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OREXINS PLAY A DUAL ROLE IN IMMOBILITY EPISODES ON TAIEP RATS A MODEL OF H-ABC

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Introduction: Leukodystrophies are a heterogenous group of congenital myelin alterations with more than 30 classified diseases was described until now. Among them there are several mutations in the a and b tubulins the so called tubulinophaties, that affect the central nervous system. The hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC) is due to a mutation in the tubulin b 4a (TUBB4A) and the taiep rats is the only available model of this human disease with similar magnetic resonance changes and a punctual mutation in the TUBB4A. Taiep rats had immobility episodes (IEs) with a peak between at 9 months of age. Importantly, electroencephalographic recordings shown that IEs had a rapid eye movement (REM) sleep characteristic pattern supporting that are equal to human cataplexy episodes that are key sign of narcolepsy. It is possible to induced IEs when taiep rats are manipulated from the tail or the thorax. Narcolepsy in humans and narcoleptic dogs had a significant decreased in orexin levels in the cerebrospinal fluid (CSF) and a concomitantly decreased of orexin neurons in the lateral hypothalamus.
Methods: We used 21 male rats from taiep at 9 months of age. All rats were kept in standard conditions and were implanted for EEG, EMG and EOG recordings to characterize IEs. We administered orexin A and B agonists and characterized the sleep-wake cycle and frequency of IEs, the peptides were administered by a intracerebroventricular (i.c.v.) injections diluted in artificial CSF. We also measured the number or positive orexin neurons in the lateral hypothalamus through immunohistochemistry.
Results: The i.c.v. administration of [Ala11, D-Leu 15] orexin B agonist significantly decrease the frequency of IEs with 3 and 10 nM doses ($P \leq 0.05$ and $P \leq 0.03$, respectively), without affecting the sleep-wake pattern. However, the i.c.v. administration of Orexin A (17-33) an agonist did not affect the sleep-wake pattern or the frequency of IEs. It is relevant that the number of orexins neurons did not differ between taiep and control Sprague-Dawley (SD) male rats.
Conclusion: Our results showed that IEs had a REM sleep EEG characteristic pattern with cataplexic-like atonia, there are sensible to orexin B agonist, but the number of orexin positive neurons do not differ with respect to SD male rats. In conclusion taiep rats a model of H-ABC is an adequate model of cataplexy-like episodes due to myelin disease.
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IMPACT OF CHRONIC SLEEP DISRUPTION ON GLYMPHATIC FUNCTION, COGNITIVE PERFORMANCE, AND NEUROPATHOLOGY IN THE 5XFAD MOUSE MODEL

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Introduction: Recent studies suggest a bidirectional relationship between sleep disruption and Alzheimer's disease, with mid-life sleep disruption associated with the development of Alzheimer's-related amyloid and tau pathology. Yet, the mechanistic link between sleep disruption, particularly over chronic time scales, and the development of Alzheimer's pathology remains unclear.
Methods: In this study, we evaluated the impact chronic sleep disruption has on the onset of cognitive impairment and neuropathologic disease progression using the 5xFAD amyloidosis mouse model. Chronic sleep disruption in male and female C57BL/6 and 5xFAD+ mice was performed in Lafayette sleep fragmentation cages from 10-18 weeks of age. Cognitive impairment was evaluated through behavioral tasks indicative of spatial memory, short-term memory, locomotion, anxiety, and activities of daily living. Upon completion of behavioral experiments, glymphatic function was assessed by measuring the influx of fluorescent cerebrospinal fluid tracers into brain tissue. Aquaporin-4 localization, amyloid plaque deposition, and markers of astroglial and microglial activation were assessed by immunofluorescence.
Results: We observed that chronic sleep disruption impaired cognitive performance and increased neuropathological outcomes in 5xFAD+ and littermate controls. The impact on glymphatic function was assessed in parallel and correlated with neuropathological and behavioral outcomes.
Conclusion: These findings highlight the critical association between dysfunctional sleep and the development of cognitive impairment and neuropathologic disease progression. They indicate that there is a potential interaction between inflammatory expression after chronic sleep disruption and neuropathologic disease progression.
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ELEVATED LEVELS OF EXTRACELLULAR VESICLE CYTOKINES ARE ASSOCIATED WITH POOR SLEEP QUALITY IN WARFIGHTERS WITH CHRONIC MILD TBI

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Introduction: Sleep disorders are common in military populations and frequently occur comorbidly with mild traumatic brain injury (mTBI), resulting in substantial health risks. Although inflammation and cytokine elevations have independently been reported both after traumatic brain injury (mTBI) and in association with sleep dysfunction, the impact of these factors on inflammatory processes in a combined context (i.e. post-mTBI sleep dysfunction) has yet to be explored. Extracellular vesicles (EVs) are a particularly promising source of these cytokines; EVs are lipid bilayer-enclosed

particles released by cells to the extracellular environment, constituting a newly discovered form of cell-to-cell communication that may afford improved signal-to-noise ratio and more functionally specific protein biomarkers than free (soluble) sources. To determine whether mTBI and sleep dysfunction may bidirectionally regulate inflammatory processes, the present study examined associations between plasma and EV levels of cytokines and sleep quality in a cohort of warfighters with and without chronic mTBI.
Methods: Participants (n=182) were enrolled in the Chronic Effects of Neurotrauma Consortium (CENC) Multicenter Prospective Longitudinal Study/ Long-Term Impact of Military Brain Injury Consortium (LIMBIC). They were divided into control (no TBI history) or mTBI groups (positive history of mTBI). EV and plasma levels of interleukin (IL)-10, IL-6, and tumor necrosis factor-alpha (TNFα) were analyzed using a Simoa HD-1 analyzer. Sleep quality was evaluated using Pittsburgh Sleep Quality Index (PSQI).
Results: Within the mTBI group, patients reporting poor sleep quality (PSQI ≥10) had elevated EV levels of IL-10 (ß(SE) = 0.12(0.04), $p<0.01$) when compared to those reporting good sleep (PSQI<10). Sleep quality was associated with EV levels of IL-10 (ß(SE)=0.11(0.04), p=0.01) and TNFα (ß(SE)=0.07(0.03), $p< 0.01$) in mTBI patients. Plasma levels of cytokines were not significantly associated with sleep quality.
Conclusion: Our findings suggest that EV levels of IL-10 and TNFα, but not their plasma levels, are associated with self-reported sleep quality warfighters with history of mTBI. Our results suggest that EVs are relevant signaling mechanisms in sleep-related inflammatory responses following mTBI. Larger prospective studies are needed to further investigate the links between EV cytokines and sleep quality in participants with mTBI.
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