mature GCs (matGC). These differences in processing are due to a difference in inhibitory circuits that mostly restrict matGC. In this work we evaluated how the neuromodulator acetylcholine affects the processing of inputs in both matGC and 4wpiGC.

Using pharmacologic and optogenetic tools combined with electrophysiological recordings, we observed that, upon cholinergic activation, matGCs increase their responses to afferent stimuli, whereas no changes were seen for 4wpiGC. At the synaptic level, we observed a reduction in the inhibitory component of the response, which was more prominent for matGC. This produced an increase in the excitation to inhibition balance that explains the differential activity pattern. Furthermore, upon a high frequency stimulation protocol that is normally insufficient to produce potentiation, we could induce LTP if we pared it with optogenetic activation of cholinergic axons. We conclude that acetycholine can provide a temporal window of reduced inhibition, in which the information processing and plasticity rules of GCs change, possibly adapting the encoding to the behavioral demands.

P231.-Modulation of Piriform Cortex Neuronal Activity by Inputs from Basolateral Amygdala and Lateral Entorhinal Cortex

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Piriform cortex is the main region of the olfactory cortex where olfactory information is encoded. It receives sensory afferences from the olfactory bulb but also from other higher order brain regions such as the entorhinal cortex and the amygdala. Here we study how the basolateral amygdala (BLA) and the lateral entorhinal cortex (LEC) are functionally connected to the posterior piriform cortex (pPC). We infected the BLA and the LEC with adeno-associated virus expressing channelrhodopsin (ChR2-AAV) under CamKIIa or Parvalbumin promoters to activate either excitatory or inhibitory neurons respectively. We recorded postsynaptic currents and spiking in different principal neurons of the pPC in response to photostimulation. We found that both excitatory and inhibitory long range projections coming from the BLA synapse preferentially onto pyramidal neurons of the deep layers of pPC and do not contact semilunar neurons. Moreover, we discover that inputs from both BLA and LEC can modulate the spiking activity of pPC neurons evoked by electric stimulation of the afferent pathway. Deciphering the interaction between sensory “bottom-up” and “top-down” projections from higher brain areas will shed light on the understanding of how the brain could adaptively shape sensory cortical activity according to behavioral needs.

P232.-Characterization of beta oscillation in the primary motor cortex after nigrostriatal degeneration and during L-DOPA-induced dyskinesias in a rodent model of Parkinson's disease

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Prolonged treatment with L-Dopa in Parkinson's disease (PD) often leads to the emergence of abnormal involuntary movements known as L-Dopa-induced dyskinesias (LIDs). Little is known about the oscillatory activity associated with LIDs, particularly in the motor cortex. On the other hand, recent studies have shown that motor symptoms of parkinsonian state correlate with the exacerbation of oscillations in the beta range (15-35 Hz) although the mechanisms which originate this activity remain unknown. Here we sought to identify such alterations by recording local field potentials (LFP) and single unit activity in primary motor cortex of hemiparkinsonian mice before and after an L-DOPA treatment to induce LIDs, by means of high density electrodes. We analyzed the oscillatory activity in the beta range and how the different cortical neuronal populations were related to this rhythm. We found that animals with lesion of nigrostriatal dopaminergic system present an increase in the number of beta events, with greater duration and power compared to sham animals. There is also a significant decrease in the firing rate prior to the beginning of beta events and a better entrainment of neuronal activity by the LFP around the middle of the events. After the L-DOPA priming we found a similar but less pronounced pattern in LIDs "off" periods. Instead, during LIDs there is a generalized decrease in cortical beta activity, with a reduction in the number of events, its duration and power.

P233.-THE ONSET OF SODIUM APPETITE: ROLE OF OXITOCINERGIC AND SEROTONERGIC CENTRAL SYSTEMS

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A temporal dissociation exists between sodium depletion(SD) and the appearance of sodium appetite(SA) 20h later; thus, an inhibitory modulation was postulated. Our previous studies demonstrated an inhibitory involvement of serotonergic(5-HT) and oxytocinergic(OT) neurons on SA regulation. Our aim was to evaluate gene expression changes of different components of central OT and 5HT systems, during the delay of SA appearance after SD. Wistar rats were SD using furosemide combined with low sodium diet, and 2h or 24h later the rats were decapitated. Specific brain areas: dorsal raphe nucleus(DRN), subfornical organ(SFO), lateral parabrachial(LPBN) and anteroventral area of third ventricle plus supraoptic nucleus(AV3V+SON), were submitted to RT-PCR of oxytocin receptor(OTR), serotonin 2A receptor(5HT2A), tryptophan hydroxylase 2(TPH2) and serotonin transporter(SERT). OTR mRNA expression significantly increased($p=0.045$) early at 2h after SD in the AV3V+SON in comparison to control and 24h-SD groups. In the DRN the OTR mRNA expression followed the same tendency increasing 2h after SD and decreasing 24h later, in comparison to control and 2h SD groups, however these differences did not reach significant levels($p=0.06$).Non-significant changes in the SERT and TPH2 mRNA expression were found in the DRN and the 5HT2A mRNA expression in the LPBN and SFO. In sum, our results suggest that OT circuits acting in nuclei previously involved in SA regulation may modulate SA appearance.

P234.-Modulatory effects of Histamine on Medial Prefrontal Cortical neurons

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FORGETTING - Forgetting Processes and Cortical Dynamics - CRNL Lyon France

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Histamine, in addition to its role as cytokine in the immune system, is an essential neuromodulator of wakefulness control. Studies show that it plays a selective role in attention, suggesting an action of histamine in brain areas involved in this cognitive process. To date, very little work has examined the cellular mechanisms by which histamine exerts this action. In this study, we examined the action of histamine in slices of the mouse medial prefrontal cortex (mPFC), an area directly involved in attention control. In particular, we studied the effects of histamine on a population of neurons, parvalbumin (PV) GABAergic interneurons, involved in this function by whole-cell patch clamp recordings. Our results show that histamine selectively increases N methyl D aspartate (NMDA) glutamatergic responses in PV neurons. On pyramidal cells, the main neuronal type in mPFC, the effect is more variable. Our recordings also show that the discharge pattern of PV interneurons is increased by HA with a frequency corresponding to a gamma rhythm. Histamine also induces a significant increase in the frequency of spontaneous synaptic excitatory activity in the PV interneurons. In addition, extracellular recordings show an increase in firing rate at theta frequency by histamine. These results suggest that histamine exerts an excitatory action on PV neurons of the prefrontal cortex that are selectively involved in attention processes.

P235.-Multisensory stimuli encoding in the hippocampus during a non-spatial goal-directed task

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The hippocampus has been at the center of neuroscience research due to its role in spatial navigation. However, new findings have shown that hippocampal CA1 cells can also encode a wide variety of non-spatial features of the environment. In parallel, it was recently established a causal role of stimulus-related hippocampal LFP signals in the execution of goal-directed behaviors. Due to the multisensory nature of experience, such behaviors requires associating sensory cues arising from different sensory modalities related to environmental events. Nevertheless, it remains unclear how CA1 encodes multisensory information at the single unit level during a goal-oriented task, and its relevance for behavioral performance. Here, we recorded CA1 activity as animals performed a non-spatial goal-directed task, which involved associations of uni- and bimodal cues. We found that 41% of recorded neurons exhibited stimulus coding, including representations of individual sensory modalities but also their conjunctive representation. Interestingly, the proportion of neurons responding to different sensory modalities correlated with performance. Moreover, the firing patterns for the different encoded sensory modalities also correlated with performance. These neurons were also differentially reactivated during ripples. Taking together, these results contribute to better understand how the hippocampus encodes non-spatial information and the importance of this coding for goal-oriented behaviors.

P236.-Stress and vulnerability to develop cocaine self-administration: restoration of glutamate homeostasis in nucleus accumbens core by minocycline

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It is well known that repeated exposure to stressful events is one of the most significant risk factors to the development of addiction. Studies from our lab showed that chronic restraint stress induces a facilitation of cocaine self-administration (SA), concomitantly to an alteration of glutamate (GLU) homeostasis and a decrease expression of the GLU transporter, GLT-1, in nucleus accumbens (NA) core. Minocycline, a potent inhibitor of microglia activation, was able to prevent chronic stress-induced facilitation of cocaine SA. The main goal of this study was to evaluate the influence of minocycline on the chronic stress-induced changes on GLU homeostasis and GLT-1 levels. Thus, Wistar rats were exposed to restraint stress 2 hs daily for a week. From day 16 after the first stress session, all animals were treated with minocycline (30mg/Kg/12hs) or vehicle (DMSO 5%/12 hs) for 5 days. After that, biochemical or neurochemical experiments were performed to quantified GLT-1 levels by western blot, or GLU levels by HPLC. The GLU dialysate samples were collected from NA core through microdialysis probes in freely-moving rats by the no-net flux technique. Our results pointed out that minocycline prevents the chronic stress-induced increase of basal GLU levels as well as the decrease of GLT-1 levels, in NA core. We propose that microglia can play a key role in the disruption of the GLU homeostasis underlying the chronic stress-induced facilitation of cocaine SA.

P237.-ALCOHOL NEUROTOXICITY EFFECT IN SPATIAL MEMORY. OMEGA 3 AS A PROTECTIVE FACTOR

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Literature shows that prenatal alcohol exposure have teratogenic effects on brain structure and occasioned long lasting cognitive and behavioral disturbances including attention deficit and deficits in memory. Omega-3, the essential fatty acids found in fish oil could have protective effects against ethanol-induced neurotoxicity.

The aim of this study was to explore the acute alcohol long term effects in spatial memory in infant rats, and study the potential protective effects of Omega 3 against these effect. Method. A 20% solution of ethanol in saline was administered to postnatal day 7 (PND) Wistar rats in two separate treatments, 2 hours apart, each treatment delivering 2.5 g/kg (sc); control rats were treated with saline only. Another group was administered with one dose of Omega3 (720mg/kg, ig) 15' after the last alcohol injection. Spatial memory was analyzed in the Barnes test on PND 20 and 30. Results. Acute ethanol exposure at PND 7 had long-lasting consequences. Preliminary data show that a single dose of Omega3 did not reverse these alcohol effects. Discussion. This is the first study to demonstrate that acute ethanol exposure occasioned spatial memory alterations that persist in the offspring. Protective propriety of Omega3 warrants further investigation. The knowledge about teratological effects induced by maternal alcohol intake a is critical for an effective prevention in vulnerable population.

P238-Phosphorylation of intracellular tyrosines modulates the ionotropic function of the α7 nicotinic receptor

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α7 is expressed in the brain and contributes to cognition, attention, and memory. It contains an extracellular domain with the agonist binding sites; a transmembrane domain, which forms the ion pore; and an intracellular domain (ICD), which contains sites for modulation and intracellular signaling. The mechanisms by which the cell can regulate the ionotropic function of α7 remain unknown. We explored how intracellular phosphorylation affects α7 activity by patch clamp recordings in HEK cells expressing α7. Wild-type α7 channel activity elicited by ACh appears as brief isolated openings and as activation episodes containing a few brief openings in quick succession (bursts). Preincubation of cells expressing α7 with the inhibitor of Src family kinases (PP2) increased significantly the mean burst duration. The exposure of cells to PP2 during the course of the recording revealed a significant increase in the frequency of channel opening in addition to the increase of burst durations. To confirm that these changes were due to the inhibition of phosphorylation of α7-ICD, we introduced mutations at potential phosphorylation sites (Y386F and Y442F). The mutations prolonged burst durations, thus mimicking the effects of PP2. Also, the mutants were insensitive to PP2, confirming that Y386 and Y442 are responsible for its effects on α7 kinetics. Our results indicate that dephosphorylation positively modulates α7 channel activity in a way compatible with decreased desensitization.

P239.-DIFFERENT SEROTONIN TYPE 3 SUBUNITS CAN COASSEMBLE INTO HETEROMERIC RECEPTORS

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5-HT3 receptors are the only serotonin (5-HT) receptors that belong to the Cys-loop receptor family. They mediate fast excitatory transmission in central and peripheral nervous system. Five different subunits (A-E) have been identified in humans. The A subunit is able to form functional homomeric receptors (5-HT3A), and it can also combine with the B subunit to form heteromeric receptors (5-HT3AB). To evaluate the capability of the C, D and E subunits to combine with the A subunit to form heteromeric receptors we performed single-channel and macroscopic recordings. After expression of the A subunit, we recorded single-channel openings with an amplitude corresponding to the 5-HT3A receptor. However, when this subunit was expressed with one of the C-E subunits, opening events with different amplitudes were detected, thus confirming the expression of heteromeric receptors. From macroscopic currents we determined that the EC50 values for 5-HT were statistically different when homomeric or heteromeric receptors were expressed. Taking together, our results demonstrate that all the 5-HT3 subunits can combine with the A subunit to form heteromeric receptors. In-silico studies provided insights into the contribution of the different subunits to the 5-HT binding site. The functional characterization of different heteromeric 5-HT3 receptors will contribute to the development of selective therapies targeting this receptor family.

P240.-Differences in ALDH2 activity in SH-SY5Y and HepG2 cell lines exposed to lead and ethanol

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Several evidences demonstrate that the neurotoxicant lead (Pb) induces neurobehavioral alterations, including an altered response to drugs. We have previously reported that perinatally-Pb-exposed rats showed elevated ethanol (EtOH) intake. It is known that EtOH metabolism determines its motivational properties. In fact, centrally-formed acetaldehyde (ACD) promotes EtOH consumption, while peripheral ACD accumulation induces aversive effects. In both cases, aldehyde dehydrogenase (ALDH) is responsible for ACD oxidation to acetic acid. In the Pb-exposed rats, the elevated EtOH intake seems to be mediated by brain ACD accumulation, probably due to a reduced mitochondrial ALDH (ALDH2) activity and expression evidenced in these animals. In search of a mechanistic approach, in vitro experiments were performed in both SH-SY5Y and HepG2 cells, aimed to evaluate ALDH2 activity in a brain and liver like-environment. Both cell lines were exposed to Pb (5-200µM), EtOH (100-200 mM) or Pb + EtOH (10µM/200mM) for 24 h. The results resembled the in vivo data showing that Pb alone (5µM and 10µM) or in combination with EtOH inhibited ALDH2 activity only in the SH-SY5Y cells. On the contrast, no differences among groups emerged in the HepG2 cells, probably related to their low basal ALDH2 activity. Current studies are focalized in the assessment of ALDH2 expression and to explore the mechanisms that modulate ALDH2 function and ACD levels in each cell line in the presence of Pb and EtOH.

P241.-CONTEXT-SPECIFIC INCREASE OF GLUTAMATE TRANSMISSION IN COCAINE- CONDITIONED PLACE PREFERENCE: AN IN VIVO MICRODIALYSIS STUDY

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The conditioned place preference (CPP) paradigm results suitable to evaluate the neurobiological changes induced by a cocaine-associated context in absence of the drug. Specifically, pharmacological evidence from our lab demonstrated the role of glutamatergic transmission within the nucleus accumbens (NAc) in different phases of cocaine- CPP. The aim of the present study was to evaluate in vivo changes in extracellular glutamate (GLU) levels in NAc as a result of cocaine conditioning and extinction. For this, a microdialysis assay was performed in male Wistar rats trained to acquire, and then to extinguish, cocaine-induced CPP. Animals were stereotaxically implanted with microdialysis probes and then GLU dialysate samples were collected in the experimental room, first in the home cage to determine basal levels and then in the cocaine-paired or in the unpaired context. Dialysate samples were quantified by HPLC coupled with electrochemical detection. Results indicate that the enhancement of GLU is specific for the cocaine-paired context since animals evaluated before conditioning or in the unpaired context did not show such increase during re-exposure to the context. Furthermore, the increase of GLU was not either observed following extinction of cocaine-CPP. These findings support the idea that pairing cocaine with a specific context can modulate glutamate transmission in nucleus accumbens influencing cocaine-seeking behavior and this can disappear after extinction of drug-CPP.

P242.-Effects of acute binge ethanol intoxication on apoptosis in hippocampus in rats with chronic restraint stress or not

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Restraint stress (RS) induces substantial neurotoxicity in the hippocampus, yet most of the studies analyzing this phenomenon have employed protracted RS (i.e., ≈ 21 days). Binge ethanol administration can induce brain toxicity, analogous to that induced by stress, an effect that is affected by age. It could be postulated that ethanol intoxication may facilitate stress-induced neurotoxicity, perhaps to a greater extent in young vs. old subjects. We analyzed if adolescents, adults or aged rats exposed to five episodes of RS exhibit neurodegeneration in the hippocampus [CA1, CA2, CA3 and dentate gyrus (DG)] and whether this was modulated by a binge, yet brief (two administrations of 2.5 g/kg ethanol, separated by 120 min), ethanol administration. Compared to adult or aged rats, adolescents exhibited significantly greater RS-induced neurotoxicity in dorsal CA1 and CA2; and significantly greater ethanol-induced neurotoxicity dorsal CA2. Across ages, there was a synergistic effect between RS and ethanol at the dorsal and ventral CA1. A similar potentiation of RS by ethanol, yet restricted to adolescents, was found at ventral CA2. The study highlights the vulnerability of the developing brain to alcohol insult and stress exposure.

P243.-PESTICIDES, TOXIC ALDEHYDES AND PARKINSONISM

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The catecholaldehyde hypothesis for the pathogenesis of Parkinson´s disease (PD) confers a main role to toxic aldehyde accumulation, including 4H-NE (4-hydroxynonenal) and the dopamine (DA) metabolite DOPAL (3,4-dihydroxiphenylacetaldehyde). DOPAL levels are not only determined by ALDH (aldehyde dehydrogenase) activity, but also by the adequate functionality of VMAT (vesicular monoamine transporter) and the DA cytosolic transporter DAT. Interestingly, ALDH is inhibited directly by benomyl and indirectly by rotenone. On this basis, we propose that the exposure to these pesticides in the model organism Caernorhabditis elegans would induce DOPAL accumulation as result of ALDH inhibition, a condition that would be potentiated by the interference in VMAT functionality, leading to the organism to develop a PD-like phenotype in a pro-oxidant environment. Thus, this project is a confluence of state-of-the-art tools to induce genetically-modified C. elegans strains exposed to rotenone or benomyl with behavioral tests (locomotor activity), semi-quantitative (DAergic neurons and ALDH fluorescence) and quantitative assays (LD50 for rotenone and benomyl, DA and metabolite levels, 4H-NE levels, mitochondrial complex I activity, and O2 consumption). Furthermore, the use of C. elegans strains exhibiting VMAT inactivation will potentiate DOPAL accumulation in the nigro striatal terminal of the pesticide-exposed animals, providing further evidences to the environmental basis of PD etiology.

P244.-Validation of a protocol for oral administration of PCPA, an inhibitor of serotonin synthesis

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Adult hippocampal neurogenesis can be enhanced by factors depleting central serotonin (5-HT), like para-Chlorophenylalanine (PCPA) that inhibits the 5-HT rate-limiting enzyme. Chronic PCPA intraperitoneal (i.p.) administration increases survival of newborn neurons, without affecting cell proliferation. Nevertheless, chronic i.p. injections affect animal welfare, as they are potentially painful. Thus, we designed and validated a protocol for PCPA oral administration. C57Bl/6J male mice received PCPA during 7 days via i.p. or by giving the drug inside jelly cubes. 5-HT levels decreased about 86,45% and 56,08% in the hippocampus of mice treated with oral and i.p PCPA respectively, whereas in the prefrontal cortex, 5-HT levels decreased about 66,31% (oral), and 49,14% (i.p.). Behavioral tests, like the Forced Swimming test (FST), the Nestlet shredding test (NST), and the Marble Burying test (MBT) were performed. In the FST, mice received fluoxetine i.p. 30 min before the test. PCPA-treated mice spent significantly more time immobile than controls, revealing an effective reduction of 5-HT levels. While a tendency to significantly increased shredding was seen in the NST, no difference was observed in the MBT. In a second phase, mice received oral PCPA for 8 weeks, and survival of newborn cells was increased in the hippocampus of hyposerotonergic mice. Therefore, neurochemical, behavioral, and neurogenic results allow us to validate the protocol for oral administration of PCPA.

P245.-Study of the possible interaction between Wnt canonical pathway and myelin proteins in cocaine-induced behavioral sensitization

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Cocaine addiction is a chronic relapsing disorder mainly characterized by loss of control over drug seeking and taking. The transition between occasional use and addiction involves long-term neuroadaptations within the brain reward circuit. Among those neuroadaptations, we recently showed that Wnt/β-catenin pathway activity is modified in cocaine-induced behavioral sensitization. Other researchers have shown a relationship between cocaine and myelin composition as well as β-catenin and myelin genes expression. Our main goal was to evaluate whether Wnt/β-catenin pathway and myelin proteins are link to cocaine-induced behavioral sensitization. Thus, we submitted male Wistar rats to a sensitization paradigm (cocaine, 2x15mg/kg i.p., 5x30mg/kg i.p.), then they received 7 injections of Lithium Chloride (LiCl, canonical pathway activator) or saline, and 2 weeks later a cocaine (15mg/kg) or saline challenge. Locomotor activity was recorded on days 1, 7 and 28 to measure sensitization. Animals were sacrificed, and their brains removed the day after the challenge to evaluate β-catenin and Myelin Basic Protein levels. So far, our preliminary results showed that LiCl treatment during cocaine abstinence differentially impact on the behavioral response as well on the protein levels depending on the previous development of sensitization. Ongoing studies are aimed to clarify the possible link between Wnt/β-catenin pathway activity, cocaine and myelin proteins.

P246.-CHRONIC BENZODIAZEPINE EXPOSURE REGULATES GABA-A RECEPTOR EXRESSION IN RAT CEREBRAL CORTEX

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Prolonged benzodiazepine exposure produces adaptive changes in GABA-A receptor structure and function that are associated with the development of tolerance. We have previously demonstrated that chronic benzodiazepine administration in rats results in tolerance to the sedative and anxiolytic effects which is accompanied with changes in the expression of GABA-A receptor alpha1 subunit in the cerebral cortex. The aim of this work was to investigate the molecular mechanism of benzodiazepine tolerance in an in vitro model of primary neuronal cultures from rat cerebral cortex. The exposure of cultured neurons to diazepam for 48 h produced a decrease in the interactions between GABA and benzodizepine binding sites (40 % uncoupling) which was prevented in the presence of nifedipine, a L-type voltage-gated calcium channel. Nifedipine also blocked the benzodiazepine-induced decrease in GABA-A receptor alpha1 subunit mRNA levels. Results from calcium mobilization and nuclear run-on assays suggested that the mechanism of tolerance is mediated by repression of alpha1 subunit gene expression induced by calcium influx through L-type voltage-gated calcium channels that would finally result in the uncoupling of GABA-A receptor allosteric interactions.

P247.-RESTRAINT STRESS-INDUCED ENHANCEMENT OF GLUTAMATE TRANSMISSION WITHIN NUCLEUS ACCUMBENS CORE AFTER EXTINCTION OF COCAINE-CONDITIONED PLACE PREFERENCE: AN IN VIVO MICRODIALYSIS STUDY

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Stress is considered an important factor that induces relapse in human addicts and in animal models of addiction. Findings from our lab demonstrated pharmacologically the role of glutamatergic transmission within Core, and not Shell, subcompartment of nucleus accumbens (NAc) in restraint stress-induced reinstatement of extinguished cocaine- conditioned place preference (CPP). The present in vivo microdialysis study aims to evaluate the effect of a single restraint stress session on extracellular levels of glutamate (GLU) in NAc Core during a re-exposure to the drug-paired context after extinction of cocaine-CPP. For this, male Wistar rats trained to acquire and then to extinguish cocaine-CPP were stereotaxically implanted with self-built microdialysis probes. The next day, GLU dialysate samples were collected in the experimental room, first in the home cage to determine basal levels and then in the cocaine-paired context after the exposure to restraint stress (30 min). Dialysate samples were quantified by HPLC coupled with electrochemical detection. Results indicate that animals submitted to restraint stress, showed a significant increase in extracellular GLU levels in NAc Core during the first 15 min of re-exposure to cocaine-paired context while the non-stress group did not show such increase. These findings are explained in the framework of a dysregulation of GLU homeostasis induced by stress and provides neurochemical basis to investigate mechanisms underpinning relapse.

P248.-GABAergic disinhibition of the anterior thalamic nucleus partly mimics behavioral responses induced by MK-801. Regional expression pattern of FRA-2

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N-methyl-d-aspartate receptor (NMDA-R) antagonists (phencyclidine, ketamine, MK-801) evoke its psychotomimetic action by selectively targeting GABAergic elements in cortical and thalamic circuits in rats, but the involvement of specific brain regions is under study. We reported that the anterior thalamic nucleus (ATN) is engaged in the psychotomimetic-like behaviors induced by MK-801 in rats, and these responses were mediated by ATN GABAergic disinhibition. It is still unknown if this action imply an increase in ATN neural activity and in its projection regions (Hipoccampus, HPC; Retrosplenial Cortex, RS and medial Prefrontal Cortex, mPFC) and if a GABAA-R blockade by bicuculline (GABAA-R antagonist, 100 ng) application in ATN would totally or partially mimic the effect of MK-801 (0.2 mg/kg i.p.). We used the expression of FRA-2 as a neuronal activity marker. Dorsal (caudate-putamen, CPu) and ventral striatum (nucleus accumbens, core and shell, NAcC and NAcSh) were also analyzed. MK-801 significantly increased FRA-2-immunoreactivity (FRA-2-IR) in the ATN, mPFC (prelimbic area, PrL) and NAcSh. No changes were detected in RS, HPC (CA1 and dentate gyrus, DG), NAcC and CPu. Intra-ATN bicuculline microinjection evoked a behavioral response similar to MK-801, yet of lower magnitude, which was associated to a different pattern of FRA-2 IR (e.g, increase in DG, and NAcSh, decrease in PrL). New insights about brain networks involved in positive symptoms of schizophrenia are provided.

P249.-In search of the serotonin role in the contrasting synapse remodeling induced by fluoxetine in cortical and hippocampal neurons.

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The antidepressant fluoxetine (FLX) is a specific serotonin (5HT) reuptake inhibitor (SSRI). We have previously showed that behavioral benefits induced by FLX in experimental depression occur concomitantly with hippocampal changes in synapse morphology and number. FLX has also shown to increase synapse number in the cerebral cortex of naïve animals, an effect not shared by all SSRIs. The aim of this work was to study the in vitro profile of FLX-induced synapse remodeling in hippocampal and cortical neurons. To this aim, primary neuronal cultures obtained from embryonic (E18) and postnatal (P1-2) rats were exposed for 24 hours to FLX or 5HT. Immunostaining of the dendritic marker MAP-2 and the synaptic marker synaptophysin (SYN) were evaluated to study dendritic and synapse remodeling, respectively. In cortical neurons (DIV7), FLX treatment (1µM) increased SYN puncta number and total puncta area without modifying the dentritic tree. This effect was mimicked by 5HT and blocked by ketanserin (5HT2R antagonist). In hippocampal neurons (DIV14), FLX treatment (0.1-1 µM) decreased SYN puncta number and total puncta area and induced dendritic retraction. 5HT treatment failed to mimic FLX effect in hippocampal neurons. Our results indicate that FLX-induced synapse remodeling depends on the neuronal phenotype and suggest that while FLX effect in cortical neurons is 5HT-mediated, it seems to involve a more complex mechanism in hippocampal neurons. *equally contributors.

P250.-AT1 receptors are essential players in the development of amphetamine-induced inflammation in prefrontal cortex: relevance for neuroinflammatory pathologies

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Amphetamine (Amph) is related to vascular damage, neuroinflammation, prefrontal cortex (PFC) hypo-function and neuropsychiatric impairments. Angiotensin II, through AT1 receptors (AT1-R), mediates neuroinflammatory responses, promoting endothelial dysfunction, oxidative damage and glial reactivity. The present work aimed to elucidate Amph-induced changes in the cell elements of brain's innate immune system within the PFC, and to unmask AT1-R' role in its development. Attention deficit was evaluated as a functional assessment of PFC activity. Male Wistar rats (250g) received AT1-R antagonist CV (3mg/kg p.o., days 1–5) and Amph (2.5mg/kg i.p., days 6–10). On day 17, after behavioral tests, brains were processed for cresyl violet staining, GFAP, CD11b and vonWillebrand factor immunohistochemistry. Otherwise, animals exposed to Amph challenge (0.5mg/kg i.p.) were evaluated for oxidative and cellular stresses in isolated brain micro-vessels. Two-way ANOVA and Bonferroni test were used. Amph promoted glial reactivity, apoptosis and vascular network rearrangement in PFC and exacerbated MDA levels and HSP70 expression in response to an Amph challenge in brain micro-vessels. These alterations were observed concomitant with attention deficit. AT1-R blockade prevented the glial reactivity and vascular network rearrangement, the modified micro-vascular responses and the attention deficit induced by Amph, highlighting AT1-R role in the development of Amph-induced neuroinflammation in PFC.

P251.-A New Old Tale: Dopamine Transporter implications in an Attention-Deficit Hyperactivity Disorder (ADHD) animal model

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Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental condition characterized by atypical levels of inattention, hyperactivity and impulsivity. We have shown that mice lacking the Cdk5 activator, p35 (p35KO), resemble ADHD characteristic phenotypes. P35KO mice show hyperactivity in novel contexts, less anxiety like behaviors and paradoxically response to Amphetamine (AMPH). Furthermore, p35KO display an increased Dopamine (DA) synthesis and a decreased DA metabolism. Given that DA Transporter (DAT) is the target of ADHD treatment drugs and it is functional only when is exposed in surface, the aim of this work was to study total and superficial DAT expression in p35KO and WT Striatal tissue and its modulation by AMPH treatment. Our results show no difference in total DAT levels between WT and p35KO mice. Nevertheless, using synaptosomal surface biotinylation technique, we show significant decreased DAT superficial levels in p35KO mice compared with WT. Besides, AMPH treatment (10 µM for 30 min) of WT synaptosomes induced a decrease in DAT superficial levels, but in p35KO these expression levels remained unaltered. Taken together, our results suggest that the decreased DAT surface expression in p35KO mice correlates with an increased DA availability in synaptic cleft and therefore, an increased locomotor activity. In these sense, our results are critical for the understanding of the mechanism underlying ADHD-like behavioral phenotypes.

P252.-NANO-FORMULATED ANANDAMIDE DECREASES NEUROINFLAMMATORY MARKERS IN SPONTANEOUSLY HYPERTENSIVE RATS

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Essential hypertension is responsible for almost 95% of all cases of hypertension. Frequently of neurogenic origin, it is linked with an over-excitation of brainstem centres, sympathetic hyperactivation and imbalance in the levels of pro- and anti-inflammatory cytokines. Spontaneously hypertensive rats (SHR) is a validated model of hypertension, plus several neurocognitive deficits. Since endocannabinoid anandamide (AEA) protects neurons from the inflammatory damage, and cannabinoid signalling decreases in brains of hypertensive animals, we applied a nano-formulated AEA in SHR. We used adult male rats (n=7) of 250-300 g normotensive (WKY) and hypertensive (SHR), treated or not with nano-formulated AEA in polycaprolactone (AEA/PCL), at a weekly dose of 5 mg/Kg IP, for four weeks. Regarding WKY, the SHR showed elevated inflammatory markers (IL-1, IL-6, FNTα, ultrasensitive PCR and plasma Hsp70, $p<0.05$) and oxidative stress markers (NADPH oxidase and nitrites). Protein expression of WT1, AT-1 and iNOS decreased after treatment, while Hsp70 increased within the cerebral cortex ($p<0.01$). On the other hand, SHR treatment with AEA/PCL returned values to normal, including abnormal behaviours. These preliminary results suggest anti-inflammatory properties of nano-formulated anandamide, both peripherally and at the level of the central nervous system, specifically within the cerebral cortex.

P253.- Withdrawn abstract

P254.-Allosteric Modulation of α7 Nicotinic Receptors by Flavonoids

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Plants have emerged as a valuable source for neuroprotective compounds like flavonoids. These polyphenolic compounds decrease neurotoxicity and the development of neurodegeneration. Potentiation of α7 nicotinic receptor, which is involved in cognition and memory, is a potential therapeutic strategy in neurodegenerative disorders. In particular, positive allosteric modulators (PAMs) are emerging as the best therapeutic tools. Some flavonoids have been reported as ligands for α7, but the molecular mechanisms underlying this interaction remain unknown. Our main goal is to unravel the molecular basis of flavonoid action at α7 by electrophysiological techniques. We analysed the effects of prototypes of distinct classes of flavonoids: quercetin, genistein and 7-dihydroxy-4-phenylcoumarin (neoflavonoid) on α7 activity. At the macroscopic level, the three compounds increased the peak current elicited by acetylcholine with minimal effects on desensitization, indicating that they behave as type I PAMs. At the single-channel level, they increased, with different efficacies, the duration of the open state. By analyzing the effects of flavonoids on mutant and chimeric α7 receptors we found that they share the transmembrane structural determinants of potentiation known for other PAMs. We conclude that, in addition to the well-known effects as antioxidants, the unique properties of flavonoids as natural α7 PAMs make them candidate compounds for the treatment of neurodegenerative disorders.

P255.-Locomotor sensitization and gene expression induced by Coca Paste in mice Nucleus Accumbens and Prefrontal Cortex

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Coca-Paste (CP) is a smokable form of cocaine consumed in several South American countries. Its chronic consumption elicited a fast and strong dependence compared to cocaine, among other psychophysical alterations. CP is sold adulterated, being caffeine one of the most common psychoactive adulterant found in seized samples of the drug. In previous studies we demonstrated that caffeine as an adulterant is able to enhance and facilitate CP locomotor sensitization.

In order to investigate the underlying mechanisms of such potentiation, the aim of this study was to evaluate the gene expression in reward-circuit related areas (Nucleo Accumbens, NAc, and medial prefrontal cortex, mPFC) after the expression of locomotor sensitization induced by caffeine-adulterated and non-adulterated CP.

After 3 days of treatment and 5 days of abstinence, adult male mice were challenged to cocaine, caffeine-adulterated CP and non-adulterated CP seized samples and the motor activity was recorded. At the end of the behavioral test mRNA levels of dopamine, adenosine, glutamate and cannabinoids receptors subunits were quantified, as well as CREB, CART and synaptophysin mRNA levels.

Only animals treated with caffeine-adulterated CP expressed locomotor sensitization, and this corresponded to specific changes in the mRNA levels in the NAc and PFC, associated to chronic stimulant induced neuroplasticity, despite de short treatment. Our results can help to understand the fast dependence induced by CP consumption.

P256.-Chronic unpredictable stress in Drosophila as a preclinical model for psychopharmacology research

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Exposition to chronic and unpredictable stress (CUS) plays a significant role in the psychiatric disorders onset. Frequent symptoms in humans include altered locomotion and anhedonia, which can be partially modeled in rodents as preclinical tests used for drug testing. However, frequent failure of predictive validity and animal welfare issues increase initiatives focused on 3Rs. Drosophila is a powerful organism for modeling human diseases mainly due to their phylogenetic relationship with rodents and their labor/cost effective maintenance advantages. We aimed at using D. melanogaster as an alternative preclinical model for stress and psychopharmacological research. Adult D. melanogaster were exposed to CUS with several stressors (random sequences of 24h isolation, 20min heat shock, 5min electric shock and 6h starvation between animals). Another group was treated with 10mM fluoxetine, 5mM diazepam (DIA) or vehicle during starvation stress. At the end of CUS, behavior in the open field (OF) and 2mM sucrose preference (SP) were analyzed. Compared to control, stressed flies exhibited higher mobility, distance, and velocity as well as less time in OF boundaries. In contrast to control group, stressed flies exhibited less SP. No treatment prevented these behavioral disturbances, however, diazepam increased freezing time. Our CUS model contributes to the construction of a stress-related model meeting face validity where we reproduced some behavioral phenotypes in Drosophila.

P257.-Impact of stress in the vulnerability to cocaine addiction: role of cofilin in nucleus accumbens

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Animals models have demonstrated that exposure to stress predisposes to developing substance use disorders. We have previously shown that repeated stress alters the capacity of a subsequent cocaine injection to modulate dendritic spine morphology and actin dynamics. Our findings indicates that the pharmacological inhibition of actin polymerization in the NA prevents stress cross-sensitization with cocaine and influences actin cytoskeleton remodeling in the nucleus accumbens (NA). Thus, the main goal of this project is to evaluate the impact of the actin cytoskeleton in the changes underling the facilitatory influence of cocaine after exposure to chronic stress in the acquisition of cocaine self-administration (SA). For this purpose, we have generated a lentivirus containing a short hairpin RNA (shRNA) specific to cofilin, to inhibit its expression in NA, and explore its function during the acquisition of cocaine SA. Thus, Sprague dawley rats pre-exposed to chronic restraint stress, will be administered intra-accumbens with shRNA of cofilin, and later they will undergo surgery for implantation of catheters in the jugular vein one week before SA sessions. In the same line of evidence, our results revealed that the inhibition of cofilin is sufficient to prevent the expression of cross-sensitization between stress and cocaine, suggesting that the cofilin regulation is crucial in the facilitatory influence of stress on the vulnerability to develop cocaine addiction.

P258.-Comorbidity between chronic restraint stress and cocaine self-administration: role of glial proteins in nucleus accumbens plasticity

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Scientific background has shown stress-induced long-lasting neuroadaptations on glutamatergic innervations to Nucleus Accumbens (NA) in animal models. Our previews studies revealed chronic restraint stress-induced increase in basal glutamate (GLU) levels- and decrease in GLU transporter, GLT-1, levels in NA core. These results have been suggested as a hallmark of the homeostatic disruption of GLU transmission and have been associated with the facilitation of cocaine self-administration (SA) induced by stress. In parallel, our data showed chronic stress-induced enhancement of TNF-α mRNA levels in NA core after a cocaine challenge. Moreover, all these alterations were prevented by minocycline, a potent inhibitor of microglia activation, suggesting the participation of these cells in the studied phenomenon. In the present project, we propose the increase of TNFα and activation of NF-kB as key contributors of the stress-induced dysregulation of GLU homeostasis, post-synaptic changes and cocaine SA. Thus, rats will be administrated with lentiviral vectors targeted TNFα or NF-kB in NA core and a cocaine SA model will be used to evaluate: 1)Glial modulation of TNFα/NF-kB on GLU homeostasis, 2)GLT-1 levels, 3)currents mediated by AMPA and NMDA receptors and morphology of dendritic spines. In this way, we put forward the use of gene manipulation techniques in order to deepen the study of the underlying neurobiological basis of the comorbidity between stress exposure and cocaine abuse.

P259.-The varieties of the psychedelic experience: association between reported subjective effects, binding affinity profiles and molecular structures of eighteen psychoactive compounds

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Classic psychedelics are substances of paramount cultural and neuroscientific importance. The observation of cross-tolerance and a series of empirical studies support partial agonism at the serotonin 5-HT2A receptor as a common mechanism for the action of psychedelics. The diversity of subjective effects elicited by different compounds has been attributed to the variables of “set” and “setting”, to the binding affinities for other serotonin receptor subtypes, and to the heterogeneity of transduction pathways initiated by conformational receptor states as they interact with different ligands (“functional selectivity”). Here we evaluated the hypothesis that such variety is related to the binding affinity profiles for a range of different neurotransmitter and transporters including (but not limited to) serotonin receptors. Building on previous experimental binding affinity data in combination with natural language processing tools applied to a large repository of reports of psychedelic experiences (Erowid’s Experience Vaults), we established that the similarity between the receptorome of eighteen psychoactive compounds correlates with the closeness of their associated subjective effects. We also showed that the highest correlation could be achieved by considering a repertoire of receptors. Our methodological developments open the way to the systematic exploration of the relationship between the binding affinity profiles and subjective effects of other psychoactive compounds.

P260.-Retinal effects of optic nerve inflammation

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Optic neuritis (ON) is a condition involving primary inflammation, demyelination, and axonal injury in the optic nerve which may provoke blindness. A subset of RGCs expressing the photopigment melanopsin (mRGCs) regulates non-image-forming visual functions such as the pupillary light reflex (PLR), and circadian rhythms. We developed an experimental model of primary ON in rats through a microinjection of bacterial lipopolysaccharide (LPS) into the optic nerve. The aim of the present work was to analyze the consequences of ON at retinal level. LPS or vehicle were injected into the optic nerve from adult male Wistar rats. At 4 days post-LPS, an increase in retinal Iba-1(+) area (a microglia/macrophage marker) that persisted until 21 days post-injection was observed, while GFAP-immunoreactivity increased at 21 days post-LPS. Moreover, at 21 days post-injection, LPS induced a significant loss of RGC number (by Brn3a immunoreactivity), whereas no changes in mRGCs number were observed. Experimental ON induced a decrease in the anterograde transport to the superior colliculus and suprachiasmatic nucleus (by CTB labeling) and a decrease in white and blue light-evoked PLR. These results suggest that experimental ON affects the retina at even early stages, and without changing mRGC number, it altered the non-image-forming visual system, supporting that alterations of circadian physiology could be a risk to the quality of life of patients with ON.

P261.-Leukocytes as key players in optic nerve neuroinflammation

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Optic neuritis (ON) is a condition involving primary inflammation, demyelination, and axonal injury in the optic nerve which leads to retinal ganglion cell (RGC) loss, and a decrease in pupil light reflex (PLR) and visual evoked potentials (VEPs). Neuroinflammatory diseases are characterized by disruption of the blood-brain barrier (BBB) and increased leukocyte infiltration. The aim of the present work was to analyze the involvement of cell infiltration on visual damage induced by experimental ON. LPS or vehicle were injected into the optic nerve from adult male Wistar rats. BBB integrity was analyzed through Evans blue perfusion on WT-GFPþ/WT chimeric rats. At 6 h post-LPS injection an increase in albumin-Evan's blue leakage and in optic nerve cellularity were observed. At 24 h post-injection, e-GFP(+) cells (likely macrophages and neutrophils) were identify in LPS-injected optic nerves. Experimental ON induced an increase in the chemokine CCL2-immunoreactivity. The injection of Bindarit (a CCL2 inhibitor) and bone marrow depletion (by gamma irradiaton) significantly prevented the effect of ON on PLR, VEP amplitude, and RGC number. In order to induce BBB breakdown, tissue plasminogen activator (tPA) was injected into the optic nerve. tPA microinjection mimicked the effect of ON on PLR and RGC number. These results indicate that BBB integrity loss and leukocyte recruitment plays a key role in the visual damage induced by experimental ON.

P262.-NEUROANATOMICAL AND FUNCTIONAL CHARACTERIZATION OF THE GHRELIN-RESPONSIVE NEURONS OF THE LATERAL HYPOTHALAMIC AREA

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Ghrelin is a stomach-derived hormone that regulates a variety of biological functions via the growth hormone secretagogue receptor (GHSR), a receptor located in key brain areas that mediate the actions of the hormone. GHSR is highly expressed in the lateral hypothalamic area (LHA), which controls essential functions, including food intake, locomotor activity and reward-related behavioral responses. Here, we used a mouse model, in which the expression of enhanced green fluorescent protein (eGFP) is controlled by the promoter of GHSR (GHSR-eGFP mice), to gain neuroanatomical and functional insights of the GHSR-expressing neurons of the LHA. We found that GHSR neurons of the LHA are present from bregma -0.34 to bregma -2.70 in the antero-posterior axis, and particularly enriched in the anterior (aLHA) and tuberal region (tLHA). GHSR neurons of the LHA increase the level of the marker of neuronal activation c-Fos in response to centrally injected ghrelin and fail to increase c-Fos in response to systemically injected ghrelin. We also identified that a subset of GHSR neurons of the LHA are GABAergic and that no GHSR neurons of the LHA express orexin. Finally, we found that local intra-LHA rostral infusions of ghrelin increase food intake. Thus, current data provide evidence that ghrelin receptor signaling seems to target a subset of GABA neurons of the LHA that, in turn, affect food intake.

P263.-IGF1 gene therapy delays reproductive senescence

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The hypothalamus, a region known to regulate many basic functions such as growth, development, reproduction and metabolism, is thought to be a regulatory center of aging. Evidence demonstrates that the inhibition or activation of the transcription factor NF-κB in microglia or in neurons of the basal hypothalamus (HMB) affects the life expectancy and the "beginning" of aging, as well as the release of GnRH. There is solid evidence that middle age (MA) rats have reduced activation of GnRH neurons, GnRH release, and an abnormal LH surge. These findings provide a link between inflammation, response to stress and systemic and cerebralaging. In this project, we implemented long-term anti-inflammatory gene therapy for IGF1 in the HMB of MA female rats (8 months) up to 12 months, in order to modulate the inflammatory response mediated by NFkB and delay the appearance of reproductive cessation. Our results show that, at the end of the experiment, rats treated with IGF1 present a higher proportion of cycling rats compared to the control group. We also observed that IGF1 group has a higher number of axonal projections of the GnRH+ neurons. These results suggest that IGF1 prolongs the reproductive life of MA rats, maintaining GnRH+ neurons functionality.

P264.-THE BLOOD-CEREBROSPINAL FLUID BARRIER TRANSPORTS CIRCULATING GHRELIN INTO THE BRAIN

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Ghrelin is a 28-amino acid hormone secreted from the stomach which mainly acts in the brain to regulate food intake and neuroendocrine axes. However, the accessibility of circulating ghrelin to the brain is restricted, with no conclusive evidence of it crossing the blood-brain barrier (BBB). In this study, we hypothesized that ghrelin can reach its brain nuclei targets by crossing the blood-cerebrospinal fluid barrier (BCSFB), which is composed of the ependymal cells of the choroid plexus and the hypothalamic tanycytes. Using systemic injections of a fluorescent ghrelin tracer (F-ghrelin), we found that the cells of the BCSFB were able to internalize ghrelin. Also, in time-response studies we found that systemically-injected F-ghrelin reached the median eminence and the ventromedial arcuate nucleus at early time points, while, at later time points F-ghrelin was found in the cerebrospinal fluid (CSF) as well as in brain parenchyma in close apposition to the dorsal wall of the third ventricle. Additionally, we found that central injections of either an anti-ghrelin antibody, which immuno-neutralizes CSF ghrelin, or a scrambled version of F-ghrelin, which was also found to be internalized by the cells of the BCSFB, partially impairs food intake and neuronal activation promoted by peripheral ghrelin. We thus conclude that the cells of the BCSFB can transport ghrelin from the circulation into the CSF and the brain parenchyma.

P265.-Effects of Diazepam Treatment on Neuroinflammation at Hippoccampus in a Chronic Model of Experimental Autoimmune Encephalomyelitis

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Experimental autoimmune encephalomyelitis (EAE) is an inflammatory demyelinating disease that mimics many of the clinical and pathological features of multiple sclerosis. Recently, we found that 2 mg/kg of chronic diazepam (Dz) treatment reversed motor signs of the disease and attenuates mRNA expression of inflammatory cytokines at hippocampus. In the present study, we aimed to analyze the mRNA expression of the highly conserved 18-kDa translocator protein (TSPO) at hippocampus as a biomarker of neuroinflammation and as the possible receptor that mediates the action of Dz in our experimental model. We also analyzed microgliosis and astrogliosis at hippocampus, as the upregulation of TSPO plays a role in the response of astrocytes and microglia during active brain disease. Female mice were immunized with MOG35-55 peptide or adjuvant alone and pertussis toxin. At first symptom, animals were injected with diazepam or saline alone every 48 h. After recovery of clinical signs, brains were harvested for immunofluorescence against Iba1 and GFAP or mRNA expression of TSPO through RT-PCR. We found that Dz ameliorated microgliosis and astrogliosis at hippocampus of EAE animals. Interestingly, Dz downregulated TSPO expression in both EAE and control animals. Further experiments are needed in order to dilucidate a possible mechanism that could explain diazepam effects on motor signs of the disease and its anti-inflammatory effect at hippocampus.

P266.-Setting up an in vitro model to study glial response to peripheric immune cells

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Healthy CNS provides limited interaction between parenchymal astrocytes and immune peripheral cells. After an ischemic event the BBB is compromised and leukocytes are drawn to the lesion, where a complex immune response arises involving both local and systemic cells. The detrimental or beneficial roles of this recruitment are still discussed. The aim of the present work is to shed some light on the systemic cues associated with the commitment of astrocytes to specific activating profiles in response to peripheral immune cells. To undertake this challenge, we set up an in vitro model were primary rat glial cells are co-cultured with eGFP+ leukocytes isolated from adult Wistar-TgN(CAG-GFP)184ys rats. Fixed leukocytes were used to analyze the effect of surface molecules. Using immunofluorescence, we evaluated astrocyte reactivity (GFAP), microglial activation (Iba1), and the formation of glial scar-like structures. Short term (6 hs) and long term (72 hs) effects were studied. Astrocytes in contact with both fresh and fixed leukocytes had a fibrillar morphology and increased GFAP expression. Cellular retraction and reorganization was evident, and scar-like structures were seen. Microglia in contact with leukocytes had an activated (round) morphology. These results indicate that both soluble factors and surface molecules in leukocytes are capable of inducing astrocytes' reactivity, but further research is necessary to determine more specific pathways involved. PICT2015-1451-UBACYT

P267.-Regenerative action and immune modulation of bone marrow cell transplant in sciatic nerve injury

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Wallerian degeneration induced by nerve lesion is a simple and useful experimental approach to study peripheral nervous system degeneration and regeneration. We have shown systemically transplanted bone marrow cells to spontaneously migrate to and remain in the injured nerve for as long as 60 days. A small number of these cells upregulated markers unexpressed before transplant, leading to cell phenotypic changes and transdifferentiation to Schwann cells, while a significantly larger proportion left the tissue once the inflammatory phase had finished. They also enhanced axonal regeneration and remyelination, promoted functional recovery and prevented lesion-induced hyperalgesia.

The aim of the present work is to evaluate whether transplanted bone marrow cells exert their well-established beneficial effect on sciatic nerve regeneration through immunomodulation. Adult C57BL/6 mice received intravenous bone marrow cell or vehicle transplant after 8-second nerve crush. Along recovery, functional aspects were evaluated through hot plate and walking track tests. Animals were then sacrificed for immunohistochemistry, ELISA and flow cytometry studies. So far, the mouse model resembles results obtained in rats in terms of remyelination. Most interestingly, qPCR results showed that transplanted animals appear to undergo a downregulation of pro-inflammatory and an upregulation of anti-inflammatory cytokines. Further studies are required to fully corroborate immunomodulation effects.

P268.-GHRELIN MODULATES HIPPOCAMPAL PLASTICITY CHANGING DENSITY AND MORPHOLOGY OF DENDRITIC SPINES

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Ghrelin (Gr) is a peptide involved in the modulation of various biological processes. In previous works we have demonstrated that intracerebroventricular or hippocampal (Hp) Gr administration improves memory retention in rats and mice, decreases the threshold for inducing long-term potentiation, increases glutamate release and the expression of the NR2B subunit of NMDA receptor.

It is well known that neuronal plasticity correlated with changes on the level of the dendritic spines (DS). DS can be classified into three classes according the morphology: stubby, spines, and mushroom spines. DS are highly dynamic in the mature nervous system and could be modulated by inputs from the environment in the form of synaptic activity which is central to memory formation.

Taking into account the functional effects of Gr the purpose of this study was to investigate morphological and quantitative changes in DS after Gr administration (2 different doses) in primary hippocampal cultures from rats.

The analysis of the DS showed that Gr increases the total density of DS (+150%) in relation to non treated cells (control). In relation to morphology the mushroom type was the most increased type. These results indicate that Gr promotes the formation of new spines as well as the enlargement and stabilization of these spines.

P269.-An insulin like-peptide, INS-3, bridges neural perception of stressors with intracellular defensive mechanisms in non-neuronal cells of C. elegans

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Multicellular organisms coordinate the systemic response to stress. We have shown that in C. elegans the acute-stress response activates neurons that release tyramine (TA), the invertebrate analog of adrenaline/noradrenaline. TA stimulates the DAF-2/Insulin/IGF-1 pathway and precludes the nuclear translocation of the DAF-16/FOXO transcription factor through the activation of an adrenergic-like receptor TYRA-3 in the intestine. In contrast, environmental long-term stressors reduce TA release allowing the induction of FOXO-dependent cytoprotective genes. However, how the insuline and tyraminergic pathway are linked is unknown. We here found that genetic silencing of an insulin like-peptide (ILP) (INS-3) increases the resistance to thermal and oxidative stress, reaching levels similar to tdc-1 (incapable of synthetizing TA) and tyra-3 null mutants. Moreover, unlike wild type animals, exogenous TA does not impair oxidative or thermal stress resistance. In addition, double null mutants between TA- deficient and ILPs null mutants (tdc-1 or tyra-3 with ins-3 or 7) showed levels of stress resistance similar to those found in INS-3 single null mutants, suggesting genetic interaction. Intestinal expression of INS-3 rescues the resistance phenotype of INS-3 null mutants to wild-type levels. We proposed that TA released form the nervous system promotes intestinal release of ILPs, which activate DAF-2 in other cells, inhibiting the systemic stress response mediated by DAF-16/FOXO.

P270.-MeCP2 regulates the immune response during an autoimmune challenge

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Rett Syndrome (RTT) is a category of pervasive developmental disorders caused by mutation of MECP2, a gene that encodes methyl-CpG binding protein 2 (MeCP2), a ubiquitously expressed transcriptional regulator. The main goal of our project is to evaluate the role of altered immunity in the pathogenesis of this disorder. To this end we evaluated the autoimmune response in the context of the experimental autoimmune encephalomyelitis (EAE). Male MeCP2 WT and MT mice, were immunized with MOG 35-55 peptide, scored daily for EAE symptoms and sacrificed at 12 dpi (acute stage) or at 30 dpi (chronic stage). We found that MT-EAE mice showed an accelerated onset of the disease and more severe clinical scores, accompanied by increased infiltration of lymphocytes in spinal cord. The level of microgliosis (Iba1+ cells) was analyzed by IHC and Real Time RT-PCR, and we found significant differences between EAE and control group. To determine the response of immune cells, we re-stimulated spleen mononuclear cells derived from WT and MT mice with MOG peptide in vitro. MT-EAE group showed increased IFN-γ levels in response to MOG in comparison with WT-EAE animals with no differences in the proliferation index. Also, the level of gene expression of TNF-α and IFN-γ were significantly increased in spinal cords from MT-EAE animals during chronic stage compared to WT. Our results indicate that Mecp2 has an active role in regulating the immune response and maintaining the neuroimmune homeostasis.

P271.-Exploring learning paradigms to study contextual modulation of olfactory-based behavior in head-fixed mice

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The ability to learn that a sensory stimulus signals a reward or punishment is one of the brain functions most critical for adaptation and survival. How animals integrate that information about learnt sensory stimuli with spatial context and animal internal state is not completely understood. Here we explore different learning paradigms to evaluate the influence of spatial context on the association of an odor with a reward. Water-restricted mice were trained in a head-fixed apparatus to perform a GO/NO GO discrimination task in which the animal learns to drink water or not depending on the context in which the odor is presented. We evaluated different contextual settings and different training protocols. Our results show that background illumination was not effective as stimulus to induce context-odor-reward learning. In contrast, virtual environments in which animals can run to arrive the different context induce a fast increase in performance. Furthermore, if animals learn in sequence, first context-reward association and later odor-context-reward association, they undergo rapid learning reaching to criterion within a few trials and maintaining their performance on time. Here we show the development of a spatial context-odor task suited to probing the neural basis of spatial context modulation of an olfactory-based behavior.

P272.-Spiral ganglion neuron degeneration in mice with impaired potassium homeostasis of the cochlea

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Spiral ganglion neurons (SGNs) relay auditory information from the cochlea to central nuclei in the CNS. Their fibers receive inputs from inner hair cells (IHCs) which are the source of sound transduction. The voltage-activated potassium channel KCNQ4 is mainly expressed in Outer hair cells (OHCs), but also has been observed in IHCs and auditory pathway nuclei. Impaired activity of this channel causes OHCs degeneration, producing a sensorineural hearing loss, named DFNA2. The phenotype is initially explained by OHC death, however it progresses over time to profound deafness exceeding OHC function. Thus, it is postulated that a neuronal component could also be involved. We set out to study the role of SGNs in the progression of the hearing loss developed by KCNQ4 knock-out mice. We analyzed cochlear cell survival through time and localization using immunofluorescence on cochlear preparations. We found a significant decrease of SGN densities in basal portions of the cochlea as early as 40 weeks of age (W). By 52W the loss was also present in apical turns, and overall density of both regions decreased more than 50% by 60W. We also found loss of IHCs starting at 40W in basal turns, progressing towards the middle turn by 58W. Exploring mechanisms of cell death we found cleaved caspase 3 to be active on both OHCs and cells of SGNs. Our findings suggest a neuronal component involved in DFNA2-like deafness, and that apoptosis could be a mechanism active during cell degeneration.

P273.-Responses to visual motion stimuli of neurons from a crab assessed by multielectrode recording

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One of the main challenges in neuroscience nowadays is to understand the concerted functioning of individual neurons dedicated to particular behaviors in the behaving animal. This goal first requires to attain an adequate characterization of the behavior as well as an identification of the key neuronal elements associated to that action. Such conditions has been considerably attained for the escape response to visual stimuli in the crab Neohelice. In fact, a combination of in vivo intracellular recording and staining, with behavioral experiments and modeling, led us to postulate that a microcircuit formed by four classes of identified lobula giant (LG) neurons operates as a decision making node for a number of important visually-guided components of the crab´s escape behavior (1). These studies, however, were done by recording LG neurons individually. In order to investigate the concerted functioning of the LG group, we began to use multielectrode extracellular recordings. Here we describe the methodology and show results of simultaneously recorded responses from different LG neurons to a variety of visual stimuli. The different LG classes can be distinguished by their electrical activity and differential responses to visual stimuli. Simulataneous recordings confirmed the rightfulness of previous interpretations about LG interactions assumed from independent intracellular recordings. The current results establish the bases for and show the feasibility of our next goal of recording the activity of LG neurons in the behaving animal.

P274.-WHY IS THE MACULA PARTICULARLY SUSCEPTIBLE TO DRY AGE-RELATED MACULAR DEGENERATION? LESSONS FROM MICE

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Dry age-related macular degeneration (dAMD), the elderly main cause of blindness, is characterized by retinal pigment epithelium (RPE) and photoreceptors atrophy circumscribed to the macula. The fact that only the macula is damaged by dAMD, raises the question as to why is this area particularly susceptible. It has been suggested that RPE oxidative damage plays an important role in dAMD pathogenesis. However, the exact mechanisms of the disease are still elusive and hard to study, as mice do not have a macula. We have developed a dAMD model induced by superior cervical ganglionectomy (SCGx) in C57BL/6J mice, which reproduces the disease hallmarks exclusively circumscribed to the temporal region of the RPE/outer retina. In this context, the aim of this work was analyzing RPE regional differences that could explain dAMD localized susceptibility. Lower melanin content, thicker basal infoldings, higher mitochondrial mass, and higher levels of antioxidant enzymes, were found in the temporal RPE compared with the nasal region. Moreover, SCGx induced a decrease in the antioxidant system, and in mitochondria mass, as well as an increase in mitochondria superoxide, lipid peroxidation products, nuclear Nrf2 and heme oxygenase-1 levels, and in the occurrence of damaged mitochondria exclusively at the temporal RPE. These findings suggest it might not be dAMD pathophysiology but the macular RPE histologic and metabolic specific attributes which conditions the localization of the disease.

P275.-ENRICHED ENVIRONMENT EXPOSURE PROTECTS THE VISUAL PATHWAY ALTERATIONS INDUCED BY EXPERIMENTAL GLAUCOMA IN ADULT RATS

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Glaucoma is a leading cause of blindness, characterized by retinal ganglion cell (RGC) loss and optic nerve (ON) damage. Increased intraocular pressure (IOP) is the most accepted risk factor for glaucomatous neuropathy, however many patients with successful IOP control continue to lose vision. Enriched environment (EE) is a paradigm that involves sensory, cognitive, motor, and social stimulation. The aim of this work was to analyze whether the exposure to EE prevents glaucomatous alterations. Adult male Wistar rats received 30% of chondroitin sulfate in the anterior chamber of one eye and vehicle in the contralateral eye, once a week, and were housed in standard environment (SE) or EE for 10 weeks. Animals were subjected to functional (electroretinogram and flash visual evoked potentials (VEPs)), and histological analysis. EE housing which did not affect IOP, prevented the decrease in VEPs and oscillatory potential amplitude, as well as the reduction in the RGC number detected by immunostaining against Brn3a. The number of axons identified by toluidine blue stain was also preserved by the exposure to EE. Morover, EE housing prevented the reduction in the positive area for myelin basic protein (MBP) and luxol fast blue stain area in the ON. The increase in Iba1 (a microglia/macrophage marker) positive area in the retina and ON was also preserved. These results suggest that the EE housing protects the visual pathway against damage induced by experimental glaucoma in adult rats.

P276.-The novel opsins Opn3 and 5 Non-visual opsins are expressed in cells of the inner vertebrate retina. Potential roles and physiological implications

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The avian retina is composed of different types of photoreceptors responsible for image and non-image forming tasks: visual photoreceptor cells (cones and rods), the intrinsically photoresponsive retinal ganglion (ipRGCs) and horizontal cells. Nonvisual opsins Opn3 and Opn5 were shown to be expressed in the inner retina of vertebrates, responding to blue and UV light respectively. The retina contains an endogenous circadian clock that temporally regulates its physiology and which is synchronized by light. To investigate expression and light regulation of Opn3 and Opn5 in the developing retina, we evaluated their expression at different embryonic (E) days and in primary cultures of neuronal and glial cells, and their light responses by PCR and immunochemistry. Opn3 and Opn5 traces were detected very early in development likely in newborn RGCs, amacrine and glial cells, and a significant increase was seen by E10 and later on. Opn3 and Opn5 were found in RGCs and Muller cell cultures by E10 and E15 respectively. In postnatal retinas, a clear light/dark difference was found in Opn3 and Opn5 proteins with higher values in the inner retina during the light phase. In addition, blue light increased expression of Opn3 in Muller cells, and it also promoted a change in its subcellular localization in neuronal cells. Results show the early appearance of these opsins during development and particularly in inner retinal cells at the light phase suggesting an important role during the day.

P277.-When senses work together: how multimodal integration helps you stay alive

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An essential task of the nervous system is to make behaviorally adaptive decisions, based on various sources of information coming from the environment. In this context, multisensory integration is the process that combines the different sensory signals associated to a single event. Multisensory integration increases the likelihood of detecting a relevant event, especially when the unimodal information is limited or ambiguous. This is especially critical when the task is related to threat avoidance: slight enhancement on detection of a predator cues can determine an animal's survival. In fish, the escape response (C-start) is a robust overt behavior easy to quantify with a well understood neuronal basis. Here we analyze behavioral responses of goldfish (Carassius auratus) to visual and auditory stimuli, shown individually or combined, and quantify the escape probability. We show how sensory cues that individually trigger responses with a low rate combine to enhance risk detection. Complete information about an event is infrequent in real life scenarios. Here we discuss how animals use available sources of information for optimal decision making.

P278.-Oxaliplatin-induced peripheral neuropathy and neuropathic pain: mechanisms involved and possible therapeutic strategies

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Chemotherapy-induced peripheral neuropathy and neuropathic pain are common and debilitating side effects of cancer therapy. No available strategies can limit the neuropathy. We evaluated the use of 17a-hydroxyprogesterone caproate (HPGC) as a neuroprotective agent and studied glial activation as a possible contributor to neuropathy. Male rats were injected with oxaliplatin (OXA) and HPGC following prophylactic (HPGCp) or therapeutic (HPGCt) schemes (starting either before or after chemotherapy) and pain development was evaluated. Animals receiving OXA showed a decrease in paw mechanical and thermal thresholds ($p<0.001$ vs CTL from day 3 in both cases). Animals treated with HPGCp showed patterns of response similar to those detected in CTL animals ($p>0.05$), while those treated with HPGCt showed a reversion of both hypersensitivities after HPGC administration ($p>0.05$ vs CTL). In addition, a significant increase in the mRNA levels of GFAP, Iba1, TNFa and IL1b was detected in the dorsal root ganglia and dorsal horn of OXA animals ($p<0.05$ vs CTL) and significantly lower levels of all markers in OXA+HPGC animals ($p<0.05$ vs OXA). These results show that HPGC administration reduces glial activation parameters and prevents/reverts mechanical and thermal hypersensitivities induced by OXA, suggesting a promising therapeutic strategy. PICT 2016/0005.

P279.-Neural circuits supporting context and experience dependent representation of olfactory information

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Olfaction is highly dependent on past experience, present context and the animal's internal state, therefore the olfactory system constitutes an interesting model to study flexible processing of sensory stimuli. The piriform cortex (PC), the largest subregion of the olfactory cortex, receives afferent sensory inputs from the olfactory bulb and top-down inputs from higher-order association areas, such as the amygdala and entorhinal cortex. The nature of these inputs to the PC suggests that its olfactory representations may be modulated by other aspects of sensory experience, like spatial context, hedonic valence and expectation. We study if associative olfactory learning modifies odor-evoked activity in the PC, in a context- and experience-dependent manner. Mice were trained in a Go-NoGo behavioral task to associate an odor with a reward when presented in a specific spatial context. By using silicon probes to record activity of individual neurons in PC, we observed that some neurons showed odor-locked spiking activities that were modulated by context, reward and licking response. In addition, analysis of the population response of neurons using Principal Components Analysis reveals different population dynamics not only dependent on the odor, but also context and reward, suggesting that the PC encodes other attributes that are relevant to the odor experience.

P280.-On and off visual channels adapt differentially to object motion allowing arthropods to recognize novel stimuli occurrence

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Object motion detection provides essential cues for a wide variety of behaviors such as mate, prey, or predator detection. In insects and decapod crustaceans, encoding of object motion is associated to visual processing in the third retinotopic optic neuropil, the lobula. Due to the thin caliber of the small-field lobula columnar neurons, almost all we know about object motion detection arises from studies on their postsynaptic and larger lobula output neurons. Here we used calcium imaging to study the activity of the columnar neurons that feed onto the crab's lobula when stimulated by object motion stimuli that varied in contrast polarity. Dark edges translating over clear backgrounds evoked more powerful responses than stimuli with the opposite contrast relation. Besides, columnar neurons that were habituated to edge motion with certain contrast polarity recovered when stimulated with the opposite one. As lobula output neurons have been implicated in driving alert and defensive responses, we also studied the modulation of the crab cardiac activity (a variable indicative of animal internal state) to variations in the same visual parameters. We found a high correlation between the activity of the columnar neurons and changes in cardiac activity. These results are consistent with the involvement of the lobula in object motion coding. Moreover, the differential adaptation observed for the on and off visual channels allows arthropods to recognize novel visual stimuli.

P281.-EFFECT OF CB1 RECEPTOR MODULATION ON GENE EXPRESION IN LIGHT INDUCED RETINAL DEGENERATION

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Light induced retinal degeneration (LIRD) is a model that resembles human retinal degenerative diseases as AMD. Endocannabinoids are neuromodulators whose effects are mediated by G protein coupled receptors named CB1 and CB2. Our previous results showed that the administration of ACEA (CB1 agonist) before continuous illumination stress is neuroprotective, decreasing apoptosis and glial reactivity, while AM251 (CB1 antagonist) worsened these parameters in LIRD. Our aim was to evaluate the effect of CB1 modulation on gene expression in LIRD. The right eyes of rats were intravitreally injected either with ACEA or AM251 while the left eyes received vehicle as controls. Later, rats were subjected to continuous illumination (12.000 lux) for 24 hs. Retinas were dissected and were processed by qRT-PCR. Data were statistically analysed using Student´s t-test and differences were considered significant when $p<0.05$. The eyes treated with ACEA showed significant lower mRNA levels of BAD, BCL2, CYP1A1, adrenomedullin and DAGL-B. Conversely, the eyes treated with AM251 showed significant higher mRNA levels of apoptotic genes BAD, BAX, BCL2, TNF; receptors CB1, TRPV1 and Arilhidrocarbon Receptor; angiogenic factors, adrenomeduline and VEGF and enzymes FAAH, DAGL-A and B and NAPE. Although further work is needed, CB1 receptor agonism may be considered a potential neuroprotective strategy in AMD.

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P282.-Effect of Rab11a in the regulated exocytosis of mouse chromaffin cells

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Chromaffin cell exocytosis is coupled to voltage dependent Ca2+ channels (VDCCs) activation. These cells present various pools of vesicles with different maturation level. The Immediately releasable pool (IRP) is composed of ready releasable vesicles very close to VDCCs and is released by short depolarizations. More prolonged stimulations are able to release the totality of the ready releasable pool and, if maintained, exocytosis depends on the transport of vesicles from reserve pools. Some RabGTPases are involved in the secretion pathway but Rab11a has not yet been studied in chromaffin cells. We evaluated the effect of Rab11a on chromaffin cell exocytosis by expressing GFP-Rab11aQ70L, a constitutively active form, and mCherry-Rab11aS25N, a dominant negative form. We used patch-clamp/whole-cell to measure membrane capacitance. We observed a strong decline in the release of the IRP when either Rab11a mutants were expressed. In addition, both mutants showed a significant reduction in the total change of the membrane capacitance in response to ten 50 ms depolarizations (2 Hz), evidencing a decrease in the whole number of ready releasable vesicles. Images taken by confocal microscopy showed that mCherry-Rab11aS25N affected the distribution of GFP-Neuropeptide Y (NPY)-labeled secretory vesicles: NPY was concentrated in one big spot. These results suggest that Rab11a modulates the generation of secretory vesicles needed for the regulated exocytosis in chromaffin cells.

P283.-Cognitive interference and NOS-1 inhibition are therapeutic strategies to prevent benzodiazepine withdrawal expression

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Prolonged diazepam (DZ) administration may lead to withdrawal expression after treatment discontinuation, induced by a context-dependent learning process. Drug abuse and learning phenomena are accompanied by alterations in synaptic plasticity in brain structures such as hippocampus (HP). Nitric oxide (NO), synthesized by neuronal NO synthase (NOS-1), is a crucial player in HP synaptic plasticity, learning process and participates in DZ withdrawal. The aim of this work is to develop therapeutic strategies to prevent DZ withdrawal expression by interfering with the learning process or NO synthesis, and evaluate how these strategies could alter HP functional plasticity or NOS-1 expression. Male Wistar rats received DZ along 18 days under 3 protocols: control, latent inhibition (LI) and NOS-1 inhibition (7NI). Forty eight hours after the last administration animals were evaluated in the plus-maze test to evidence an "anxiety-like behavior" as withdrawal sign. Animals where then sacrificed for assessment of synaptic plasticity and NOS-1 expression by extracellular multi-unitary recordings and western-blot respectively. Our results show that control protocol induces anxiety, increased HP plasticity and NOS-1 expression. Interestingly, LI and 7NI protocols reversed these effects. In conclusion, we can hypothesize that learning interference and NOS-1 inhibition during DZ administration may be considered as possible avenues for therapeutic interventions to prevent DZ withdrawal.

P284.-Mesenchymal stem cells therapy reversed hippocampal atrophy, neurodegeneration, loss of presynaptic proteins, reactive microglia and behavior impaired in a rat model of sporadic Alzheimer's disease

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Sporadic Alzheimer's disease (SAD) is a progressive neurodegenerative disorder with no efficient therapy. We are interested in developing therapeutic strategies to overcome the degenerative changes in SAD. In this context, we explored the neuroprotective effect of human mesenchymal stem cells (MSC), using a SAD rat model by intracerebroventricular injection of streptozotocin (icv-STZ). Animals were divided into 3 experimental groups: Sham, STZ and STZ+MSC. STZ and STZ+MSC received 3 mg/kg icv-STZ and, 24 days after, STZ+MSC received, every 18 days, 1x106 MSC in a tail vein. During the last two weeks until the end of the study (3 months post-icv-STZ), we performed different behavioral tests. Our results show that STZ treated rats were behaviorally impaired, whereas the STZ+MSC group improved its spatial memory and decreased the anxiety. Immunohistochemistry in the Stratum Radiatum (SR) of the hippocampus revealed that neurons, astrocytes and microglial cells were affected by STZ, and MSC therapy reversed the observed changes in neurons, microglial cells, and in the volume of the SR, previously atrophied by the STZ. Interestingly, Western Blots of hippocampal lysates on presynaptic proteins (SYT1, SYT2, SYP and SV2) and GABAergic neuron marker (GAD65/67) show decreased protein levels in the STZ group, whereas MSC therapy led to a recovery of SYT1, SYP and GAD65 levels. We conclude that MSC therapy is a suitable biological tool in neurodegenerative disorders.

P285.-D1/D5 dopamine receptor stimulation increases striatal cholinergic interneuron excitability in a mouse model of L-DOPA-induced dyskinesia

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Striatal cholinergic interneurons (SCIN) are important modulators of the striatal circuitry controlling goal directed behavior and voluntary movement. Enhanced striatal cholinergic signaling has been related to the genesis of movement disorders such as Parkinson's disease (PD) and L-DOPA-induced dyskinesia (LID). Indeed, recent studies provide evidence that reducing striatal cholinergic activity may be beneficial for the treatment of LID. However, the mechanisms underlying SCIN hyperactivity in the context of LID remain poorly understood. Here we aim to clarify how dopamine D1/D5 signaling modulates SCIN excitability in PD and LID. We used slice electrophysiological recordings of mice fluorescently reporting SCIN to evaluate D1/D5 receptor agonism/antagonism on SCIN excitability in control and 6-OHDA lesioned mice with/without L-DOPA treatment. Current clamp recordings revealed that L-DOPA treatment exacerbates SCIN hyperexcitability and alters their pattern of autonomous discharge. D1/D5 agonism markedly increases SCIN excitability in control and parkinsonian mice, whereas SCIN of dyskinetic animals are already hyperexcitable and less sensitive to D1/D5 stimulation. Dopamine receptors modulate multiple membrane currents that could explain this phenomenon. However, our preliminary results indicate that D1/D5 receptor stimulation decreases a KIR-mediated potassium current in SCIN of control mice. These results point to novel molecular targets for potentially alleviating LID.

P286.-Altered pacemarker currents in thalamic ventrobasal neurons of leptin-deficient mice

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The Hyperpolarization-activated Cyclic Nucleotide-gated (HCN) and KV7 (M) channels are voltage-gated ion channels that carry h and M currents, respectively (Ih, IM). The expression of HCN1-4, Kv7.2 and Kv7.3 isoforms is abundant in the thalamus. Both channels are activated at sub-threshold potentials and have biophysical properties that mirror each other. Because of their opposite voltage dependences and directions, they both function similarly as intrinsic, slow 'voltage clamps', tending to stabilize the resting membrane potential (RMP) by opposing depolarizing or hyperpolarizing inputs. Subtle modifications of RMP impact on T-type calcium channels, and this has profound consequences for action potential (AP) generation. Here, we studied the electrophysiological expression of h, M and T-type currents in ventrobasal (VB) neurons in brain slices from wildtype (WT) or the leptin-deficient mouse (ob/ob). Ih density and its kinetic properties were altered in the ob/ob mice. Ih density decreased by 30% (WT, n=19; ob/ob, n=21) and both, time constants of activation and deactivation were increased (WT, n=14; ob/ob, n=20). The IM blocker XE991 sped up Ih activation and deactivation kinetics but only in the ob/ob (n=7) and not in the WT (n=9), suggesting an IM overexpression. Depolarization conveyed by a decreased Ih activation in the ob/ob diminished the de-inactivation of T-type channels, thereby altering the generation of an LTS, which in turn triggers a burst of APs.

P287.-Effect of inhomogeneous sub-cellular distribution of ion conductances on the oscillatory activity of thalamocortical neurons

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Thalomocortical neurons (TC) have two firing modes: tonic and bursting. These firing modes, in combination with the synaptic connectivity, create thalamocortical physiological oscillations that are correlated with global brain states, like sleep and arousal; and pathological oscillations, like spike and wave discharges, which are characteristic of idiopathic epilepsies. To study the role of TC neurons on the generation and maintenance of theses oscillations, we developed a multicompartment model that includes seven ionic conductances, which have been previously measured in our laboratory. In this study we began with a model tuned to generate intrinsically repetitive bursting. Then, we explored the parameter space and found the combinations of parameters that are consistent with this firing mode. We also incorporated the main synaptic inputs into the model (sensory, cortical and from the reticular thalamus), to determine how TC neurons bursting behavior is affected by the combination of these inputs when the compartmentalized distribution ion channels is considered.