Neurodag 2009 Abstract book

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1.

Genomic deletions in OPA1 are common in Autosomal Dominant Optic Atrophy

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Poster submitted by Gitte Juul Almind on Tuesday, November 03, 2009

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Abstract

Background: Autosomal Dominant Optic Atrophy (ADOA, OMIN #165500), also known as Kjer's optic atrophy is the most common form of hereditary optic neuropathy. The characteristic expression is characterized by bilateral subnormal visual acuity, deficient color vision, central visual field defects, and optic nerve pallor. The prevalence is relatively high in Denmark (1/12,000) compared to other countries (1/50,000). Large family studies have found that the OPA1 locus on chromosome 3q28 is the predominant gene-locus for the disease and more than 200 mutations in OPA1 have been identified. However, the mutations only explain between 60 and 80% of the cases of ADOA. Therefore we initiated a study of copy number variation and other genomic rearrangements at the OPA1 locus to supplement the results of direct sequencing. Aim/Purpose: The aim of this study was to identify and report copy number variation in the OPA1 gene in Danish patients with ADOA without demonstrable mutations in OPA1 and to describe the phenotypic association with the rearrangements. Methods: 42 unrelated probands clinically diagnosed with ADOA were analyzed for genomic rearrangements in OPA1 by means of multiplex ligation probe amplification (MLPA). Abnormal results were confirmed by additional manually added probes and by long distance PCR. The results were compared with visual acuity and color vision data. Results: Among 42 patients with clinically diagnosed ADOA but no identifiable mutation in OPA1 we identified 9 patients (21%) with genomic rearrangements in OPA1. These included two independent probands with deletions of exon 26, two with deletions of exon 9-15, two with deletions of intron 28, and one patient with deletion of exon 17. In addition, we identified two probands harboring deletions of the entire OPA1 gene on one allele. Phenotypically, the patients were comparable to patients with point mutations in OPA1. Conclusion: OPA1 deletion is a frequent cause of ADOA, contributing substantially to the established linkage to 3q28.

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2.

Strain- and Test-Dependent Effects of Nicotine and Mecamylamine in the Mouse Forced Swim and Tail Suspension Tests

Authors: Andreasen, JT, Redrobe JP

Poster submitted by Jesper Tobias Andreasen on Saturday, October 31, 2009

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Abstract

Clinical evidence suggests a role for nicotinic acetylcholine receptors (nAChRs) in major depression. For example, depressed patients have a higher smoking rate than healthy subjects and nicotine improves mood in non-smoking depressed patients. While these studies seemingly point to antidepressant effects of nAChR activation most clinically effective antidepressants antagonize nAChRs. Also, recent clinical evidence suggests beneficial effects against depressive symptoms with the non-selective nAChR antagonist mecamylamine, suggesting that nAChR antagonism may contribute to antidepressant action. Similarly, preclinical literature reflects the controversial evidence of nAChR activation/inactivation: In rats, the most consistent finding is antidepressant-like effects of nicotine, but not mecamylamine. Conversely, in mice, several studies demonstrate antidepressant-like effects of mecamylamine, while nicotine has shown modest or no effects. These contradictory results might result from genetic differences and/or the fact that only relatively few mouse strains have been tested. Here, we compared the effects of nicotine and mecamylamine in NMRI, C57BL/6J and BALB/c mice using the mouse forced swim (mFST) and tail suspension tests (mTST). Although these two tests are similar in the constructs that they claim to measure, the biological substrates underlying the behaviour is most likely different. Thus, both tests were therefore included in this study. Further, as sex differences in responses to behaviourally active drugs have been reported, both males and females were included in this study. Locomotor activity measures were included to control for non-specific stimulant effects that might interfere with the interpretation of the data from the mFST and mTST. Data were analysed by analysis of variance (ANOVA), with three independent factors corresponding to strain, sex and the level of nicotine or mecamylamine, respectively. In the mFST, mecamylamine, but not nicotine, increased swim distance in NMRI mice. By contrast, nicotine, but not mecamylamine, increased swim distance in C57BL/6J mice. Both drugs increased swim distance in BALB/c mice. Effects in the mFST were independent of sex. In the mTST, mecamylamine decreased immobility in NMRI mice only, independent of sex. Nicotine was devoid of effects in the mTST, except in female C57BL/6J mice, where it increased immobility. Overall, the mFST appeared to be more sensitive to the behavioural effects of nAChR modulation than the mTST. Finally, nicotine and mecamylamine probably exert their effects in the mFST via partly different mechanisms, although the possible involvement of facilitation of monoamine neurotransmission would suggest partly overlapping mechanisms. Selective monoamine depletion might elucidate the roles of monoamines in antidepressant-like effects of nAChR modulation.

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3.

Chronic Oral Nicotine Increases Brain (3H)Epibatidine Binding and Responsiveness to Antidepressant Drugs, but not Nicotine, in the

Authors: Andreasen JT , Nielsen EØ, Redrobe JP

Poster submitted by Jesper Tobias Andreasen on Saturday, October 31, 2009

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Abstract

Smoking rates among depressed individuals is higher than among healthy subjects, and nicotine alleviates depressive symptoms. Nicotine increases serotonergic and noradrenergic neuronal activity and facilitates serotonin and noradrenaline release. In mice, acute nicotine administration enhances the activity of antidepressants in the mouse forced swim (mFST) and tail suspension tests (mTST). Here, we investigated if this action of nicotine is also reflected in a chronic treatment regimen. Given that chronic nicotine produces a chronic facilitation of 5-HT and NE transmission, it is possible that adaptive changes similar to those observed after chronic administration with antidepressants may occur. In rodents, chronic administration with selective serotonin (5-HT) reuptake inhibitor (SSRI) and selective noradrenaline (NE) reuptake inhibitor (NRI) antidepressants is associated with blunted hypothermic responses to agonists at the inhibitory 5-HT1A receptor and Î±2-adrenoceptors, respectively. Furthermore, chronic antidepressant treatment is accompanied by decreased expression levels of the transporters for 5-HT (SERT) and NE (NET). After chronic treatment with nicotine in the drinking water, mice were challenged with nicotine, duloxetine, citalopram and reboxetine in the mFST. In addition, 8-OH-DPAT- and clonidine-induced hypothermia was tested in vehicle- and nicotine-pretreated mice, as a measure of 5-HT1a and Î±2-adrenoceptor function, respectively. Finally, the effects on the brain expression levels of high- and low-affinity nicotinic acetylcholine receptors (nAChRs), and the transporters for serotonin (SERT) and noradrenaline (NET), were assessed using (3H)epibatidine, (3H)Î±-bungarotoxin, (3H)citalopram and (3H)nisoxetine binding, respectively. Behavioural and hypothermia data were analysed by two-way analysis of variance (ANOVA) and three-way repeated measures ANOVA, respectively. Radioligand binding data were analysed with Studentâ€™s t-test. In the mFST, nicotine-pretreated mice did not show altered response to the nicotine challenge, but increased responses to all three antidepressants tested was observed when compared to mice that had been administered drinking water without nicotine. There was no change in hypothermic responses to 8-OH-DPAT or clonidine. (3H)epibatidine binding was significantly increased in all brain regions investigated, whereas (3H)Î±-bungarotoxin, (3H)citalopram and (3H)nisoxetine binding was not altered, indicating that chronic oral nicotine increases the expression and/or affinity of high-affinity nAChRs, but not low-affinity nAChRs, SERT or NET. It is suggested that the increased sensitivity to antidepressants after chronic nicotine exposure involves increased high-affinity nAChRs-mediated neurotransmission.

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4.

Subtype-Selective Nicotinic Receptor Agonists Enhance the Activity of the Antidepressants Citalopram and Reboxetine in the Mouse Forced Swim Test (mFST)

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Abstract

Clinical and preclinical literature suggests that nicotinic acetylcholine receptors (nAChRs) are involved in major depression. Nicotine increases serotonergic and noradrenergic neuronal activity and facilitates release of serotonin and noradrenaline. Accordingly, nicotine enhances the activities of the selective serotonin reuptake inhibitor (SSRI) citalopram and the selective noradrenaline reuptake inhibitor (NRI) in the mouse forced swim test (mFST) and the mouse tail suspension test (mTST), two widely recognized tests for antidepressant action. To ascertain the roles of Î±4Î²2 and Î±7 nAChR subtypes in the nicotine-enhanced action of antidepressants we tested if the effects of citalopram and reboxetine in the mFST are affected by nAChR agonists selective for Î±4Î²2 or Î±7 nAChRs. Sub-threshold and threshold doses of citalopram (3 and 10mg/kg) or reboxetine (10 and 20mg/kg) were tested alone and in combination with the novel Î±4Î²2-selective partial nAChR agonist, NS3956 (0.3 and 1.0 mg/kg) or the Î±7-selective nAChR agonist, PNU-282987 (10 and 30 mg/kg). Thus, the four mFST experiments performed were: NS3956+citalopram, NS3956+reboxetine, PNU-282987+citalopram, and PNU-282987+reboxetine. Corresponding locomotor activity experiments were performed to control for non-specific stimulant effects. All experiments were performed as full factorial designs. Data were analysed by two-way analysis of variance (ANOVA) with two independent factors corresponding to the level of NS3956/PNU-282987 and citalopram/reboxetine, respectively, and followed by Planned Comparisons of the predicted means. Alone, NS3956 and PNU-282987 were devoid of activity in the mFST. Also, when given alone, citalopram and reboxetine showed minor or no activity in the mFST at the doses tested. However, both 1.0 mg/kg NS3956 and 30 mg/kg PNU-282987 markedly enhanced the effect of citalopram and reboxetine. Both increased, decreased and no effects on locomotor activity was observed at the dose combination of NS3956 or PNU-282987 with citalopram or reboxetine producing enhanced swimming in the mFST, suggesting that changes in locomotor activity were dissociated from effects on swim distance in the mFST. The data show that the action of citalopram and reboxetine in the mFST is enhanced by activation of both Î±4Î²2 and Î±7 nAChRs, suggesting that both receptor subtypes may be involved in nicotine-induced enhancement of the action of antidepressants in the mFST, and that this enhancement is observed with both SSRI and NRI antidepressants. In pursuit of more efficacious treatments for depression, combining actions at nAChRs with classical monoamine reuptake inhibitor mechanisms may prove beneficial.

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5.

Effects of Antipsychotics and Subtype-Selective Monoamine Receptor Ligands on Basal and PCP-Disrupted Prepulse Inhibition in Mice

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Poster submitted by Jesper Tobias Andreasen on Saturday, October 31, 2009

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Abstract

Prepulse inhibition (PPI) is the inhibition of the response to a startling stimulus by a weak pre-stimulus. PPI is a model of sensorimotor gating, i.e. the ability to filter out irrelevant sensory information, and schizophrenic subjects show deficits in PPI. Phencyclidine (PCP) mimics schizophrenia in healthy humans. PCP-disrupted PPI in rodents has often been used as an operational tool to predict antipsychotic action. To date, no studies have systematically examined the sensitivity of the mouse PPI paradigm to a broad range of standard antipsychotic drugs. Also, it remains to be established if disruption by PCP increases the sensitivity of the PPI paradigm to effects of antipsychotics. Here, we compare the effects of the antipsychotics haloperidol, amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone on mouse PPI. Receptors targeted by antipsychotics are mainly dopamine D2, serotonin(5-HT)1A and 5-HT2A, Î±1 and Î±2 adrenoceptors, and histamine H1 receptors. To examine the contribution of these receptors we also tested drugs selectively targeting each of these receptor subtypes: raclopride (D2), M100907 (5-HT2A), 8-OH-DPAT (5-HT1A), prazosin (Î±1) idazoxan (Î±2), and pyrilamine (H1). All studies were performed as complete 4 x 2 factorial designs, with vehicle and three doses of each drug tested in both saline- (VEH) and in PCP-treated mice. Prepulse intensities were 8, 16, and 24 dB above a 65 dB background. Startle stimulus was a 110 dB 40 ms white noise burst. Data were analyzed using three-way repeated measures ANOVA with pretreatment (vehicle/drug dose) and treatment (VEH/PCP) as categorical predictors and prepulse intensity as repeated factor, and followed by Planned Comparisons of the predicted means. All antipsychotic drugs tested, except amisulpride and risperidone, enhanced PPI (p smaller than 0.05). Except for aripiprazole, PPI-enhancing effects were more prominent in PCP-treated than in VEH-treated mice. This suggests that to detect antipsychotic-like action, the PCP deficit model may be a more sensitive assay than baseline PPI, although the high PPI levels observed with 24 dB prepulses in VEH-treated mice may have hampered the detection of PPI-enhancing effects at this pp-intensity. Of the subtype-selective ligands, 8-OH-DPAT enhanced PPI, especially in PCP-treated mice (p smaller than 0.01). The other subtype-selective ligands tested showed no or equivocal effects. These data suggest that 5-HT1A receptor activation produces antipsychotic-like effects in the mouse PPI paradigm. However, the lack of or equivocal effects of the other subtype-selective ligands does not preclude a role for the receptors targeted by these ligands in the PPI-enhancing action of the antipsychotics investigated here.

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6.

Alteplase (rtPA) treatment of IVH (a clinical pilot study)

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Abstract

Intraventricular hemorrhage (IVH) is seen in approximately 40% of all patients with spontaneous hypertensive hemorrhage (ICH) and with approximately 30% of all patients with subarachnoidal hemorrhage (SAH). IVH is associated with a very poor prognosis, and a mortality rate of up to 91 % has been reported in literature. Surgical removal of intraventricular haematoma has been shown to reduce mortality and morbidity, but is invasive and associated with additional risks. The current standardized treatment by external ventricular drain (EVD) insertion to treat high intracranial pressure (ICP) due to hydrocephalus is important, but it doesnÂ´t influence the mortality rate. It is also associated with complications, for instance clotting of the drain and ventriculitis. Therefore, for the past two years, we have been working on improving a method in which we use a thrombolytic agent â€' Alteplase (trPA) to remove the intraventricular haematoma by injecting the agent directly into the ventricles of the brain through a previousy inserted external ventricular drain (EVD), which is a standardised treatment of these patients. In our pilot study, by injecting Alteplase (rtPA), we have been able to remove up to 90 % of the haematoma within only a couple of days, compared to the non treated patients, who needed about three weeks to evacuate the ventricular haematoma spontaneously. There were no incidents of drain clotting as is otherwise often seen with this patient category. Furthermore, we have notably reduced the need for the patients to stay in a neurosurgical intensive care unit (ICU), in some cases down to just a couple of days, compared to weeks in the non treated patients. With regards to complications, of which re-bleeding is a major concern, none were observed that could be directly related to the Alteplase (rtPA) treatment. In conclusion; treatment of intraventricular hemorrhage with Alteplase (rtPA) has shown some promising results in our pilot trial. Further evaluations also on the improvement in neurological outcome in these patients, compared to those treated with the standard regime will be performed in a nation-wide multicenter clinical randomised prospective trial, that has recently been approved by the Danish Medicines Agency and the Danish Board of Ethics to begin ultimo 2009.

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7.

Expression studies and pharmacological characterization of VIP and PACAP receptors in the cerebral circulation of the rat

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Poster submitted by Michael Baun on Saturday, October 31, 2009

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Abstract

Objective: To study the expression and function of VIP- and PACAP-receptors in the intracranial circulation of the rat in relation to migraine. Introduction: Endogenous peptides VIP (vasoactive intestinal polypeptide) and PACAP (pituitary adenylate cyclase activating peptide) partially share receptors, and display potent vasodilatory properties in different vascular beds. PACAP exists in two isoforms, PACAP-27 and PACAP-38. Both VIP and the PACAPs activate the VPAC1 and VPAC2 receptors with nearly equal affinity, whereas the PAC1 receptor is almost exclusively dedicated to the PACAPs. Studies in migraineurs reported that infusion of PACAP-38 induces a stronger immediate headache than VIP, and contrary to VIP causes a delayed-phase migraine-like attack. This difference calls for further investigation of the distribution and effect of the receptors for these peptides. Methods: The vascular effect of VIP, PACAP-27 and PACAP-38 was examined by wire myograph experiments on the isolated, precontracted middle cerebral artery (MCA) and basilar artery (BA) of the rat. The vasodilatory effect was challenged with peptide antagonists for the VPAC1 and/or VPAC2 receptors. Preliminary experiments were done with the pure PAC1 peptide agonist Maxadilan. mRNA expression of the receptors VPAC1, VPAC2 and PAC1 in the MCA, BA and middle meningeal artery (MMA) of the rat was examined by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Results: VIP, PACAP-27 and PACAP-38 elicited comparable vasorelaxant action in isolated rat MCA and BA. Respective pEC50 MCA: 7.87Â±0.17, 7.88Â±0.12, 7.52Â±0.10, respective pEC50 BA: 8.31Â±0.27, 7.19Â±1.14, 7.81Â±0.17. PACAP-27 and PACAP-38 were equipotent in the two arteries, while VIP proved more potent in BA than in the MCA. The VPAC1 antagonist PG97-269 demonstrated more efficient blocking of the relaxant effects than the VPAC2 antagonist PG99-465 for all peptides in both vascular beds. The combination of the two antagonists blocked more efficiently than either alone. No marked dilatory effect was observed with the PAC1-agonist Maxadilan. qRT-PCR studies demonstrated that all 3 receptors were present in the tested vascular beds, but with the PAC1 receptor in relatively small amounts. Preliminary experiments in human cerebral arteries support this pattern. Conclusion: The difference in headache-inducing potency of PACAP and VIP can not be attributed to higher dilatory potency of PACAP over VIP. The PAC1 receptor was found in relatively low abundance in the vascular tissue tested. These results correspond with preliminary results in human vessels. Combined results indicate that the higher tendency of PACAP over VIP to cause headache is due to non-vascular effects. Earlier presentations: The poster has been presented at International Headache Conference, IHC, Philadelphia, USA 2009

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8.

Pharmacological characterization and mRNA expression studies of VIP and PACAP receptors in human coronary arteries

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Abstract

Objective: To study the expression and function of VPAC1, VPAC2 and PAC1-receptors in human coronary arteries (CAs). Background: VIP (vasoactive intestinal peptide) and PACAP (pituitary adenylate cyclase activating peptide) are endogenous peptides, which partially share receptors. It has been shown that infusion of PACAP-38 causes migraine-like attacks, in migraineurs and strong headaches in healthy volunteers, while VIP causes only mild, transient headaches. VIP and PACAP both activate VPAC1 and VPAC2 receptors with almost equal affinity, while PACAP has ~1000 fold higher affinity for the PAC1 receptor. This may point to PAC1-receptor antagonism as a putative mechanism for acute or prophylactic migraine treatment, depending on the peripheral side effects. The role of the PAC1 receptor in human CA was characterized through myograph- and expression studies. Methods: Human CAs were obtained from heart-beating donors. The fresh arteries were used in myograph experiments, and separate segments saved for mRNA expression studies. In the myograph setup, the arteries were pre-treated with the VPAC1 antagonist PG-97269 or the PAC1 antagonist PACAP (6-38), precontracted, and concentration-response curves to VIP and PACAP-38 were recorded. mRNA expression of VPAC1, VPAC2 and PAC1 in the arteries was studied by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). Results: In the myographs, PACAP-38, PACAP-27 and VIP caused concentration-dependent relaxations of human CA, with the order of potency being VIP>PACAP-27>PACAP-38. The respective pEC50 values were 8.42Â±0.15, 7.66Â±0.24 and 7.01Â±0.15. Treatment with the PAC1-receptor antagonist PACAP(6-38) did not induce contraction per se. PACAP(6-38) caused no significant shift in response to neither VIP or the PACAPs. The VPAC1-antagonist caused a reduction of the potency of VIP. Expression studies showed that mRNA for the PAC1 receptor was present in low abundance compared to neuronal tissue and heart muscle. mRNA for VPAC1 and VPAC2 receptors was present in relatively high amounts. Conclusion: The predominant vasodilatory component of PACAP seems to be mediated by VPAC-receptors. The PAC1 receptor is present in low abundance in the coronary arteries, and antagonism causes no apparent contraction. Thus, this study suggests that if a PAC1 -receptor antagonist is employed in migraine therapy, the risk of coronary constriction as a side effect will be minor. Previous presentation: The poster has been presented at International Headache Conference, IHC, Philadelphia, USA 2009

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9.

Functional gain modulation in spinal motoneurons by sub-threshold Vm-fluctuations due to balanced synaptic inhibition and excitation

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Abstract

The mechanisms underlying the large dynamic range in motor systems are poorly understood. We have previously shown that the intensity of synaptic inhibition and excitation co-vary in phase (rather than out of phase) during rhythmic limb movements (Berg et al. Science 2007). This could provide a mechanism for gain modulation in motoneurons. Fluctuations in membrane potential due to balanced synaptic input is a possible candidate for gain modulation in neurons, as suggested (Berg et al PLoS ONE 2008), but issues still remain: 1) is gain modulation by balanced synaptic fluctuations in fact used by the nervous system to adjust the dynamical range? 2) does this mechanism also adjust dynamical range and improve precision in motor systems? Scratch spinal network activity in the turtle is an ideal model for addressing both issues. Here we quantify the motor output during scratching and relate it to the intensity of the synaptic fluctuations and the gain recorded in individual motoneurons. We find that: 1) the FI-gain of individual motoneurons is modulated during motor behavior. 2) the motor output (quantified as the integrated electroneurogram (ENG) of hip flexor nerves) correlates with this gain. Interestingly, this relation represents a functionally meaningful gain modulation because it scales the force precision with the absolute force in analogy to Weberâ€™s law for sensory perception, i.e. î'Force/Force â‰ˆ constant. Gain is equivalent to î'Force and the ENG is equivalent to Force. 3) the gain is reversely related to the magnitude of the fluctuations in membrane potential (i.e. sigma of Vm, figure B), as previously predicted from theory (see e. g. Tuckwell 1988).

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10.

Validation of a schizophrenia animal model: brain activation vs. behaviour.

Authors: Brian V. Broberg1,2,3, Börje Bjelke3, Christina K. Olsen1, Niels Plath1, Birte Y. Glenthøj2, Olaf B. Paulson3,4 and Lise V. Søgaard

Poster submitted by Brian V. Broberg on Saturday, October 31, 2009

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Abstract

Schizophrenia is characterized by positive symptoms (hallucinations, delusions, thought disorganisations), negative symptoms (affective blunting, anhedonia, social withdrawal), and cognitive symptoms (including deficits in executive functioning, attention, and memory). Current available treatment is successful in treating only to some degree positive symptoms and to small (if any) degree negative and cognitive symptoms. To develop novel and more effective treatment approaches, the use of valid animal disease models is essential. Dosing the NMDA antagonist phencyclidine (PCP) to healthy human subjects provokes a schizophrenia-like psychotic state. Concordantly, injections of PCP in laboratory animals induce abnormalities similar to those observed in patients with schizophrenia. First, we investigated a psychosis-like stage induced by acute PCP in a putative neurodevelopmental animal model of schizophrenia. To produce the animal model we dosed PCP (20 mg base/kg, s.c., 10 ml/kg) to Lister Hooded (LH) rat pups at postnatal days (PNDs) 7, 9, and 11. At PND 59-65 (early adulthood) we tested an acute PCP (5 mg/kg, s.c., 5 ml/kg) dose for its effect on locomotor activity. After a one hour habituation phase rats were dosed (PCP or Veh) and the number of horizontal photo beam interruptions was recorded for an additional two hours. Dosing of acute PCP (5 mg/kg) to early postnatal treated PCP rats, significantly elevated the hyperactivity (p less than 0.001) compared to their vehicle counterparts. This shows that rats treated at an early postnatal state were more sensitive to an acute dose of PCP than those treated with vehicle. Second, we plan to utilize the functional magnetic resonance imaging (fMRI) method to identify differences in brain activation patterns between early postnatal PCP and vehicle animals, which can be correlated to the behavioural data. This will be done by applying a cerebral blood volume (CBV) sensitive fMRI method. For acute PCP stimulation we use a dose of 0.5 mg/kg i.v. (1 ml/kg), which has shown to produce comparable plasma levels to the 5 mg/kg s.c. challenge applied during locomotor activity testing. We hypothesize to find differences in brain activation patterns between early postnatal treated vehicle and PCP (20 mg/kg, s.c.) animals, when given an acute dose of PCP (0.5 mg/kg, i.v.). Here, we will especially screen for altered neuronal activation in early postnatal PCP treated animals in brain areas associated with schizophrenia - caudate putamen, nucleus accumbens, hippocampus, and medial pre-frontal cortex. At present our system has shown appropriate sensitivity to perform these studies. Furthermore, pilot studies suggest that measurement of PCP induced neuronal activation is possible in both normal and schizophrenia-like animals without affecting physiological parameters such as respiration and blood pressure to any significant extent.

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11.

Discovery of UCPH-101 - The First Selective Inhibitor of EAAT1

Authors:

Poster submitted by Lennart Bunch on Saturday, October 31, 2009

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Abstract

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12.

Functional electrical stimulation: the role of proprioceptive feedback

Authors: Mark Schram Christensen 1,2,3 Michael J. Grey 1,2

Poster submitted by Mark Schram Christensen on Saturday, October 31, 2009

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Abstract

Introduction: Therapeutic functional electrical stimulation (TFES) uses patterned electrical stimulation of muscle synergies (i.e. functional electrical stimulation, FES) to augment voluntary motor drive (VOL). It can be used in neurorehabilitation in situations where the patient cannot perform movements themselves[1]. It has beendemonstrated that cortical areas responsible for sensory-motor integration are active during TFES[2]. In this study we investigate if peripheral sensory feedback is required for the cortical activation patterns revealed during movements performed with VOL, FES, or with TFES. To investigate this question we used ischemic nerve block (INB) to block transmission of peripheral afferents while subjects performed finger movements with or without electrical stimulation during fMRI. We test the hypothesis that cortical activation will decrease during INB in regions responsible for sensory motor integration during the TFES and FES conditions. Results: â€¢ Secondary somatosensory cortex (SII) activation increased during FES and TFES [2] â€¢ SII activation was reduced during INB but only significantly for the FES condition â€¢ Peripheral ischemia reduced sensory motor cortex activation for the FES condition but only slightly for TFES. â€¢ For voluntary movements (VOL) activation is preserved in sensory motor cortex [3] and decreased in precuneus and superior parietal lobule during peripheral ischemia. Discussion: Proprioception and/or cutaneous stimulation may be involved in generating activation related to FES but the addition of voluntary movement does not reduce sensory motor activation during peripheral ischemia. This may be related to the generation of an internal model that predicts the sensory consequences of the movement. The study may provide insight into the underlying physiology for the clinical benefits previously reported for therapeutically applied FES. References: [1] Sheffler and Chae (2007) Muscle Nerve 35:562-90 [2] Iftime et al (2005) SfN abstract [3] Christensen et al (2007) Nat Neurosci 10: 417-19

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13.

Apopleksi og Aldring - en prospektiv analyse af de ældste. Et planlagt ph.D. projekt

Authors: Louisa Christensen og Hanne Christensen

Poster submitted by Louisa M Christensen on Saturday, October 31, 2009

Affiliations: Neurologisk afdeling, Bispebjerg hospital

Abstract

Baggrund: Hvert Ã¥r fÃ¥r ca. 13.000 personer i Danmark en apopleksi, efter et Ã¥r er 20 % af disse personer dÃ¸de og 30 % har behov for hjÃ¦lp til personlig pleje. De samfundsmÃ¦ssige omkostninger ved apopleksi anslÃ¥s til over 2,5 mia. kr. om Ã¥ret. Vores viden om apopleksi hos gamle er mindre end hos de midaldrende, pÃ¥ trods af at forekomsten af apopleksi stiger med alderen og langt flere personer opnÃ¥r hÃ¸j alder. FormÃ¥l: Projektet vil sammenligne de Ã¦ldste med apopleksi med personer i samme aldersgruppe uden klinisk cerebrovaskulÃ¦r sygdom og med yngre apopleksipatienter. FormÃ¥let er at afklare hvorledes, de gamle adskiller sig fra de yngre og bedre undersÃ¸gte aldersgrupper, hvad angÃ¥r risikofaktorer, behandlingseffekt og behandlingstilbud. Patienter og metoder: Vi undersÃ¸ger tre populationer: (1) >=80 Ã¥r med apopleksi: Der forventes inklusion af 125 konsekutive patienter til studiet. Patienterne registreres i den eksisterende OSCAR-database, der indeholder information om indlÃ¦ggelse, behandling, ventetider samt diagnose, risikofaktorer, undersÃ¸gelser og resultat af disse. Der tages blodprÃ¸ve til genetisk testning udover de for indlÃ¦ggelsen almindelige indlÃ¦ggelsesprÃ¸ver. Derudover foretages MR af cerebrum. Patienterne ses efterfÃ¸lgende ambulant efter 3 mÃ¥neder med henblik pÃ¥ kognitiv screening (ACE), depressions screening (GDS), vurdering af livskvalitet (SF-36) og fysisk aktivitet fÃ¸r og efter apopleksi (PASE). Herudover vurderes funktionsniveau (modified Rankin Scale, modified Glasgow Outcome Scale og Barthel Index), neurologisk funktion (Scandinavian Stroke Scale og NIHSS) og eventuelle lÃ¦geverificerede recidiver registreres. (2) less than 80 Ã¥rige med apopleksi: Der anvendes data fra OSCAR-registreringen og inkluderes 125 konsekutive patienter fra afdelingen. (3) >=80 Ã¥rige uden apopleksi: Der rekrutteres 125 alders-, og kÃ¸ns-matchede kontrolpersoner uden kendt cerebrovaskulÃ¦r sygdom. Der indsamles svarende til apopleksipatienterne i gruppe 1. Perspektiver En bedre patofysiologisk forstÃ¥else gÃ¸r, at man kan lave et udredningsprogram der er specifikt for gamle, og bedre kan forebygge apopleksi i denne aldersgruppe. En organisatorisk gennemgang giver oplysninger om hÃ¦mmende og fremmende faktorer i patientbehandlingen, og opnÃ¥r bedring af prognosen hos denne gruppe, gennem bedre adgang til evidensbaseret behandling.

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14.

Changes in action potential waveform in isolated dorsal root ganglion neurons after chronic constriction injury operation in adult rats - a model of neuropathic pain

Authors: Christensen RK, Strøbæk D, Holst D.

Poster submitted by Rasmus Kordt Christensen on Monday, November 02, 2009

Affiliations: NeuroSearch, University of Copenhagen

Abstract

Animal models of neuropathic pain have been established and used intensively over the last decade, but the molecular mechanisms underlying neuropathic pain conditions are heterogeneous and not yet fully elucidated. We have used chronic constriction injury (CCI) as a model of neuropathic pain and analysed action potential (AP) waveforms and other membrane properties in isolated dorsal root ganglion (DRG) neurons from the lumbar 4 and 5 section. The excitability of DRG neurons (n=29) from CCI operated animals appears to be similar to DRG neurons (n=55) from naive rats, but there are indications of a significant change in the AP waveform in a subgroup of middle sized neurons (9 out of 25). These neurons exhibits a shoulder or hump on the evoked APs (half width increased from less than 6 ms to >6 ms). The AP shoulder can be reversibly removed by the specific N-type Ca2+ channel blocker w-conotoxin MVII C, 1uM (n=3). The toxin has no effect on APs from control animals (n=4) indicating a change in the conduction balance in the DRGs with the CCI operation. Due to the electrophysiological diversity in DRG neurons we need to conduct further studies, before any final conclusions can be put forward.

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15.

General behavioural and cognitive impairment after cholinergic lesion in APPswe/PS1dE9 mice

Authors: B. Clausen 1; S.L. Hansen 2; N. Plath 3; A. Mørk 1 and J.F. Bastlund 1

Poster submitted by Bettina Clausen on Saturday, October 31, 2009

Affiliations: 1 H. Lundbeck, Department of Neurophysiology; 2 University of Copenhagen, Department of Pharmacology and Pharmacotherapy; 3 H. Lundbeck A/S, Department of Cognition

Abstract

The APPswe/PS1dE9 mouse is a double transgenic model of AlzheimerÂ´s disease (AD), carrying both mutant amyloid precursor protein and presenilin-1 transgenes. The mice develop Î²â€'amyloid plaques at 4-6 months of age comparable to those seen in the post-mortem brain of human AD patients. The ability to selectively lesion forebrain cholinergic neurons with the toxin mu p75-saporin makes it possible to improve the existing model so it also expresses cholinergic degeneration - another hallmark of AD. In this study, transgenic mice [Tg(+)] and wild-type littermates [Tg(-)] received either PBS or saporin (0,6Âµg) bilaterally into the lateral ventricles at age 6 months. We have previously demonstrated that this saporin lesion diminishes the amount of cholinergic innervation in the hippocampus by 80%. Two months after the surgery, the animals were subjected to different behavioural tests, including general locomotor and cognitive assays. Levels of horizontal locomotor activity were measured in a cage using an automated infra-red beam break monitoring system. The test revealed a hyperactive phenotype in the saporin treated animals, with a tendency for the PBS treated Tg(+) to have a higher level of activity than the PBS treated Tg(-) mice. A beam walking test was also used to evaluate behavioural performances such as ataxia in the mice. Tg(+) with cholinergic lesions performed significantly worse than Tg(+) treated with PBS. This difference was not apparent in the Tg(-) groups. After the assessment of the motor performances, the animals were tested in cognitive tasks addressing intact hippocampal-dependent spatial short-term memory in a Y-maze. Tg(-) treated with PBS were the only group to distinguish significantly between new and familiar areas and thus memorize the task. Thus, the Tg(+) genotype as well as saporin treatment resulted in significant deficits in short-term memory. Working memory performance was tested in a continuous alternation paradigm. The Tg(+) mice treated with saporin had significantly fewer correct alternations than the Tg(+) treated with PBS. This difference following saporin treatment was not apparent in the Tg(-) mice. In summary, the spatial Y-maze revealed mnemonic deficits in all treatment groups besides the Tg(-) animals treated with PBS. However, in the beam walking test and in the T-maze, there were only significant behavioural and mnemonic deficits apparent when the Tg(+) genotype was combined with the cholinergic lesion. This suggests a strong effect when combining transgenic APPswe/PS1dE9 animals with forebrain cholinergic lesions.

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16.

General behavioural and cognitive impairment after cholinergic lesion in APPswe/PS1dE9 mice

Authors: B. Clausen 1; S.L. Hansen 2; N. Plath 3; A. Mørk 1 and J.F. Bastlund 1

Poster submitted by Bettina Clausen on Saturday, October 31, 2009

Affiliations: 1 H. Lundbeck A/S, Department of Neurophysiology; 2 University of Copenhagen, Department of Pharmacology and Pharmacotherapy; 3 H. Lundbeck A/S, Department of Cognition

Abstract

The APPswe/PS1dE9 mouse is a double transgenic model of AlzheimerÂ´s disease (AD), carrying both mutant amyloid precursor protein and presenilin-1 transgenes. The mice develop Î²â€'amyloid plaques at 4-6 months of age comparable to those seen in the post-mortem brain of human AD patients. The ability to selectively lesion forebrain cholinergic neurons with the toxin mu p75-saporin makes it possible to improve the existing model so it also expresses cholinergic degeneration - another hallmark of AD. In this study, transgenic mice [Tg(+)] and wild-type littermates [Tg(-)] received either PBS or saporin (0,6Âµg) bilaterally into the lateral ventricles at age 6 months. We have previously demonstrated that this saporin lesion diminishes the amount of cholinergic innervation in the hippocampus by 80%. Two months after the surgery, the animals were subjected to different behavioural tests, including general locomotor and cognitive assays. Levels of horizontal locomotor activity were measured in a cage using an automated infra-red beam break monitoring system. The test revealed a hyperactive phenotype in the saporin treated animals, with a tendency for the PBS treated Tg(+) to have a higher level of activity than the PBS treated Tg(-) mice. A beam walking test was also used to evaluate behavioural performances such as ataxia in the mice. Tg(+) with cholinergic lesions performed significantly worse than Tg(+) treated with PBS. This difference was not apparent in the Tg(-) groups. After the assessment of the motor performances, the animals were tested in cognitive tasks addressing intact hippocampal-dependent spatial short-term memory in a Y-maze. Tg(-) treated with PBS were the only group to distinguish significantly between new and familiar areas and thus memorize the task. Thus, the Tg(+) genotype as well as saporin treatment resulted in significant deficits in short-term memory. Working memory performance was tested in a continuous alternation paradigm. The Tg(+) mice treated with saporin had significantly fewer correct alternations than the Tg(+) treated with PBS. This difference following saporin treatment was not apparent in the Tg(-) mice. In summary, the spatial Y-maze revealed mnemonic deficits in all treatment groups besides the Tg(-) animals treated with PBS. However, in the beam walking test and in the T-maze, there were only significant behavioural and mnemonic deficits apparent when the Tg(+) genotype was combined with the cholinergic lesion. This suggests a strong effect when combining transgenic APPswe/PS1dE9 animals with forebrain cholinergic lesions.

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17.

Computational Analysis of Dopamine Release, Diffusion and Uptake

Authors: Jakob Kisbye Dreyer, Kjartan Herrik Frisch, Rune W Berg

Poster submitted by Jakob Kisbye Dreyer on Saturday, October 31, 2009

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Abstract

The dopamine system is usually investigated from 3 different perspectives: Electrophysiology, Voltametry, and Microdialysis. Here, electrophysiological recordings show that dopamine (DA) neurons in the ventral midbrain are spontaneously active with firing patterns ranging from regular (tonic) to bursts (phasic) [Grace 1984]. Voltametric recordings find region-specific spontaneous transients of ~50 nM amplitude [Aragona 2009]. Finally, tonic levels are measured using microdialysis. We present a computational model of the dopamine system based on the current experimental data that bridges these observations.

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18.

Determinants of hKv11.1 (hERG) localization in the brain

Authors: Einarsen K., RAsmussen HB., Olesen SP., Scmitt N.

Poster submitted by Karoline Einarsen on Saturday, October 31, 2009

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Abstract

The Kv11.1, or ether-a-go-go-related (ERG) voltage-gated potassium channel, is recognized for its major role in repolarization of the cardiac action potential, and its susceptibility to pharmacological blockade by diverse groups of pharmacological agents. Additionally, Kv11.1 RNA expression is found throughout the rodent brain as shown by in situ hybridization studies (Papa et al., J. Comp Neurol 2003; 466:119-135; Saganich et al.; 2001 J Neurosci 21: 4604-4624). In line with this expression profile recent studies have revealed important functions for Kv11.1 also in the nervous system. Yet, to our knowledge the subcellular localization of Kv11.1 has not been described to date. We have investigated the localization of Kv11.1 channels by immunostaining of heterologously expressed channel subunits in neurons from rat primary hippocampal cultures. The resulting localization pattern of Kv11.1 is chiefly intracellular. This intracellular localization indicates that Kv11.1 surface expression in neurons may depend on one or more interaction partners, possible other alpha or beta subunits. We investigated two groups of possible interaction partners, the KCNE family of beta-subunits and KvÎ²2 from the KvÎ² family of beta-subunits. We did not find any changes in localization pattern upon KCNE co-expression, however KvÎ²2 co-expression led to an increase in Kv11.1 surface localization. We further investigated the possible Kv11.1 â€' KvÎ²2 interaction by patch-clamp recordings using transfected HEK cells, where we found altered Kv11.1 current kinetics upon KvÎ²2 co-expression.

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19.

Identification of a dual agonist of the fibroblast growth factor receptor and the neural cell adhesion molecule

Authors: Maj Enevoldsen, Artur Kochoyan, Shizhong Li, Elisabeth Bock and Vladimir Berezin

Poster submitted by Maj Enevoldsen on Saturday, October 31, 2009

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Abstract

The fibroblast growth factor receptor (FGFR) family includes four receptor tyrosine kinases and their main ligands are fibroblast growth factors (FGFs). The receptors consist of an extracellular domain which contains two or three immunoglobulin-like modules (Ig1-Ig3), a transmembrane helix and a cytoplasmic tyrosine kinase domain. Other molecules than FGFs have also been shown to interact with FGFRs, including the neural cell adhesion molecule (NCAM), which is known to play an important role in neuronal development, regeneration and synaptic plasticity. However, several aspects regarding the interactions between the FGFR and NCAM still need to be clarified. In the present study a peptide derived from the Ig2 module of FGFR, encompassing amino acid residues involved in NCAM binding, termed Enreptin, was tested in various biological assays. We report that Enreptin is able to bind directly to both NCAM and FGFR and activate them both leading to several biological responses.

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20.

[11C]NS12857 is a novel PET ligand for imaging □7-nicotinic receptors: Preliminary data from the pig brain

Authors: Anders Ettrup1, Jens D Mikkelsen1, Anders B Marcussen1, Szabolcs Lehel2, Jacob Madsen2, Daniel B Timmermann3, Dan Peters3 and Gitte M Knudsen1

Poster submitted by Anders Ettrup on Saturday, October 31, 2009

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Abstract

The ïi7-nicotinic acetylcholine receptor (ïi7nAChR) is proposed to play a role in the pathophysiology of schizophrenia and in Alzheimerâ€™s disease, and is considered a potential therapeutic target. Accordingly, access to a suitable radiolabeled ïi7-nAChR positron emission tomography (PET) tracer would enable in vivo quantification of the cerebral ïi7-nAChR binding. However, only very few ïi7nAChR PET ligands are available today. Here we present the in vivo distribution of [11C]NS12857, a novel selective ïi7-nAChR agonist PET ligand, in the pig brain along with agonist and antagonist blocking studies. The high-affinity ïi7-nAChR selective agonist NS12857 was radiolabelled by methylation of its precursor using [11C]methyl triflate. Three Danish Landrace pigs were studied at baseline and after blocking doses of either the ïi7-nAChR agonist SSR180711 (n=2) or the ïi7-nAChR functional antagonist NS6740 (n=1). [11C]NS12857 was given as an intravenous bolus injection (n=6, mean injected dose (ID): 525 MBq, range 381-669 MBq), and the pigs were subsequently scanned for 90 minutes with a high resolution research tomography (HRRT) PET camera. Hereafter, the pigs were re-scanned after pre-treatment with either SSR180711 (5 mg/kg bolus + 2 mg/kg*h constant infusion) or NS6740 (10 mg/kg bolus + 4 mg/kg*h constant infusion). Arterial whole blood and plasma radioactivity were measured during four of the scanning sessions, along with measurements of plasma parent compound and radiolabelled metabolites. Receptor autoradiography on pig brain sections was conducted to verify the in vitro capability of SSR180711 and NS6740 to displace [11C]NS12857 binding. The PET scans showed a high uptake of [11C]NS12857 in the pig brain in vivo, and the distribution in the pig brain was in accordance with the expected brain distribution as reported in primates. The highest binding was observed in the thalamus, moderate binding seen in cerebral cortical and striatal areas, whereas low uptake was observed in the cerebellum. The brain uptake (as %ID) of [11C]NS12857 was somewhat higher than previously reported. No radiolabelled lipophilic metabolites of [11C]NS12857 were detected in the pig plasma. Pre-treatment with SSR180711 or NS6740 did not lead to the anticipated decline in the distribution volume (VT) of [11C]NS12857, as determined with 1- or 2-tissue compartment kinetic modelling. The autoradiographic studies confirmed that both SSR180711 and NS6740 displace [11C]NS12857 binding in pig brain sections. Conclusively, [11C]NS12857 is a promising radiotracer for in vivo imaging of ïi7-nAChRs, although the lack of in vivo displacement of [11C]NS12857 requires further studies.

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21.

Validation of the isolation rearing (IR) model

Authors: Katrine Fabricius, Bjørn Steiniger-Brach, Lone Helboe, Anders Fink-Jensen, Gitta Wörtwein and Bente Pakkenberg

Poster submitted by Katrine Fabricius on Saturday, October 31, 2009

Affiliations: Anders Fink-Jensen (Main supervisor, Neuropsychiatric research lab, RH), Gitta Wörtwein (Neuropsychiatric research lab, RH) Lone Helboe (Project Supervisor, Discovery Biology Research, H. Lundbeck A/S), Bjørn Steiniger-Brach (Discovery Pharmacology Research; H. Lundbeck A/S) and Bente Pakkenberg (Research lab for stereology and neuroscience, Bispebjerg Univ Hosp).

Abstract

Validation of animal models of psychiatric disorders is challenging due to the human nature of these disorders. The isolation rearing (IR) model is based on the neurodevelopmental hypothesis of schizophrenia and has been used by others as an animal model to mimic some of the hallmarks seen in schizophrenic patients. The aim of our studies was to validate the IR model in Lister-hooded male rats, using a combination of behavioural, neurochemical and immunohistochemical approaches. Data presented here support an overactive mesocortico-limbic system, which has been hypothesized to be critically involved in the pathophysiology of schizophrenia. In this line we show that isolated animals have; a robust hyperactive locomotor response to a novel arena, which can be reversed with a second generation antipsychotic, sensory gating deficit in the prepulse inhibition (PPI) assay and deficits in the novel object recognition. Neurochemical alterations include an exacerbated dopamine efflux in the nucleus accumbens to an amphetamine challenge without any changes in the basal dopamine level. Neurostructual findings include differences in stereological volume estimations where isolated animals showed smaller overall brain volume followed by a tendency of enlarged ventricles. Non-stereological estimations of immunohistochemical stained parvalbumin positive neurons in the prefrontal cortex of IR animals revealed a significant reduction compared to group housed (GH) controls. Taken together, these results support the use of the isolation rearing model as an animal disease model for some aspect of schizophrenia.

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22.

The Drummer's High

Authors: Line Gebauer(1, 2), Doris Doudet (2, 4), Albert Gjedde (2, 3), Arne Møller (2), Jacob Linnet (1,2) and Peter Vuust (1)

Poster submitted by Line Gebauer on Saturday, October 31, 2009

Affiliations: Center of Functionally Integrative Neuroscience, Århus University, PET-center, Århus University Hospital, Institut for Neurovidenskab og Farmakologi, Københavns Universitet, Dept. of Neurology, University of British Columbia.

Abstract

Abstract: â€˜The drummerâ€™s high â€' A pilot study of midbrain dopamine release in musiciansâ€™ Line Gebauer, Doris Doudet, Albert Gjedde, Arne MÃ¸ller, Jacob Linnet and Peter Vuust Humans all over the world engage in music listening and performance, and most people canâ€™t imagine a life without it. Despite the truly pleasant effects we experience from music, we do not know why we play and listen to music. Pleasant responses to music listening, such as chills, have been found to activate areas in the midbrain associated with dopaminergic reward mechanisms. Similar reward mechanisms play a key role in reinforcing adaptive behaviors such as eating and reproduction. The involvement of dopmainergic reward mechanisms in music might therefore help us to understand the evolutionary origin of music. Not only listening to music is rewarding, but playing music seems to be extremely rewarding too. Musicians report to experience a euphoric feeling, almost like getting high, when playing. However no study to date have looked at dopamine release in response to live music playing. We propose to investigate dopamine release in performing musicians to see whether the pleasure derived from playing is associated with reward mechanisms similar to those of adaptive biological stimuli. The data we are presenting here are very preliminary, since only one participant has been included. Our participant was a professional drummer and he was PET-scanned on three consecutive days, after listening to music, practice rythms or performing in a live jazz concert together with a jazz-band in front of an audience. We used the tracer [11C] raclopride that binds to available dopamine receptors to measure changes in dopamine release in ventral striatum, caudate nucleus and putamen. Contrary to what was expected, our data did not show any correlation between selfreported euphoria and dopamine release. We found increased dopamine in both the active conditions (practice and performance) compared to the passive listening baseline. These data lead us to suggest that dopamine might not be involved in music-induced hedonia per se. Future research should investigate the involvement of the opiodergic and endocannabiodergic neurotransmitter systems in euphoric experiences during music playing.

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23.

Neuronal stem cells are stimulated to migrate and differentiate due to erythropoietin treatment in an experimental model of cerebral malaria.

Authors: Andrew Core 1,2; Casper Hempel 2,3; Lothar Wiese 3, Jørgen Kurtzhals 3 and Milena Penkowa 2

Poster submitted by Casper Hempel on Saturday, October 31, 2009

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Abstract

Cerebral malaria accounts for substantial mortality and morbidity. Currently, no neuroprotective treatment ameliorates the seizures or reduces the risk of coma in acutely ill patients. Murine models are in use to investigate the pathogenesis and erythropoietin has recently been shown to decrease mortality and pathology. Using a mouse model and life-saving treatment with erythropoietin, we investigated whether the neuroprotective effects included regeneration of neural stem cells within specific niches of the murine brain. We used immuohistochemical methods to assess the changes in situ. Using markers of different maturation stages of the neural stem cells, we showed an increased number of nestin- and PSA-NCAM positive cells in the dentate gyrus and in the sub-ventricular zone of infected erythropoietin-treated mice. Moreover, this group of mice had more neurite growth in the dentate gyrus visualised by alpha-internexin indicating neuronal regeneration. The neural stem cells and neuronal progenitors co-expressed the epo receptor. These results indicate a rapid, erythropoietin-dependent activation of neural stem cells in relation to cerebral malaria pathology.

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24.

BKCa channels are expressed in the trigeminal ganglion and the trigeminal nucleus caudalis in rat

Authors: H. Wulf-Johansson1, A. Hay-Schmidt, A. Nyander Poulsen, D. Klaerke, J. Olesen and I. Jansen-Olesen

Poster submitted by Helle Wulf Johansson on Saturday, October 31, 2009

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Abstract

Objectives: To characterize the expression profile of the large conductance calcium-activated po-tassium (BKCa) channels in the trigeminal ganglion and the trigeminal nucleus causdalis. Background: Migraine pain is thought to arise from the trigeminovascular pathway involving large cerebral- and meningeal blood vessels, trigeminal sensory nerve fibers, trigeminal ganglion and the trigeminal nucleus caudalis. We have previously shown the presence of BKCa channels in pial and dura arteries and hypothesized that a BKCa channel blocker may counteract a vasodilatation. Moreover, we showed the presence of BKCa channels in the trigeminal ganglion and suggested a role for BKCa channel openers as possible treatment of migraine. However, it was recently shown that BKCa channels openers might be important targets in suppressing hyperexcitability of sensory neurons in the trigeminal nucleus caudalis (Storer et al. 2009). We have therefore in the present study compared the BKCa channel expression profile in the trigeminal ganglion and the trigeminal nucleus caudalis. Methods: Three Sprague Dawley rats were included. We investigated the mRNA expression of BKCa channel in rat TG and TNC by reverse transcription polymerase chain reaction (RT-PCR). Quantitative real-time PCR (qPCR) was used to compare TG- and TNC mRNA transcript levels. Western blotting was performed to investigate the BKCa channel protein expression profile in TG and TNC. Results: BKCa channel mRNA expression was detected in rat TG and TNC. There was no signifi-cantly difference in BKCa channel mRNA comparing TG and TNC using qPCR. Immunoblots showed higher expression pattern of BKCa channel protein in TNC as compared to TG. Conclusion: The present study showed BKCa channel mRNA and protein expression in the rat TG and TNC. Interestingly, BKCa channels are more abundantly expressed in the TNC as the TG. The findings may further support that BKCa channels may have a role in modulating trigeminovascular nociceptive signalling to the trigeminal nucleus caudalis

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25.

Molecular investigations of BKCa channels and the modulatory β-subunits in por-cine trigeminal ganglion

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Abstract

Objectives: Ion channel function has been implicated in migraine pathology. We hypothesize that the large conductance calcium-activated potassium (BKCa) channel alpha- and beta-subunits are present in the porcine trigeminal ganglion and co-localize with calcitonin gene-related peptide (CGRP). Background: Migraine is associated with activation and sensitization of trigeminal neurons. The BKCa channels are essential for ion fluxes across the cell membrane contributing to electrical impulses regulating cell excitability and neurotransmitter release. The native BKCa channel is composed of Î±- and Î²-subunits (Î²1-Î²4). Co-expression with the Î²-subunit modulates the channel activity changing Ca2+ sensitivity, kinetic behaviour and pharmacology. Studies from the dorsal root ganglion have shown that BKCa blockers increase neuronal firing in the dorsal root ganglion whereas the BKCa openers suppress neuronal firing activity. Methods: We investigated the mRNA expression of BKCa channel and the modulatory Î²-subunits in the por-cine trigeminal ganglion by reverse transcription polymerase chain reaction (RT-PCR). The distri-bution patterns of BKCa channel Î±-subunit mRNA and protein were investigated using in situ hy-bridization and histochemistry, respectively. Western blotting was used to investigate the protein expression of the modulatory Î²1-Î²4 subunits. Results: BKCa channel mRNA expression was detected in porcine trigeminal ganglion. In situ hybridization also verified BKCa channel mRNA transcripts in the trigeminal ganglion. Histochemistry showed immunoreactivity for the BKCa channel protein. Immunofluorescence imaging revealed co-expression of BKCa channels with CGRP immunopositive trigeminal ganglion cells. The modulatory Î²2- and Î²4â€'subunit mRNA was detected in the trigeminal ganglion using RT-PCR. Western blot-ting detected Î²2- and Î²4-subunit protein in the porcine trigeminal ganglion. Conclusion: The present study showed expression of BKCa channel mRNA and protein in the porcine trigeminal ganglion. The modulatory Î²2- and Î²4-subunits were expressed in the porcine trigeminal ganglia. We suggest that BKCa channels may be involved in pain transmission through the trigeminal gan-glion pathway. Furthermore, BKCa openers may be potential drugs for the suppression of hyperex-citable neurons and Î²-subunits may be important modulators of the BKCa channel conductance. Future experiments should clarify the importance of BKCa channels in the trigeminal ganglion path-way in relation to migraine and pain signalling

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26.

Identification of kinase pathways regulating monoamine transporter function by kinome-wide siRNA screening

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Poster submitted by Trine Nygaard Jørgensen on Saturday, October 31, 2009

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Abstract

The transporters for dopamine (DAT), serotonin (SERT) and norepinephrine (NET), collectively termed the monamine transporters, are known to be regulated by protein kinases such as protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K), and calcium/calmodulin-dependent protein kinase II (CaMKII). However, little is known about the entire ensemble of kinases and kinase pathways controlling monoamine transporter function. To address this question, we carried out a small interfering RNA (siRNA) screen of the entire human kinome and assessed the effect of knockdown on the uptake properties of human DAT, NET or SERT stably expressed in human embryonic kidney 293 cells. We used a human siRNA kinome library from Ambion consisting of 3 siRNAs per gene, at 33 nM each, targeting 710 genes, giving 2130 unique siRNAs. The screen was performed in triplicates. As a negative control, siRNA not targeting any annotated genes in the human genome was applied. An assay testing for cell viability was performed in parallel. Before conducting the screen, several parameters for use in 96 well plates were optimized, including cell line, type of transfection reagent used, number of cells seeded, and concentration of siRNA. Furthermore, stable cell clones expressing DAT, NET or SERT were selected according to the expression level and the response to kinase inhibitors previously shown to alter transport activity. The initial screen provided a plethora of kinases that directly or indirectly regulate the activity of the monoamine transporters. Further studies in cell lines as well as in primary neuronal cultures are needed to validate these preliminary findings.

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27.

PDE5 inhibitor pre-treatment of human brain microvascular endothelial cells leads to a decreased activation of MAPK upon stimulation with TNFa

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Poster submitted by Carina Jørgensen on Monday, November 02, 2009

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Abstract

Background: Stroke is the leading cause of disability in adults and the 3. leading cause of death. Cerebral ischemia induces a multitude of cellular and intracellular signaling cascades involved in the inflammatory response to tissue damage. Such response includes production and release of e.g. cytokines, which may modulate production of intracellular signaling molecules such as cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate. The cytokine TNFa is associated to the inflammatory, thrombogenic and vascular changes seen during ischemic stroke, and the level of TNFa is increased during the acute-phase of stroke. In rodent stroke models treatment with phosphodiesterase (PDE) 5 inhibitors, which increase intracellular levels of cGMP, leads to better recovery post stroke, however the mechanisms for such effects are not fully understood, but may involve endothelial function. The binding of TNFa to its receptor activates the mitogen-activated protein kinases (MAPK) Erk1/2, p38 and Jnk. We have studied the possible interplay of PDE5 inhibitors on the TNFa associated signaling pathway in endothelial cells. Materials and methods: An in vitro system of primary human brain microvascular endothelial cells (pHBMECs) was used. pHBMECs were pre-incubated with PDE5 inhibitors followed by TNFa stimulation and the effect of PDE5 inhibitors on MAPK pathway activation were investigated. Results: Results show that TNFa stimulation leads to an activation of the MAPK pathways in pHBMECs. This activation is sensitive to pre-incubation with PDE5 inhibitors. Conclusion: PDE5 inhibitors affect the TNFa associated signaling in pHBMECs and this may decrease endothelial cell damage. Whether or not this is the mechanism by which PDE5 inhibitors may be effective in cerebral ischemia needs to be further investigated.

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28.

Stereological quantification of parvalbumin-expressing neurons in hippocampus of two animal models of schizophrenia

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Abstract

Imbalance in glutamate signaling in prefrontal cortex (PFC) and hippocampus (HPC) has been suggested to play a major role for cognitive symptoms such as amnesia, and learning and concentration disabilities seen in schizophrenic patients. Since astrocytes and GABAergic interneurons are functionally involved in regulation of glutamate signaling in the brain, altered expression of these cells in PFC and HPC may play a role for the symptomatology in schizophrenia. In this study we apply a stereological approach to analyze the involvement of a subtype of GABAergic neuron and astrocytes in cognitive deficits in schizophrenia. Using immunohistochemistry techniques, we have quantified the total number of these two neuronal cell types in hippocampus in two neurodevelopmental animal models for cognitive dysfunction in schizophrenia.

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29.

Total number of neocortical cells in mental retardation - a stereological study of the brain in adults with Down syndrome

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Abstract

Mental retardation is a consistent phenotype in many developmental disorders. Although the genetic backgrounds for most of these disorders are known, knowledge on the interplay between genes, mind and behavior is lacking. One way to link these entities is to describe the physical parameters in brains of people with impaired mental capacity and compare with brains of normal subjects to thoroughly identify differences as well as similarities. Down syndrome (DS) or trisomy 21 involves mental impairment, delayed growth, accelerated aging and dementia; and is a proper model for investigating the mentally retarded brain and the physical consequences of genetic anomalies due to its high prevalence (1 in 700-1000 live births). The aim of this study was to estimate the total number of neocortical neurons and glial cells in formalin-fixed, paraffin-embedded brains from adult female DS subjects (mean age 69.3 years, N = 5) and compare with female controls (mean age 70.0 years, N = 6). For this purpose volume and cell density were estimated in the neocortex and its four major sub-divisions using the stereological tools - the Cavalieri estimator of volume and the optical disector. In this first stereological study on brains from adults with DS, a total number of 11.1 × 109 neocortical neurons (CE = 0.04, range 9.55 - 12.0 × 109) was estimated and compared to controls having 17.8 × 109 neurons (CE = 0.04, range 15.2 - 21.1 × 109); showing a global difference of almost 40 %, which was highly statistically significant (2p = less than 0.001). The sum of glial cells was 12.8 × 109 in DS (CE = 0.04, range 11.5-13.6 × 109) and 18.2 × 109 in controls (CE = 0.03, range 15.0- 21.8 × 109); a difference of almost 30 % (2p = 0.004). This lower number of neocortical cells followed by reduced volumes of the four neocortical regions with no changes in the cell densities, emphasizes that the delayed development observed in DS fetuses is not compensated for later in life. In relation to the general population showing neocortical neuron numbers from 15 – 35 billions, the findings from these brains suggest that some of the mental impairment in DS is a result of a reduced number of neocortical neurons.

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30.

An in vivo mutational analysis of the endophilin-A N-BAR domain

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Abstract

Endophilin is a cytoplasmic protein with important functions in clathrin-dependent endocytosis at synapses and elsewhere. Endophilin has a BAR (Bin/Amphiphysin/Rvs-homology) domain, which is implicated in the sensing and induction of membrane curvature, a central aspect of synaptic vesicle reformation. Previous structure-function studies of the endophilin-A BAR domain in Drosophila have almost exclusively been made in reduced systems, either in vitro or ex vivo in cultured cells. To extend and complement this work, we have analyzed the in vivo role played by the structural features of the endophilin-A BAR domain in Drosophila, employing genetic rescue of endophilin-A (endoA) null mutants with wild type or mutated endoA transgenes. We evaluated the viability and locomotor behavior of the rescuants, and their neurotransmission at the neuromuscular junction. We find that whereas mutating the endophilin BAR domain clearly affects adult flies, larval endophilin function is surprisingly resistant to mutagenesis. The charge-negative substitution A66D, which completely disrupt the ability of endophilin-BAR to tubulate liposomes in vitro, rescued the viability and neurotransmission with the same efficacy as wild type endoA transgenes, even in adults. A similar discrepancy was found for the hydrophilic substitutions A63S/A66S and A63S/A66S/M70Q. The A66W mutation, which introduces a bulky hydrophobic side chain and induces massive vesiculation of liposomes in vitro, strongly impeded fly eye development, even in presence of the endogenous endoA gene. In general, more extensive structural perturbation of the central helix-loop appendage severely affected endophilin-A function. However, substantial residual function was observed in larvae rescued with EndoA(Arf), which encodes a form of endophilin-A that completely lacks the appendage. Whereas a mutation (D150P) designed to increase the BAR curvature was tolerated, another mutation (P143A, DeltaLEN), designed to decrease it, was not. Our results provide novel insight into the primary structure/function relationship of the endophilin-A BAR domain in vivo, especially with relation to synaptic function.

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31.

Expression and localization of PDE8A in the nervous system of the Sprague-Dawley rat

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Abstract

Phosphodiesterases are essential regulators of cyclic nucleotide signalling. In total, 11 families of PDEs have been described so far. The PDE8A was isolated and characterized about 10 years ago but information about the distribution of this isoform in the brain is still scarce. We have in serial coronal sections of the brain of male Spraque-Dawley rats and the trigeminal ganglion mapped the location of PDE8A immunoreactivity and supplemented our study by Western blotting. We show that PDE8A is widely distributed in neurons in the brain and trigeminal ganglion and is present in areas involved in pain transmission, motor function, cognition, vegetative function, and olfaction.

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32.

Expression of PAX6, OTX2, and OTX1 together with total cell numbers in the ganglionic eminence in the early developing human forebrain.

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Abstract

The development of the human neocortex is a complex and highly regulated process involving the time-related expression of many transcription factors including the homeobox genes: PAX6 , OTX2, and OTX1. During early development, Pax6 is expressed in nuclei of radial glia cells in the neocortical proliferative zones in rodents and controls the differentiation and neurogenetic fate of these cells in the dorsal telencephalon. Otx2 and Otx1 are known to cooperate with other genes to develop the caudal forebrain in rodents and further, Otx1 is involved in differentiation of the neurons of the deeper cortical layers. We have studied the spatial and temporal expression of the homeobox genes PAX6, OTX2 and OTX1 using a developmental series of human fetal brains aged from 7 to 19 weeks post-conception with focus on the forebrain. In this study, we demonstrate by in situ hybridization and immunohistochemistry that all three homeobox genes PAX6, OTX2 and OTX1 are expressed during early human fetal brain development. PAX6 mRNA and protein were not only located in the proliferative zones of the neocortex, but also in single cells in the cortical preplate and cortical plate. Expression of PAX6 was observed in the ganglionic eminence, which increased just prior to the stage when a stereological estimation of the total cell numbers showed an exponential rise in cell proliferation. A cytoplasmatic localization of the PAX6 protein in the neocortex of the older fetuses indicates a non-transciptional function of this protein in late human prenatal life. OTX2 was expressed in the ventricular zones of the diencephalon, mesencephalon, archichortex, and choroid plexus with minor expression in the basal telencephalon. Contrarily, the OTX1 expression was predominantly located in the cerebral hemispheres.

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33.

MEK inhibition as a potential treatment of cerebral vasospasm and late cerebral ischemia associated with subarachnoid hemorrhage

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Abstract

Subarachnoid hemorrhage (SAH) associated with cerebral vasospasms that may cause late cerebral ischemia, which is a major cause of mortality and morbidity. We have earlier demonstrated that experimental SAH in rats induces upregulation in the ETB receptor for endothelin-1 (ET-1) and the 5-HT1B for 5-hydroxytryptamine (5-HT) on cerebrovascular smooth muscles mediated by intracellular signalling via the Ras-Raf-MEK-ERK1/2 pathway. We hypothesise that these changes are crucial for the pathogenesis of cerebral vasospasms and that the ERK1/2 pathway is a novel therapeutic target in SAH treatment. The aim of this study was to investigate the effect of the MEK inhibitor U0126 on cerebrovascular expression of vasoconstrictor ET-1 and 5-HT receptors and neurological deficits following experimental SAH in rats. Methods: Experimental SAH was induced in male Sprague-Dawley rats. 6, 12, 24, and 36 hours following SAH animals were treated with 85 µg/kg U0126 intrathecally. 48 hours after SAH rats were neurologically examined by means of a rotating pole test and sacrificed. Cerebral arteries were dissected out and 1 mm long segments were mounted on two steel wires in a wire myograph in which the contractile responses of the vessels to cumulative doses of ET-1 and 5-carboamidotryptamine (5-CT) were measured. Results: Treatment with U0126 prevents SAH-induced ETB and 5-HT1B receptor upregulation as well as SAH-induced increases in the contractile responses of basilar and middle cerebral arteries to ET-1 (ETA and ETB receptor agonist) and 5-CT (5-HT1 receptor agonist). Treatment with U0126 also prevents SAH-induced deficits in motor function, coordination and balance determined by a rotating pole test. Conclusion: These results indicates that the MEK inhibitor U0126 is a potential therapeutic agent for prevention of vasospasms after SAH.

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34.

Addressing the Problem of Path-Length Dependency in Probabilistic Tractography of the Brain - The ICE-T Framework

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Poster submitted by Matthew Liptrot on Saturday, October 31, 2009

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Abstract

Introduction: Probabilistic tractography [1] affords a potentially quantitative method for non-invasively generating a â€œconnection probability mapâ€, a frequency measure of successful vs. attempted fibre-tracking trials to remote brain areas from a given seed region. However, one of the limitations with the approach is that of path-length dependency, where the values thus produced are modulated by a gradual decline in the likelihood of successful propagation as the distance from the seed region increases [2]. This bias is unfortunately inherent to the method, as it is derived from a propagation, along a potential fibre, of the very uncertainty per voxel which is required in order to generate the probability maps. Hence, in so favouring short-range connections over longer-range ones, the method's ability to perform fibre-tracking to distal regions is compromised. Surprisingly, little focus has been directed towards the path-length dependency problem (e.g. [2]). Here, we address the issue with a novel tractography framework, Iterative Confidence Enhancement for Tractography (ICE-T). This retains the stages of conventional probabilistic streamlining tractography, but then attempts to overcome the path-length dependency via the introduction of an extra stage, and a subsequent feedback loop to allow iteration of the fibre tracking stage. In this way, the ICE-T framework can be used with any conventional streamlining tractography method. The present study was based on the same DWI dataset acquired on perfusion-fixated mini pig brains recently used to validate conventional probabilistic tractography using in-vivo tracers [4]. Method: Consider the probabilistic tractography analysis framework as a modular processing pipeline with the following stages: (1) acquisition of diffusion-weighted (DW) images; (2) fibre reconstruction; (3) generation of fibre-orientation probability density functions (FO-pdf); (4) fibre tracking: repeated streamlining from a given seed region, via voxelwise sampling of the FO-pdfs; (5) generation of connection probability maps. The non-deterministic nature of probabilistic tractography, and hence also the cause of the path-length dependency, is introduced in stages (3) and (4). Traditionally, to segment a tract emanating from the seed region, the results of (5) are (arbitrarily) thresholded at some appropriate level. Our approach takes its inspiration from the region-growing algorithms commonly used in image processing to obtain segmentation [5]. The principle is simple - the neighbourhood of a given seed region is considered and those voxels which match a user-defined predicate are aggregated within it. Once merged, a feedback loop is followed, and the neighbours of the newly-updated seed region are considered. Hence the region iteratively grows whilst the predicate rule is fulfilled. Data: Diffusion weighted images were obtained from the perfusion fixed brains on an experimental 4.7T Varian Inova scanner. Postmortem DWI data excludes the well known in-vivo related physiological noise sources whilst retaining the anatomical structures as if in vivo. A b-value of 4009 s/mm2 was selected according to [6], with a voxel size of 0.51x0.51x0.50 mm3 (for details [1]). The DWI dataset included 61 dw-directions and 3 non-dw image volumes. Multi-fibre reconstruction, based upon a mixture tensor model of up to two fibre populations [7], was performed. An ROI was hand-drawn in the somatosensory area and tractography seeded from it using the proposed (ICE-T) and traditional (conventional probabilistic tractography, with free-tracking using 64,000 streamlines) methods. In both cases, the tractography routines utilised the Camino Toolbox [3], whilst the ICE-T framework was implemented in Matlab. Results: The ICE-T method stabilised well, segmenting out a great deal more potential white-matter tracts than the conventional tractography. Note the clear influence of the path-length dependency in the contra-lateral hemisphere compared to the ICE-T result. Previous work [4] has confirmed the existence of such contra-lateral cortico- cortical connections, and also demonstrated the path-length dependency issues incurred by conventional methods when attempting to extract them. Conclusion: The ICE-T algorithm's use of region-growing encourages homogeneity of the seed region, and we purport that it is this feature which helps to subdue the path-length dependency as observed in conventional probabilistic tractography. In the very near future, we hope to be able to use the method to enable comparison of connectivity probabilities across subjects, something unobtainable with conventional methods today. References: [1] G. Parker, et al, A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements, J Magn Reson Imaging, 18(2), 2003, pp242-54 [2] D. Morris, et al, Probabilistic fibre tracking: Differentiation of connections from chance events, Neuroimage 42, 2008, pp1329-1339 [3] P. 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35.

Interference in ballistic motor learning - is motor interference sensory?

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Poster submitted by Jesper Lundbye-jensen on Saturday, October 31, 2009

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Abstract

Skill gained after a short period of practice in one motor task can be abolished if a second task is learned shortly afterwards. We hypothesised that interference requires the same circuits to be engaged in the two tasks and provoke competing processes of synaptic plasticity. To test this, subjects learned a ballistic ankle plantarflexion task. Interference was observed following subsequent learning of a precision tracking task with the same movement direction and agonist muscles, but not by learning involving the opposite movement and antagonist muscles or by voluntary agonist contractions that did not require learning. Repeated transcranial magnetic stimulation (rTMS) of corticospinal motor output at intensities below ankle movement threshold did not cause interference, whereas suprathreshold rTMS did. Furthermore, electrical stimulation of the peripheral nerve to the plantarflexors (but not extensors) caused interference. We conclude that interference is remarkably specific for circuits involved in a specific movement direction / activation of individual muscles and depends crucially on sensory error signals. One possible mechanism of interference may be disruption of early motor memory consolidation.

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36.

Crossing fibers in lateral white matter of the cervical spinal cord detected with diffusion MRI in monkey postmortem

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Abstract

Introduction The corticospinal control of the spinal cord is the key for understanding generation of voluntary motion and might be essential for functional recovery of spinal cord injuries in humans. The course of the corticospinal tract in the dorsolateral parts of the white matter (WM) column is here of interest [8]. This tract contains fibers crossing the main superior-inferior direction as they branch off towards the gray matter (GM). The aim of this study is to evaluate the possibility of using Diffusion weighted imaging (DWI) to investigate those fibers. As a good model of the human, the green monkey was used. The animal was perfusion fixed, the spinal cord was excised and scanned postmortem. Postmortem acquisitions benefits from high-field scanners, long scanning times and thereby low noise and high spatial resolution and no physiological noise. Three different methods were used to reconstruct the fiber orientation: the diffusion tensor (DT) and two multifiber reconstruction techniques Q-ball imaging (QBI) and Persistent Angular Structure (PAS). One of the methods, PAS, resolved crossing fiber structures in the corticospinal tract. Methods Image acquisition: A cervical spinal cord sample was excised from a green monkey (age: 3.5 years), which was perfusion fixed and prepared as in [1]. All procedures followed guidelines for the care and use of experimental animals according to the local ethic committee on the island of StKitts and postmortem scanning was approved by the Danish Animal Experiments Inspectorate. DWI was obtained on an experimental 4.7 T Varian Inova scanner using a small one channel surface coil. The spinal cord was rinsed in PBS-buffer to remove residual fixative and thereafter drained to reduce signal from surrounding liquid. To reduce mechanic and thermal transient effects, the DWI dataset used was obtained 9 hours after the scanning session was started. A diffusion weighted spin-echo sequence was used with TE: 68 ms; TR: 2500 ms; axial matrix: 65x64x10; voxel size: 0.23x0.23x0.8 mm3. Diffusion weighting b-value of 4090 s/mm2 was used as found optimal for detecting crossing fibers in postmortem tissue [2]. Each DWI dataset consisted of 3 non-DW and 61 non-colinear DW image volumes. Three repetitions resulted in a SNR of 33 in lateral white matter. Data analysis: One axial slice centered over the cervical enlargement was selected for the analysis. Three different fiber reconstruction methods where used to assess the underlying fiber orientations: i) DT [4]; ii) QBI [5] represented by 4th order spherical harmonics and iii) PAS with radial basis functions [6]. The fiber orientations where extracted from the peaks of the fiber distribution estimated with QBI and PAS with a maximum of three fiber directions. All methods used in this study are available in the Camino diffusion toolkit [7]. Results The first eigenvector of the DT analysis clearly show the orientation of descending and ascending tracts in WM. An in plane symmetric structure of fiber orientations in GM with the dorsal roots is also visible. In addition to that, the QBI reconstructed the fiber crossings of the motorneurons in the ventral roots. This is in agreement with earlier findings [3, 9]. In addition to the orientations found by DT and QBI, PAS was able to detect consistent structures of crossing fibers in the corticospinal tract resulting in a changed color coded GFA. The additional fiber orientation in WM is fibers radially entering GM. A visual inspection of fiber distributions estimated by PAS were in general sharper than those of QBI (results not shown). PAS also found more voxels with two or three fiber orientations, though some were found in GM with less consistency. Discussion Fiber reconstruction has been carried out on a green monkey spinal cord postmortem using an experimental high-field scanner with a DWI protocol optimized for postmortem tissue. Crossing fiber structures of the corticospinal tract with good correlations to histological studies were resolved using the PAS reconstruction method only. The position of those fibers indicate the termination points in gray matter and is crucial for understanding motorcortical interaction in generation of motion in normal subjects and may help to better understand mechanisms involved in rehabilitation of spinal cord injuries. References: [1] Dyrby, T. B., et al, Neuroimage, 37, 1267-1277, 2007. [2] Dyrby, T. B. et al, 16th ISMRM, Toronto, Canada, 2008. [3] Cohen-Adad, J., et al, Neuroimage, 42(2), 739-749, 2008. [4] Basser PJ, et al, Journal of Magnetic Resonance, 103, 247-54, 1994. [5] Tuch DS, Q-ball imaging MRM, 52(6), 1358-1372, 2004. [6] Jansons K.M., et al, Inverse Problems, 19, 1031-1046, 2003. [7] Cook, P. A., et al, 14th ISMRM, Seattle, USA, 2006. [8] Porter, R., Lemon, R., Corticospinal Function and Voluntary Movement, Oxford University Press, 1993. [9] Özarslan, E., Neuroimage Jul 1;31(3):1086-103, 2006.

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37.

Analysis of microglial morphology in the molecular layer of the dentate gyrus in C57Bl6-mice using stereology and histomorphometry

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Poster submitted by Lise Lyck on Saturday, October 31, 2009

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Abstract

A histological evaluation of experimental and pathological specimens, the degree of microglial activation is often evaluated on the basis of morphological features of the cells including the size and shape of the cells, the number and length of cell processes, as well as by increased expression of markers such as CD11b, CD45 (LCA) and Iba-1. From stereological studies it is known that microglial activation is followed by proliferation of microglial cells and change in the morphology of the cells. To extend the list of morphological parameters that can be measured quantitatively for comparative studies, we combined digital image analysis and stereological methods for analysis of the morphology of microglia labeled by Iba-1. In the molecular layer of fascia dentata of the hippocampus from 6 male C57Bl6-mice the total number of microglial cells was 16 906 cells, the mean cell size was 151.3 Âµm3, and the average length of cell processes was 80.0 Âµm/cell. We found microglial cell bodies were ovoid in shape, as judged by the ratio of the shortest and longest diameter (ratio = 0.61) and that on average 5.65 cell processes were extending at the equatorial plane of the cell.

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38.

Inferior Cingulum Bundle Asymmetry Predicts Extroversion: A DTI study

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Abstract

Introduction Extroversion relates to the social dimensions of personality and has been positively associated with positive emotionality, and negatively with psychiatric disorders, e.g. anxiety disorders 1. Imaging studies have found extroversion to correlate positively with left amygdala activation to happy faces 2 and with left amygdala and parahippocampal gyral grey matter concentration 3. Moreover, extroversion has been positively associated with fractional anisotropy (FA) in the right uncinate fasciculus in subjects with schizotypical personality disorder 4. Here we report associations between extroversion and inferior (hippocampal part) cingulum white matter microstructure in healthy adults. We hypothesised that extroversion, adjusted for age and gender, would be associated with FA in left and right inferior cinguli, and possibly with extent of laterality. Secondarily we examined whether such a relationship existed for the uncinate fasciculus. Parallel (Î»||) and perpendicular (Î»âŠ¥) diffusivities were studied to further explore observed effects. Methods Forty-five healthy adults (14 females) aged 20-82 (37.5Â±20.5) were included in the study. Extroversion, which consists of six subscales (facets), was assessed using the Revised NEO Personality Inventory (NEO-PI-R) 5. Diffusion-weighted images were acquired in 61 directions (b=1200 s/mm2) using a 3T MR-scanner. The diffusion tensor was fitted using the RESTORE algorithm implemented in Camino to derive FA, Î»|| and Î»âŠ¥. TBSS 6 (part of FSL) was performed to project all subjectsâ€™ FA or diffusivity data onto a mean tract skeleton in MNI standard space. Mean FA and diffusivity values were extracted from ROIs drawn in the right and left inferior cingulum and uncinate fasciculus (Fig. 1). The laterality index (LI) = (2*(Left â€' Right) / (Left + Right)) of the cingulum was calculated for FA, Î»|| and Î»âŠ¥. Multiple linear regression models were used to predict extroversion. Post hoc analyses explored which extroversion subscales contributed to observed effects. Results Neither left ($Î²^2$=0.19, p=0.19), nor right ($Î²^2$=-0.11, p=0.45) inferior cingulum FA, adjusted for age and gender were significantly associated with extroversion. However, inferior cingulum FA LI, adjusted for age and gender, significantly predicted extroversion (Fig.2, Table). Moreover, inferior cingulum Î»âŠ¥ LI (r2=0.262 $Î²^2$=-0,369 p=0.013), but not Î»|| (p=0.39), adjusted for age and gender were significantly correlated with extroversion. Neither right ($Î²^2$=0.29, p=0.066), nor left ($Î²^2$=0.15, p=0.35) uncinate fasciculus FA, adjusted for age and gender, were significantly associated with extroversion, though the right side exhibited a trend. Conclusion The results suggest that higher FA in the left relative to the right inferior cingulum is associated with higher extroversion scores. The association was mainly driven by variability in inferior cingulum Î»âŠ¥, indicating that the observed asymmetry may be related to differences in axonal density. Post hoc analysis revealed that the facets warmth, gregariousness, activity and positive emotion were the main contributors to the observed associations. These findings are consistent with previous studies linking left hemisphere limbic structures to positive affect. Additional studies are needed to address the possible role of inferior cingulum asymmetry in extroversion. Acknowledgements The Lundbeck Foundation is acknowledged for financial support. References [1] Bienvenu et al. (2001) J Nerv Ment Dis, 189(3):154-161. [2] Canli et al. (2002) Science, 296(5576):2291. [3] Omura et al. (2005) Neuroreport 16(17):1905-1908. [4] Gurrera et al. (2007) 90(1-3):360-362. [5] Costa and McCrae. NEO-PI-R: Professional Manual, 1992. [6] Smith et al. (2006) Neuroimage, 31:1487-1505.

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39.

Cingulum bundle asymmetry predicts trait neuroticism: A DTI study

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Abstract

Introduction Amygdala and subgenual cingulate have been linked with anxiety and mood disorders, for which the trait neuroticism is a risk factor. Neuroticism has been negatively associated with right amygdala grey matter concentration 1. Moreover, functional connectivity between amygdala and subgenual cingulate predicts the anxiety and depression related personality trait harm avoidance 2. Larger right anterior cingulate surface has been correlated with higher harm avoidance scores 3. Reduced left subgenual cingulate grey matter volume has been found in bipolar and unipolar depressives 4. An altered balance between left and right subgenual cingulate function has been hypothesized to contribute to heightened affective, neuroendocrine, and sympathetic autonomic arousal observed in depression 5. The major fibre bundle connecting anterior cingulate and amygdala, hippocampus and hypothalamus is the cingulum. Here we report associations between neuroticism and cingulum white matter microstructure in healthy adults. The major hypothesis was that neuroticism, adjusted for age and gender, would be associated with fractional anisotropy (FA) in left and right cingulum, possibly reflected in the extent of laterality. The secondary hypothesis was that such relationship might also be observed for the uncinate fasciculus. Parallel (Î»||) and perpendicular (Î»âŠ¥) diffusivities were studied to further explore observed effects. Materials and Methods Forty-five healthy adults (14 females, 31 males) aged 20-82 (37.5Â±20.5) were included in the study. Neuroticism, which consists of six subscores (facets), was assessed using the Danish version of the 240-item self-report Revised NEO Personality Inventory (NEO-PI-R) 6. Diffusion-weighted images were acquired in 61 directions (b=1200 s/mm2) using a 3T MR-scanner. The diffusion tensor was fitted using the RESTORE algorithm implemented in Camino to derive FA, Î»|| and Î»âŠ¥. Tract-based spatial statistics (TBSS 7, part of FSL) analysis was conducted, in which all subjectsâ€™ FA or diffusivity data are projected onto a mean tract skeleton, representing the centres of all tracts common to the group. ROIs where drawn in the right and left cingulum and uncinate fasciculus. Mean FA and diffusivity values were extracted from all four ROIs for each subject for statistical analyses. The laterality index (LI) = (2*(Left â€' Right) / (Left + Right)) of the cingulum was calculated for FA, Î»|| and Î»âŠ¥ and used in multiple linear regression models predicting neuroticism. Post hoc analyses were conducted to explore which neuroticism subscales contributed to observed effects. Results Multiple linear regression models showed that neither left (r2 = 0.15, Î² = â€'0.102, p = 0.56), nor right (r2 = 0.15, Î² = 0.13, p = 0.45) cingulum FA, adjusted for age and gender, were significantly associated with neuroticism. However, cingulum FA LI, adjusted for age and gender, significantly predicted neuroticism (r2 = 0.269, Î² = â€'0.372, p = 0.01). Note that left cingulum FA was significantly higher than right cingulum FA (p less than 0.0001). When exploring the diffusivities, cingulum Î»âŠ¥ LI (r2 =0.25, Î² =0.346, p=0.02), but not cingulum Î»|| LI (p=0.46), adjusted for age and gender, was significantly associated with neuroticism. No significant effects were observed for the uncinate fasciculus FA (p>0.49). Discussion/Conclusion The results suggest that diminished left-right asymmetry in cingulum FA (higher in right relative to left) is associated with higher neuroticism scores after adjusting for age and gender effects. The association was mainly driven by variability in cingulum Î»âŠ¥. Post hoc analysis revealed that the facets anxiety, angry hostility, depression and vulnerability were the main contributors to the observed associations. All these facets have previously been linked to major depression and anxiety disorders 8. One might speculate whether cingulum FA and Î»âŠ¥ asymmetries are possible markers of increased risk of developing anxiety and mood disorders. Future studies are necessary to address this question. Acknowledgments The Lundbeck Foundation is acknowledged for financial support. References [1] Omura et al. 2005 Neuroreport, 16(17): 1905-1908. [2] Pezawas et al. Nat Neurosci, 2005, 8(6): 828-834. [3] Pujol et al. Neuroimage, 2002, 15: 847-855. [4] Drevets et al., Nature, 1997, 386: 824-827. [5] Drevets and Savitz, CNS Spectr, 2008, 13(8): 663-681. [6] Costa and McCrae. NEO-PI-R: Professional Manual, 1992. [7] Smith et al. Neuroimage, 2006, 31(4), 1487-1505. [8] Bienvenu et al. J Nerv Ment Dis, 2001, 189:154-161.

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40.

The linker region between the PDZ and the BAR domain in PICK1 mediates curvature sensitive membrane binding

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Abstract

PICK1 (Protein Interacting with C Kinase 1) is a dimeric scaffolding protein containing a single PDZ domain in its amino-terminal part, and a BAR (Bin/amphyphysin/Rvs) domain in its C-terminal part. The PICK1-PDZ domain is known to mediate interaction with the C-termini of several receptors, transporters and kinases expressed in the CNS, including the GluR2/3 subunits of AMPA-type ionotropic glutamate receptors (AMPA receptors), the metabotrobic glutamate receptor mGluR7, the dopamine transporter (DAT), the norepinephrine transporter (NET) the Glt1b glutamate transporter and protein kinase CÎ±.The PICK1-BAR domain dimer is believed to mediate lipid membrane binding and remodelling. Within the BAR domain superfamily of proteins, the PICK1 BAR family, including also ICA69 and the Arfaptins, has so far been described to have classical BAR domains with the lipid binding property primarily attributed to the crescent shaped BAR dimer. Using a newly developed fluorescent based lipid binding assay that allows for single liposome detection, we show that the PICK1 group of BAR domain proteins all have N-terminal amphipathic helices like the N-BAR family containing Endophilin and Amphiphysin. Similar to the N-BAR family we demonstrate that the amphipatic helices are the major lipid binding motifs in PICK1, ICA69 and Arfatin. Moreover, the helices confer curvature dependent binding to these proteins independent of the BAR domains. PICK1 has been shown to be necessary for long term depression (LTD) probably by regulating trafficking rates of the GluR2 containing AMPA receptors, both by promoting internalization rates and slowing down recycling. By means of mutations and truncations in the helix of PICK1 we are currently investigating the role of curvature sensitive lipid binding for the function of PICK1 in relation trafficking of its interactions partners, including the AMPA receptor.

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41.

In vivo and in vitro Studies of PGE2 Receptors in the Rat Cranio-vascular System

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Abstract

Objective The objective of this study was to investigate the expression and function of prostaglandin E2 (PGE2) dilatory receptors, EP2 and EP4, in tissues relevant to headache pain. Background PGE2 is synthesized in substantial amounts at sites of inflammation where it acts as a potent vasodilator and mediator of pain. PGE2 exerts its dilatory response by two G-protein coupled receptors (EP2 and EP4) through cyclic adenosine monophosphate (cAMP) mediated in peripheral vascular beds. Clinical studies reported increased ictal levels of PGE2 in both blood and saliva of migraineurs. Furthermore, PGE2 can induce migraine-like headaches with the concomitant vasodilatation of cerebral vessels. Methods In vivo: Sprague-Dawley rats were used for intravital microscopy on a closed cranial window. We studied PGE2 (1-3000 ng kg-1), butaprost (EP2 receptor agonist) (1-100 Âµg kg-1) and ONO-AE1-329 (EP4 receptor agonist) (1-3000 ng kg-1) induced dilatation of the middle meningeal artery (MMA) (n=4-6/group). Furthermore, PGE2 (300 ng kg-1 i.c.) induced dilatation was studied in the absence and presence of: â€¢ BGC20-1531 (EP4 receptor antagonist) (100-3000 Âµg kg-1 i.c.) â€¢ AH6809 (EP2 receptor antagonist) (30-120 Âµg kg-1 i.c.) â€¢ SQ22536 (adenylate cyclase inhibitor) (30-100 Âµg kg-1 i.c.) (n=4-5/group). In vitro: Isolated rat MMA and middle cerebral artery (MCA) were investigated in organ baths. PGE2 (10 nM-10ÂµM) induced vasodilatation was studied in the absence and presence of BGC20-1531 (1 ÂµM), L-161,982 (1 ÂµM), AH6809 (10 ÂµM) and SQ22536 (30 ÂµM) (n=4-7/group). PGE2 receptor mRNA expression was investigated in MMA, MCA, basilar artery, trigeminal ganglion and trigeminus nucleus caudalis by use of conventional PCR. EP2 and EP4 receptors mRNA expression levels was performed with quantitative real-time PCR in the same tissues. Results In vivo experiments showed that dilatation to butaprost (Emax 110Â±18%, pED50 5.0Â±0.17) was less pronounced compared to PGE2 (Emax 207Â±43%, pED50 7.0Â±0.31) and ONO-AE1-329 (127Â±15%, pED50 7.4Â±0.09) in the MMA in vivo. BGC20-1531, AH6809 and SQ22536 significantly inhibited the PGE2 induced vasodilatory response in rats. Likewise, the used antagonists significantly inhibited the PGE2 relaxation in rat MMA and MCA in vitro. Conventional RT-PCR showed that all PGE2 receptors (EP1-EP4) mRNA were expressed in the tested neuronal tissues and arteries. However, quantification of the mRNA expression profile of the dilatory receptors (EP2 and EP4) showed dominance of these receptors in MMA and MCA as compared to the investigated neuronal tissues. Conclusions In conclusion, PGE2 induced vasodilatory responses both in vivo and in vitro. The response could be inhibited by EP2 and EP4 receptor antagonists, possibly via cAMP mechanisms. mRNA expression of the EP2 and EP4 receptors show that they are predominant in the arteries. Thus, these receptors could be potential and specific targets in the development of anti-headache drugs.

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42.

Alleviation of PCP-induced object recognition deficits in rats by modulation of GABAergic transmission

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Abstract

Schizophrenia is a complex psychiatric disorder in which several neurotransmitter systems are affected. Alterations have been shown in the GABAergic systems schizophrenic patients. Targeting GABAergic signalling pathways may thus present treatments strategies for schizophrenia. The psychotomimetic NMDA receptor antagonist phencyclidine (PCP) has been shown to induce schizophrenia-like symptoms in healthy individuals and exacerbate symptoms in schizophrenic patients. Sub-chronic dosing of rats with PCP induces several schizophrenia-like symptoms including cognitive deficits. In female Lister hooded rats sub-chronic PCP treatment induces deficits in the Novel Object Recognition (NOR) task. Inhibition via the GABAergic transmitter system is responsible for the synchronisation of neuronal activity and this synchronisation may be of importance in learning and memory. The present studies focus on the effect of the selective extrasynaptic GABAA receptor agonist Gaboxadol (THIP) and the positive modulator of extrasynaptic GABAA receptors AA29504 ([2-Amino-4-(2,4,6-trimethyl-benzylamino)-phenyl]-carbamic acid ethyl ester) on a PCP induced object recognition deficit. In several electrophysiological assays AA29504 has been shown to potentiate the effect of gaboxadol and this aspect was also tested in the NOR task. A positive effect of modulating GABAergic transmission in this animal model of schizophrenia was observed. In addition hereto AA29504 was shown to potentiate the effect of gaboxadol. These results indicate that positive modulation of GABAergic transmission may represent a novel target for the treatment of cognitive deficits in schizophrenia.

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43.

Systemic COMT Inhibition Enables the D1 Agonist Radiotracer [11C]-(R)-SKF82957

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Abstract

Objectives: The catechol D1 agonist, [11C]-(R)-SKF82957, ([11C]-SKF), is metabolised to a labelled, lipophilic, brain penetrating metabolite, limiting its use as a radiotracer for imaging dopamine D1 receptors. We investigated the effect of catechol-O-methyltransferase (COMT) inhibitors on the formation of the interfering metabolite. The objective was to obtain conditions whereby [11C]-SKF could be used to image the high-affinity state of the D1 receptor. Methods: Groups of rats were pre-treated with various doses of two COMT inhibitors, entacapone and tolcapone, prior to injection of [11C]-SKF. Radiolabelled metabolites in plasma and brain extracts were quantified by radio-HPLC. To determine specific binding to D1 receptors, rats were also pre-treated with the D1 antagonist, SCH 23390 (2 mg/kg) and activity in striatum and cerebellum counted to determine specific binding ratios (SBR). Results: All doses of either COMT inhibitor reduced the metabolism of [11C]-SKF. Concentrations of lipophilic metabolite in brain and plasma were concomitant. Under best conditions (20 mg/kg tolcapone IP) essentially no lipophilic metabolite could be detected in brain or plasma. SBR increased from 14.4±1.6 in the non-COMT treated group to 23.3±3.3 upon best COMT treatment (n=>6). Pretreatment with SCH 23390 reduced the SBR to 0.66±0.2, demonstrating the specificity of binding of [11C]-SKF to D1 receptors. Conclusions: Conditions have been determined which enable the use of [11C]SKF as an agonist radiotracer for PET imaging of dopamine D1 receptors. Inhibiition of radiolabeled lipophilic metabolites enables the assessment of the sensitivity of [11C]SKF dopamine D1 binding to changes in endogenous dopamine levels.

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44.

Neuroprotective properties of a novel, non-hematopoietic agonist of the erythropoietin (EPO) receptor

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Abstract

Erythropoietin (EPO) is a cytokine that controls proliferation and differentiation of erythroid progenitor cells through binding to and dimerization of the EPO receptor (EPOR). EPO and EPOR are also expressed in the central nervous system, where they are involved in tissue protection. However, the use of EPO as a neuroprotective agent may be hampered by its erythropoietic activity. Therefore, developing non-hematopoietic EPO mimetics with neuroprotective activities is important. Here we designed a peptide, termed Epotris, corresponding to the a-C helix region of human EPO. The peptide specifically bound to EPOR and induced neurite outgrowth from cerebellar and hippocampal primary neurons. Knockdown of EPOR, as well as interference of EPOR downstream signaling, abrogated the peptide-induced neuritogenic response, indicating that the effects of Epotris were mediated by EPOR. We also demonstrate that systemically administered Epotris penetrates the blood-brain barrier and has both anti-epileptic and neuroprotective effects in an animal model of KA-induced neurotoxicity. Multiple neuroprotective doses of Epotris do not stimulate hematopoiesis in vivo, what makes Epotris an attractive drug candidate for the treatment of neurodegenerative disorders.

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45.

Metallic gold treatment induces neuroprotective astrocytosis and evokes stem cell response in a rodent model of Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is the most common neurodegenerative disease in the Western world. MS mainly affects younger, healthy individuals and as of today no curative treatment against the disease exists. Recurring attacks of demyelination and the underlying neuroinflamation, ultimately leads to loss of neurons and focus is thus given to treatments slowing down the course of the disease. Recent research has revealed that localized bio-liberation of gold ions from metallic gold implants ameliorate inflammation, reduce apoptosis and promote proliferation of neural stem cells in a mouse model of focal brain injury. Based on these findings, the present study is the first to investigate whether metallic gold implants induce a neuro protective response, in Experimental Autoimmune Encephalomyelitis (EAE), a rodent model of MS. Metallic gold particles 20-45 Âµm suspended in hyaluronic acid were injected bilaterally in the lateral ventricles (LV) of young Lewis rats prior to EAE induction. Gold-treated animals were compared to vehicle (vehicle). A statistically significant up-regulation of GFAP positive reactive astrocytes was seen in periventricular areas, both next to the lateral fourth ventricle. Selective immune staining for NSC proliferation was performed using frizzled-9, showing a statistically significant up-regulation of the number of NSCs migrating from the subventricular zone into the surrounding area. Furthermore an up-regulation of MT1+2 was seen in corpus callosum. Microgliosis, as evaluated by lectin stain was, however, not affected by gold treatment in the present model. In conclusion: Gold implants induce astrogliosis throughout the brain and elicit a NSC response in an animal model of MS. Such implants could thus prove beneficial in future treatments against MS.

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46.

Serotonin induces central fatigue by inhibiting sodium channels at the axon initial segment of motoneurons

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Abstract

Fatigue is the companion of everyday activities. Fatigue is in part related to the energy depletion of muscles induced by intense or repeated motor activity. In addition, fatigue has a significant component that originates in the central nervous system. Part of this â€œcentral fatigueâ€ is caused by a decrease in the excitability of motoneurons (Butler et al., J Neurosci. 2003; 23(32):10224-30). Moreover, indirect evidence suggests that central fatigue is increased by serotonin (5-HT). However, no mechanism linking serotonin and fatigue has been found. The goal of the present study was to investigate cellular mechanisms that could explain how 5-HT induces central fatigue. First, we tested if a massive synaptic release of 5-HT could induce central fatigue. For this purpose, we used an isolated carapace-spinal cord preparation of the adult turtle. This preparation can produce reproducible scratch reflexes. We found that the intensity of firing recorded in a hip flexor nerve during scratch episodes was strongly reduced after a prolonged stimulation of the dorsolateral funiculus (DLF) (3 minutes, 5-10 Hz). This effect disappeared when the spinal cord was perfused with the 5-HT1A receptor antagonist WAY100635 (10ÂµM). We then tested if the inhibitory effect occurred at the level of motoneurons. For this, we made a thin slice preparation from the spinal cord of the turtle. We recorded motoneurons with the visually guided whole-cell patch clamp technique. We applied the 5-HT1A/7 receptor agonist 8-OH-DPAT (20 - 40 mM) with a microiontophoresis electrode positioned at different compartments of the recorded motoneuron. The release of 8-OH-DPAT at the axon initial segment (AIS) inhibited the genesis of action potentials. This effect persisted in the presence of the 5-HT7 receptor antagonist SB267790 (10ÂµM). Electrophysiological tests showed that the activation of 5-HT1A receptors inhibited a sodium current. When tested in other compartments of the motoneuron (soma, dendrite, distal axon), 8-OH-DPAT did not show any effect on sodium currents. This demonstrates that the activation of 5-HT1A receptors at the AIS can regulate the output of motoneurons. Immunohistochemical observations have shown that the somatodendritic membrane of motoneurons is covered with synaptic buttons. However, no serotonergic synapses has been reported on the AIS. For this reason we suggest that the 5-HT1A receptors at the AIS are activated only during massive release of serotonin from synaptic buttons, by a spillover mechanism.

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47.

Respiratory activity at the level of the facial nucleus revealed by field recordings and calcium imaging in P0-P4 mice.

Authors: Persson, K, Fortin, G and Rekling, J.C.

Poster submitted by Karin Sigrid maria Persson on Saturday, October 31, 2009

Affiliations: Department of Neuroscience and Pharmacology, Copenhagen University, Denmark and Laboratoire de Neurobiologie Génétique et Intégrative, Institut Alfred Fessard, Centre National de la Recherche Scientifique, 91198 Gif sur Yvette, France.

Abstract

Respiratory-related activity can be recorded in facial nerves in vivo, and has been linked to activation of facial muscles controlling the air passage through the nose. In vitro experiments in rats suggest that the facial nucleus receive respiratory drive from inspiratory neurons in the preBÃ¶tzinger Complex, but also from pre-I neurons located in the para-facial respiratory group. To further understand the spatiotemporal organization of respiratory-related activity in the facial and para-facial region we performed electrical field recordings and calcium imaging in brainstem-spinal cords preparations from newborn mice (P0-4). The brainstem was cut at level of the facial nucleus (on one or both sides), maintained under standard in vitro conditions, and we used patch-clamp type glass pipettes to record field potentials at visually identified positions within the facial nucleus. Field potentials in phase with spontaneous activity on the contralateral VII nerve root was found predominantly in the lateral part of the facial nucleus. Next, we loaded brainstem spinal cord preparations with a calcium-sensitive dye (Fluo-8,am) and recorded calcium transients in neurons located at the cut surface. Calcium transients in phase with respiratory-related activity on cervical nerves (C3-C5) were observed within the boundaries of the facial nucleus. The strongest signals were observed over the lateral part of the facial nucleus. In conclusion, we suggest that the respiratory-related activity in the lateral part of the facial nucleus observed here may reflect activity in nasolabial motoneurons that innerve muscles in the alae nasi, which may be important for maintaining upper airway patency.

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48.

INCREASED VOLTAGE-DEPENDENT Na INFLUX IN MOUSE MOTOR AXONS DEFICIENT OF THE MYELIN PROTEIN P0

Authors: M. Moldovan (1); S. Alvarez (1); V. Pinchenko (1); F.C. Nielsen (2); R. Martini (3) C. Krarup (1, 4)

Poster submitted by Volodymyr Pinchenko on Saturday, October 31, 2009

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Abstract

Mice expressing half of the normal dose of the myelin protein zero (P0+/- mice) and mice completely deficient of P0 (P0-/- mice) are models for distinct forms of inherited neuropathies. P0+/- mice have almost normal myelin during the first months of life and later develop a slowly progressing demyelinating neuropathy. In contrast, P0 -/- mice display a severe neuropathy with compromised myelin compaction and axonal loss from birth. In a previous histological study we reported that P0-deficient motor nerves may have an altered expression of Na channel isoforms, however, the extent and functional consequences of this abnormality remained unknown. The aim of this study was to investigate in vivo the motor axon membrane function in P0 -/- and P0 +/- mice. Conventional nerve conduction studies and nerve excitability studies by â€œthreshold-trackingâ€ were carried out under anesthesia in 2-16 month-old P0-deficient mice. Tibial nerves were stimulated at the ankle and the evoked motor responses were recorded from the plantar muscles. At 2 months, P0 +/- mice were undistinguishable from controls. In contrast, P0 -/- mice already showed motor responses delayed at least 200% , amplitudes reduced below 20% and marked excitability abnormalities consistent with membrane depolarization and increased voltage-dependent Na+ currents. At 16 months P0 +/- mice showed a 50% delay in motor conduction, however, the deviations in excitability measures were reminiscent of those observed in regenerated axons and were attributed to the short internodal length acquired after demyelination and remyelination. Our data suggest that increased voltage-dependent Na+ influx in motor axons is a gain-of-function in P0 deficiency, depending on the P0 expression levels. Na-mediated axonal degeneration should therefore be considered as a potential pathogenic mechanism in inherited neuropathies with P0 mutations.

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49.

Spontaneous calcium transients in inferior olive neurons recorded in slices from newborn mice

Authors: Jens. C. Rekling and Henrik Jahnsen

Poster submitted by Jens Rekling on Saturday, October 31, 2009

Affiliations: INF

Abstract

One model (Jacobsen et al. TINS, 31, 617-625, 2008) of the function of the olivo-cerebellar system posits that synchronized activity in the inferior olive (IO) supply the cerebellum with patterned temporal information necessary for execution of precisely timed movements. In rodents complex coordinated movements develop over the course of the first two postnatal weeks, and we hypothesized that this motor development could be accompanied by a development of patterned activity in the IO. To record activity in the IO we euthanized P0-P14 mice, dissected out the brainstem, and cut 850 Âµm thick slices with the rostral cut placed at the rostral part of the IO. The slices were loaded with a calcium-sensitive dye (Fluo-8,am, 20 ÂµM) for 1Â½ h, placed in a recording chamber, and fluorescence from the IO area and individual IO neurons located at the cut surface was recorded. The entire IO showed spontaneous calcium transients, visible as 0.05-0.2 Hz oscillatory signals in individual neurons. Coherence analysis showed that calcium signals from nearby neurons (less than 200 Âµm) intermittently were synchronized in older animals (>P5), in particular in the region of the medial accessory olive. Gap junctions between individual IO neurons in rats are believed to begin to form around P7-10, which corresponds well with the occurrence of intermittently synchronized activity reported here. Thus, spontaneous synchronizing mechanisms in the IO are present in in vitro slices obtained from early postnatal mice, and may reflect the development of functional gap junctions.

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50.

The total number of myelinated fibers in the Corpus Callosum of normal Danish males

Authors: Riise J. (1), Gundersen HJ. (2), Pakkenberg B. (1)

Poster submitted by Jesper Riise on Saturday, October 31, 2009

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Abstract

For decades, Corpus Callosum (CC) has been an object of extensive research in the understanding of interhemispheric connectivity as well as elucidating callosal changes in a wide variety of neurodegenerative disorders incl. ALS, Parkinsons and Alzheimers and psychiatric disorders such as Schizophrenia. However, quantitative investigations concerning the total number of callosal fibers have received little attention and in vitro studies addressing the issue show considerable variations. In recent years in vivo studies using different variations of MRI such as Diffusion Tensor Image (DTI) and Fiber Tractography has been the preferred method in the investigation of corpus callosum morphology. However, the resolution of the images has been too weak to distinguish individual fibers and provide a true estimate of the total number of fibers. In the present study a stereological method based on the fractionator principle was applied to quantitatively estimate the total number of myelinated callosal fibers, their distribution and average diameters along the CC in ten males ranging from the age of 39 years to 60 years. Additionally, correlation to neocortical neuron numbers and age was examined.

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51.

Investigations of circadian gene expression in the pineal gland of the 129SV and the cone-rod knock out mouse (Crx-/-)

Authors: 1,2 Louise Rovsing, 1 Martin F. Rath, 2 David C. Klein and 1 Morten møller

Poster submitted by Louise Rovsing on Sunday, November 01, 2009

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Abstract

The cone-rod homeobox gene (Crx) encodes a transcription factor, which is specifically expressed in the retinal photoreceptors and in the melatonin secreting pinealocytes of the pineal gland. In the retina, Crx-expression is essential for the development and maintenance of cones and rods. In the pineal gland, Crx is involved in the transcriptional regulation of two important enzymes in the melatonin synthesis, HIOMT (hydroxyindole O-methyltransferase), and AANAT (arylalkylamine N-acetyltransferase). Both of these enzymes show a strong circadian expression with zenith during night time. We have in this study examined whether Crx is important for the expression of other rhythmic genes in the mouse pineal gland. This was done by Affymetrix mouse GeneChip analysis of the gene expression during night and day (ZT6 and ZT20) in 48 wild type mice and comparing of these data to the expression of 48 Crx-knock out (Crx-/-) mice. We found in the pineal of the Crx-/- mouse a down regulation of 562 genes (2 fold) and an up regulation of 745 genes (2 fold) compared to the wild type. Surprisingly, the homeobox gene, Hoxc4, which has been shown to be involved in development of oesophagus and spinal cord was, in the Crx-/- mouse 17.5 fold up regulated compared to the wild type. Further, in the Crx-/- mouse, 49 genes exhibited a circadian expression compared to 51 genes in the wild type mouse. In the Crx-/- mouse, 55% of the rhythmic genes were up regulated during the night time compared to 33% in the wild type mouse.

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52.

Comparison of the effects of modafinil, erythropoietin, sertindole and CX516 in the sub-chronic and neo-natal PCP models of schizophenia in the rat attentional set-shifting assay.

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Poster submitted by Trine Lund Ruus on Saturday, October 31, 2009

Affiliations: In-vivo Neurobiology, H. Lundbeck A/S, Valby

Abstract

Impairment in cognitive function is a major hallmark in schizophrenia that remains inadequately treated by existing antipsychotics. Executive function, the cognitive domain that is responsible for planning and rule acquisition, is among the most severely affected abilities in schizophrenia with an impact on shifting strategy and adapting to novel situations. Schizophrenic patients display impaired extra-dimensional set-shifting performance in clinical attentional set-shifting tasks (ID/ED), a readout for executive function. Acute and repeated administration of the NMDA receptor antagonist (phencyclidine) PCP is known to induce schizophrenia-like symptoms in healthy subjects and to worsen these symptoms in schizophrenic patients. Along these observations, neonatal PCP administration in rats has previously been shown to impair executive function in a rat ID/ED task. In schizophrenic patients, erythropoietin (EPO) and the wake-promoting agent modafinil have been shown to improve executive function evident by increased ED shift performance in an ID/ED task. Moreover, compounds targeting the glutaminergic system such as the ampakine CX516 has been shown to improve cognitive dysfunction in schizophrenic patients. The second generation antipsychotic sertindole has previously been shown to reverse an impairment executive functioning in animals subchronically treated with PCP, whereas the effect of sertindole in animals administered PCP neonatally has not been addressed. In this study, we compared the effects of modafinil, erythropoietin, sertindole and CX516 in the sub-chronic and neonatal PCP models of schizophrenia in the rat attentional set-shifting assay.

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53.

Cutaneous nociception and neurogenic inflammation evoked by VIP and PACAP38: a human experimental study

Authors: Henrik Winther Schytz1, Helle Holst2, Lars Arendt-Nielsen2, Jes Olesen1 and Messoud Ashina1

Poster submitted by Henrik Winther Schytz on Saturday, October 31, 2009

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Abstract

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide-38 (PACAP38) are found in nerve fibres surrounding cephalic vessels, but only PACAP38 infusion induces migraine-like attacks. The present study aimed to investigate the nociceptive and vasomotor responses following VIP and PACAP38 in a human experimental model. In a double-blind, placebo-controlled, crossover design 16 healthy subjects were allocated to receive intradermal injections of 200 pmol VIP, 200 pmol PACAP38 and placebo into the volar forearm. Measurements included pain intensity, allodynia, alloknesis, pinprick hyperalgesia, visual flare and wheal. Skin blood ï¬‚ow was measured by laser Doppler ï¬‚owmetry. Pain intensities after VIP and PACAP38 were mild and limited to a short time of about 100 s after injection. The area under the VAS-time curve was larger following VIP (P = 0.01) and PACAP38 (P = 0.004) compared to placebo. The pain distribution area was larger after VIP (P = 0.023) and PACAP38 (P = 0.001) compared to placebo. The area of punctuate hyperalgesia was larger after VIP (P = 0.006) and PACAP38 (P = 0.011) compared to placebo. Skin blood flow increase, flare and wheal were larger after both VIP (P = 0.001) and PACAP38 (P = 0.011) compared to placebo. VIP induced a considerably larger increase in skin blood flow, flare and wheal than PACAP38 (P = 0.002). These data show that VIP and PACAP38 induce pain, central sensitization, neurogenic inflammation and mast cell degranulation in the human skin, which are likely mediated via the VPAC receptors.

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54.

Spatiotemporal regulation of aquaporin-4 in the kaolin induced hydrocephalic rat brain – experimental study using in vivo MRI and immunological methods.

Authors: AD Skjolding1,5, I Rowland2, L Soegaard3, J Praetorius4, M Penkowa5 and M Juhler1.

Poster submitted by Anders Dæhli Skjolding on Saturday, October 31, 2009

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Abstract

Background AQP4 is responsible for compensatory cerebrospinal fluid (CSF) circulation pathways and we study the spatiotemporal regulation of aquaporin-4 (AQP4) in hydrocephalus. Main hypothesis: Aquaporins (AQP) can be a pharmacological target in treatment of hydrocephalus and other brain diseases with disturbances in CSF circulation. We hypothesize that: â€¢ Aquaporin expression is regulated spatiotemporal during hydrocephalus. â€¢ Pharmacologic intervention, resulting in regulation of AQP can change the course of hydrocephalus and mediate a neurobiological response. â€¢ Histopathology in hydrocephalus is correlated to AQP-exspression. Marterials and methods 33 rats (Tac:SPRD, ~290g) received a intracisternal injection of 0,050 ml of sterile kaolin suspension, and were randomized into 3 groups (2 days (n=10), 1 week (n=10), 2 weeks (n=10)). Eleven control rats received an injection of 0,050 ml Ringers Lactate. 91% of all rats survived the injection procedure. MR-imaging was performed after the observation period using a 4.7T system. Three optimized sequences were used. Brain tissue samples were prepared for AQP4 immunoblotting and immunohistochemistry. Differences between groups (Mean Â± SE) were statistically evaluated. Results We found significant difference (p less than 0.01) in ventricular size between control group and all other groups. Furthermore we found significant difference in periventricular ADC value in the control group and the 3 groups. This indicates periventricular edema in the hydrocephalic rats. No difference in BBB integrity was found. Using immunoblotting we found significant dowregulation of AQP4 expression in both cerebral and periventricular ROIs after 2 days. After 1 week the expression of AQP4 was normalized, and in the 2 week group the AQP4 expression was significantly increased in the periventricular region. Conclusion Data from immunoflourescence and immunohistochemistry are still preliminary. Our results show that the AQP4 expression is changed through spatiotemporal regulation in our experimental model. Final data analysis of all ROIs is needed for clear out any correlation between AQP4 expression and ventricular enlargement and oedema (quantified by MRI) in the hydrocephalic brain. Further studies on regulation of aquaporins and histopahology in our model are needed to answer our hypothesis.

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55.

In Search of AMPA-Receptor Subtype Selective Agonists. Convergent Synthesis, Pharmacology, and X-ray Crystallography of Substituted Tetrazolyl-AMPA Analogs.

Authors: Stine B. Vogensen,† Karla Frydenvang,† Jeremy R. Greenwood,† Birgitte Nielsen,† Darryl S. Pickering,‡ Bjarke Ebert,§ Tommy N. Johansen,† Rasmus P. Clausen† and Povl Krogsgaard-Larsen†

Poster submitted by Stine Byskov Vogensen on Saturday, October 31, 2009

Affiliations: †Department of Medicinal Chemistry and ‡Department of Pharmacology and Pharmacotherapy, The Faculty of Pharmaceutical Sciences, University of Copenhagen and §Department of Electrophysiology, H. Lundbeck A/S, Denmark

Abstract

Purpose: To investigate the structure-activity relationship of a series of 1- and 2-substituted tetrazolyl-AMPA analogs with the aim of designing subtype selective agonists for the pharmacological characterization of the different AMPA-receptor subtypes. Methods: A new convergent synthesis method was developed for the synthesis of analogs of 2-Me-Tet-AMPA. The in vitro pharmacological characteri-zation included receptor [3H]-binding (AMPA, NMDA and KA) on rat brain homogenate and on cloned AMPA-receptor subtypes expressed in Xenopus oocytes. Functional characterization was done using the rat cortical wedge preparation. An X-ray crystal structure of the 2-benzyl analog in complex with the GluR2-S1S2J construct was obtained. Results: Unlike the 1-substituted alkyl isomers, which were devoid of activity at AMPA receptors, the 2-substituted alkyl isomers were selective agonists, and their activity correlated inversely with the size of the alkyl substituent in the tetrazole ring. The 2-benzyl analog showed a more than 10-fold subtype selectivity preferring GluR2âˆ’4 to GluR1. The X-ray crystallographic analysis of this new 2-benzyl analog in complex with the GluR2-S1S2J construct showed that accommodation of the benzyl group creates a previously unobserved pocket in the receptor, which may explain the remarkable pharmacological profile. Conclusions: Increasing the size of the alkyl substituent at the potent AMPA agonist 2-Me-Tet-AMPA resulted in a decreased agonist activity. Surprisingly, introduction of the large 2-benzyl substituent resulted in an increased subtype selectivity. These results are important for the further rational design of subtype selective ligands targeting the AMPA receptor.

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56.

In Search of AMPA-Receptor Subtype Selective Agonists. Convergent Synthesis, Pharmacology, and X-ray Crystallography of Substituted Tetrazolyl-AMPA Analogs.

Authors: Stine B. Vogensen,† Karla Frydenvang,† Jeremy R. Greenwood,† Birgitte Nielsen,† Darryl S. Pickering,‡ Bjarke Ebert,§ Tommy N. Johansen,† Rasmus P. Clausen† and Povl Krogsgaard-Larsen†

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Abstract

Purpose: To investigate the structure-activity relationship of a series of 1- and 2-substituted tetrazolyl-AMPA analogs with the aim of designing subtype selective agonists for the pharmacological characterization of the different AMPA-receptor subtypes. Methods: A new convergent synthesis method was developed for the synthesis of analogs of 2-Me-Tet-AMPA. The in vitro pharmacological characteri-zation included receptor [3H]-binding (AMPA, NMDA and KA) on rat brain homogenate and on cloned AMPA-receptor subtypes expressed in Xenopus oocytes. Functional characterization was done using the rat cortical wedge preparation. An X-ray crystal structure of the 2-benzyl analog in complex with the GluR2-S1S2J construct was obtained. Results: Unlike the 1-substituted alkyl isomers, which were devoid of activity at AMPA receptors, the 2-substituted alkyl isomers were selective agonists, and their activity correlated inversely with the size of the alkyl substituent in the tetrazole ring. The 2-benzyl analog showed a more than 10-fold subtype selectivity preferring GluR2âˆ’4 to GluR1. The X-ray crystallographic analysis of this new 2-benzyl analog in complex with the GluR2-S1S2J construct showed that accommodation of the benzyl group creates a previously unobserved pocket in the receptor, which may explain the remarkable pharmacological profile. Conclusions: Increasing the size of the alkyl substituent at the potent AMPA agonist 2-Me-Tet-AMPA resulted in a decreased agonist activity. Surprisingly, introduction of the large 2-benzyl substituent resulted in an increased subtype selectivity. These results are important for the further rational design of subtype selective ligands targeting the AMPA receptor.

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57.

Effects of HSP90 inhibitors on tau hyperphosphorylation in neurons

Authors: Christiane Volbracht, Rachel M. Bailey, Jada Lewis

Poster submitted by Christiane Volbracht on Saturday, October 31, 2009

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Abstract

The molecular chaperones have been implicated in numerous neurodegenerative disorders in which the defining pathology is misfolded proteins and the accumulation of protein aggregates. In Alzheimerâ€™s disease (AD), the tau protein dissociates from microtubules and forms aggregates of hyperphosphorylated tau protein termed neurofibrillary tangles (NFT), which are neuropathological hallmarks of the disease. Misfolded proteins can undergo refolding and stabilization mediated by the 90 kDa heat shock proteins (HSP90). Inhibitors of HSP90 trigger HSP90 complexes inter alia with HSP70 and chaperone carboxyl terminus of Hsc70-interacting protein (CHIP) driving misfolded proteins such as phosphorylated tau species towards proteasome-mediated degradation. We established neuronal cultures from wildtype mice and characterized different cell-permeable HSP90 inhibitors, which displayed a concentration-dependent upregulation of HSP70 and HSP40 in the 100-1000 nM range. The HSP90 inhibitors exhibited no cytotoxicity in primary neurons at the highest concentration (10 ÂµM) tested. We observed significant reduction of tau phosphorylation at phospho-specific epitopes shown to be phosphorylated in AD brains without affecting the total tau protein expression in neurons. The HSP90 inhibitors were effective on HSP70 induction and reduction of phosphorylated tau in a similar concentration range. Additionally, we characterized HSP90 inhibitors in CHO cells overexpressing human mutant tau (TauP301L). Here, we observed a substantial decrease of total and phosphorylated mutant tau in a concentration dependent manner with the HSP90 inhibitors. Our results suggest that HSP90 inhibitors may indeed help neurons to clear misfolded proteins such as hyperphosphorylated tau that contribute to the pathogenesis of AD.

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58.

Association of an potential anti-cancer inhibitor, Inherbin3 with ErbB receptor in primary rat neurons

Authors: Ruodan Xu

Poster submitted by Ruodan Xu on Saturday, October 31, 2009

Affiliations: Elisabeth Bock, Vladimir Berezin

Abstract

Tyrosine kinase receptors and their ligands allow communication between cells in the developing and adult organism. Like other tyrosine kinase receptors, ErbB receptors function not only in cancer, but are key developmental regulators. In previous study, we showed that an ErbB derived peptide, Inherbin3 functions as an antagonist of epidermal growth factor (EGF) â€' ErbB1 signalling in cancer cells. In present study, we examined the expression of ErbB1, ErbB3 and ErbB4 in cerebellar granule neurons, and ErbB1 and ErbB4 are shown to play opposite roles in neurite outgrowth regulation in CGNs. It is demonstrated that EGF removal affects human neural precursor cells (hNPC) fate and plasticity (Telma et al. 2009), Thus, Inherbin3 may has potential broader effect for NPC differentiation.

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