miRNA profiling in plasma from patients with sleep disorders reveals dysregulation of miRNAs in narcolepsy and other central hypersomnias

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Introduction: miRNAs have been implicated in the pathogenesis of human diseases including neurological disorders. The aim is to address the involvement of miRNAs in the pathophysiology of central hypersomnias including narcolepsy with cataplexy and hypocretin deficiency (NC), narcolepsy without cataplexy (NwC) and idiopathic hypersomnia (IH) in comparison with healthy controls (HC).

Materials and methods: We conducted high-throughput analysis of miRNA in plasma from patients with NC, NwC and IH in comparison with HC using quantitative real-time polymerase chain reaction (qRT-PCR) panels. Data were analyzed with the following softwares: GenEx qRT-PCR data analysis, miRNA expression atlas in normal tissues and DIANA-mirPath pathway analysis.

Results: Using analysis of miRNA in plasma with qRT-PCR we identified 50, 24 and 6 miRNAs that were changed in patients with NC, NwC, IH, respectively, compared to HC. Twenty miRNA candidates which fulfilled the criteria of twofold change and p-value < 0.05 were selected for validation of miRNA changes in an independent cohort of patients. Four miRNAs were significantly changed between NC patients and HC. Levels of miR-30c, let-7f and miR- 26a were increased, whereas the level of miR-130a was decreased in NC compared to HC. The miRNAs changes were not specific for NC, since the levels of the four miRNAs were also altered in patients with NwC and IH compared with HC.

Conclusion: The levels of four miRNAs are changed in plasma from patients with NC, NwC and IH suggesting that alterations of miRNAs can be involved in the pathophysiology of central hypersomnias.

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Analysis of ciclic alternating patterns in Agrypnia Excitata (AE): insights from a case of limbic autoinmune encephalopathy (AE-LAE)

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Introduction: Agrypnia Excitata'' (AE) is a term coined originally by Lugaresi and Provini to describe a syndrome caused by a dysfunction in thalamo-limbic circuits producing severe insomnia, mental confusion, dream enactment, motor and autonomic activation. This syndrome is observed in fatal familial insomnia (FFI), limbic autoinmune encephalopathy, delirium tremens and the Mulvihill-Smith syndrome. Oscillatory EEG rhythms could be observed in these patients, resembling the named cyclic alternating pattern (CAP) in NoREM sleep, but, during REM sleep (''pseudosleep'') in patients with FFI (Garay A., Neurology 1994). Now, we attempt to characterize a peculiar CAP rhythm observed in our case of proven LAE.

Materials and methods: We analyzed polysomnograms of our case of LAE-VGKC (PSGs, $n = 3$). During PSGs the following variables were monitored: electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), nasal and oral airflow, thoracic and abdominal effort and pulse oximetry. Sleep-wake patterns were scored in 30 s. epochs according standard criteria (AAMS2007) and 3–5 s epochs for spectral analysis of the frequency components from Fast Fourier Transform (FFT) of the raw data of EEG and ECG activities and thorough continuous wavelet transform (CWT) using a multirresolution wavelet filter (Daubechies-level 7) we analyzed synchronized EEG–ECG activity removing muscular artifacts related to CAP rhythm.

Results: (a) LAE was characterized by a drastic decrease of TST, sparse atypical REM/NoREM sleep and for a CAP rhythm during states named as quiet and active wakefulness (qW–aW), (b) LAE intrawakefulness structure showed a CAP rhythm with an increase of 30–60 s centered bursts ($p < 0.05$. K.W. NP test), (c) wakefulness EEG activity showed oscillations bellow 1 Hz, (d) CWT ECG R-R interval analysis showed reduced variability when analyzing qW–aW transitions.

Conclusion: The AE-LAE case of this study presented sparse episodes of atypical sleep and showed presleep behavior during quiet and active wakefulness with a CAP behavior expressed as brief episodes of motor quiescence and overactivity. The observed reduction of variability of CWT R-R interval analysis and background FFT EEG activity bellow 1 Hz could be related to thalamo-cortico-limbic alterated modulation/disconnection and to the appearance of cortical top-down oscillations liberated of caudal- rostral influences (Kuhn B. et al. PNAS, 2008). Thus, subtyping AEs could be a way to the understanding of the role of thalamus regulation in wakefulness and sleep during health and illness.

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Facial muscle contractions during REM sleep and its association to emotional dreamed content

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Introduction: Facial muscle contractions (FMC) are features commonly associated with emotional expression during waking, yet poorly studied during sleep. Recent studies show a pattern in both healthy subjects and patients with major depression during sleep in which FMC have a significantly higher frequency and amplitude during Rapid Eye Movement (REM) sleep than in non-REM (NREM) sleep and that they are associated to the Rapid Eye Movements (REMs) in this sleep stage. Notably, REMs are also associated with emotional dream mentation (EDM). Yet, the possible functional relationship between FMC and EDM, remains unexplored. This study analysed FMC of the corrugator and zygomatic major – two facial muscles typically associated with emotional expression – and explores possible temporal correlations of EDM in healthy subjects during REM sleep. Additionally, it examined the interaction between FMC and REMs with EDM.

Materials and methods: Two 8 h sleep recordings were obtained from 6 female volunteers. Facial EMG recordings were obtained from the corrugator supercilii and zygomatic major (left and right) muscles. Sleep was scored using the standard AASM criteria. On the second night, FMC were visually measured. Experimental awakenings exploring EDM (through narration, rating of a dream scale, and Dreams Qualified Report) were performed during REM sleep stages that lasted at least three minutes, they were determined by a FMC

that lasted more than 100 ms and by the amplitude of any facial muscle that exceeded by 500% the background EMG activity. Additionally, experimental awakenings were performed during NREM and REM sleep stages without FMC. Following sleep recordings, FMC and REMs were quantified and analyzed for possible correlations between them. EDM global scores were gauged by exploring their correlation coefficients.

Results: Periods with FMC and REMs were associated to higher levels of EDM in healthy subjects as compared to periods without FMC. Moreover, EDM modality (e.g. happy vs. anxious) was linked to certain muscle activation (e.g. higher FMC of zygomatic vs. lower corrugator).

Conclusion: The present study shows that during REM sleep with FMC (vs. periods without FMC) the corrugator, zygomatic muscles and REMs are associated to EDM. Additionally, FMC were differentially associated to emotional modality according to the activated facial muscle. Altogether, these findings are consistent with theoretical perspectives of higher emotional variations during REM sleep associated to dream content. Implications are discussed.

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Sleep deprivation induce morphology changes in the hippocampus and prefrontal cortex in young and old rats

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Introduction: During normal aging several changes in sleep/wake patterns are observed, which include frequent awakenings during sleep and increased daytime naps, among others. Likewise, aging has also been associated with a deterioration of cognitive function, learning and memory, although widespread loss of nerve cells does not occur, the most of age-related structural changes observed in nerve cells are modifications in dendrites, dendritic spines or even axons. Evidence accumulated over the last years indicates that these functional changes observed during sleep loss, aging, or both could be due to modifications in synaptic connectivity and intracellular signaling; for example, excitatory synaptic transmission at the hippocampal CA1 region is affected by sleep deprivation; in the locus coeruleus (involved in both arousal system and cognitive performance) the number of neurons projecting to areas such as the cortex and the hippocampus declines with age. Therefore, it has been hypothesized that sleep deprivation may compromise neurophysiological and behavioral events; however, relatively few studies have investigated links between sleep loss and structural changes in neurons and, despite the seemingly similar effects of age and sleep deprivation on cognition and the prevalence of sleep changes with age, little is known about the impact of sleep loss on cellular morphology in aging neurons. For that reasons, the aim of this study was to evaluate the effects of total sleep deprivation on neuronal morphology in the hippocampus and prefrontal cortex of both young and aged animals.

Materials and methods: A total of 28 male Wistar rats (14 ''young-adult'' rats, 3–4 months old; 14 ''aged rats'', 22–23 months old; 7 for control and 7 for sleep deprivation for each age) were used in this study. Total sleep deprivation was carried out in both experimental groups (young-adult and aged, $n = 7$ per group) by gentle handling: once sleep-behaviour was observed or low amplitude waves first appear in sleep recording, rats were softly touched in their tails, whiskers or handling them to prevent falling asleep during 24 h. Immediately after sleep deprivation finished, animals were deeply anesthetized with sodium pentobarbital (75 mg/kg, i.p.) and then perfused intracardially with 0.9% saline solution. Brains were removed and stained by modified Golgi-Cox method. Pyramidal neurons from layer 3 of prefrontal cortex and hippocampus (CA1 area) were selected for study. Five neurons from each region of each brain hemisphere per animal were drawn using a camera lucida. Basal dendrites, including all branches, were reconstructed for each neuron and their dendritic tracings were quantified by Sholl analysis.

Results: Results showed that total dendritic length of prefrontal cortex and hippocampus was not affected either age or after 24 h of sleep deprivation compared to their corresponding control group. However, after 24 h of sleep deprivation (SD) aged animals had an increase in spine density in prefrontal cortex but not in hippocampus.

Conclusion: Sleep deprivation could be considered a factor that induces neuronal plasticity, which may depend on age.

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Melatonin for sleep disorders: a bibliometric approach during the last 20 years

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Introduction: Melatonin is a neurohormone that it has high interest for sleep researchers. There are some substances uses for sleep disorders. In this sense, melatonin prolonged release has been approved like drug for treatment of primary sleep disorder, and included in a new class of drugs: melatoninergic agonist. We would like to review, first of all the evolution of scientific research about use of melatonin in sleep disorder, and then the evolution of scientist's paper about melatonin's formulation, covering the period 1993- 2012.

Materials and methods: Using Medline database we selected those document that content in their title one or several of the following descriptors: ''sleep disorder*'' and ''melatonin*''. This study took into account all original articles, brief reports, reviews, editorials, letters to the editor, and so on. One of main bibliometric laws were applied: Price's Law on the increase in scientific literature. This law, undoubtedly the most widely used indicator for the analysis of productivity in a specific discipline or a particular country, takes into account an essential feature of scientific production, which is its exponential growth. Moreover, we conduct a sub-analysis for evolution to different formulation (immediate release and prolonged release melatonin).

Results: From the search on Pubmed 36,128 documents (sleep disorder) and 1,140 (combined with melatonin) were selected. In order to assess whether the growth of scientific production in sleep disorder and melatonin follows Price's Law of Exponential Growth, we carried out a linear adjustment of the data obtained, according to the equation $y = 5.9707x+23.258$, and another adjustment to an exponential curve, according to the equation $y = 27{,}915e0.0927x$. Mathematical adjustment to an exponential curve, allows us to obtain a correlation coefficient $r = 0.828$. On the other hand, linear adjustment to the measured values provides an $r = 0.924$. The reper-