was measured using the Ford Insomnia Response to Stress Test (FIRST). Linear regressions were conducted with PSG sleep parameters as outcome variables: difficulty falling asleep (Sleep Onset Latency [SOL] and Latency to Persistent Sleep [LPS]), difficulty staying asleep (Wake After Sleep Onset [WASO]), and sleep duration (Total Sleep Time [TST]). FIRST was tested as a predictor controlling for DLMO.
Results: After controlling for circadian phase, higher FIRST scores was associated with more difficulty staying asleep (WASO: $t[45]=4.059$, $p<0.001$) and shorter sleep duration (TST: $t[45] = -4.403$, $p<0.0001$), but not predictive of difficulty falling asleep (SOL: $p>0.05$). However, higher FIRST scores did predict a longer latency to persistent sleep (LPS: $t[45]=2.272$, $p<0.05$).
Conclusion: These results suggest that sleep reactivity to stress and circadian misalignment are independent processes that are both associated with disrupted daytime sleep in night shift workers. Given that night shift work can also cause psychosocial stress, treatments focused on circadian misalignment alone may not be sufficient. Our study highlights the need to consider sleep reactivity in the clinical management of shift work disorder.
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0007

DAYTIME SLEEP IN NIGHT SHIFT WORKERS: QUANTIFYING THE ROLE OF CIRCADIAN MISALIGNMENT

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Introduction: Circadian misalignment is commonly cited as a culprit of daytime sleep disturbances in night shift workers; however, the specific impact and magnitude that circadian misalignment has on daytime sleep has not been well-characterized in larger samples of night shift workers.
Methods: Participants included fixed-night shift workers (n=52, ages 18–50) who completed an 8-hour daytime polysomnography (PSG) in the lab following a night shift. Measures of sleep disturbances included: difficulty falling asleep (sleep onset latency [SOL], latency to persistent sleep [LPS]), difficulty staying asleep (sleep efficiency [SE], wake after sleep onset [WASO]), and sleep duration (total sleep time [TST]). Melatonin samples were collected hourly for 24 hours under dim light (<10 lux) and used to determine dim light melatonin offset (DLMOff). Circadian misalignment (CM) was calculated as the time difference between bedtime and DLMOff (higher values represented sleeping after DLMOff), and correlated with PSG sleep variables.
Results: CM was significantly associated with difficulty staying asleep (WASO: r=0.48, p<0.001; SE: r=-0.45, p<0.001), and sleep duration (TST: r=-0.38, p<0.01). Specifically, every 3 hours of CM on average added 19.2 minutes of WASO and reduced TST by 15 minutes. In contrast, CM was not significantly correlated with sleep onset difficulties (SOL: r=-0.27; LPS: r=-0.02).
Conclusion: These data suggest that circadian misalignment in shift workers may be a better predictor of difficulties staying asleep and sleep duration during the day relative to difficulties falling asleep. Because longer work hours (10–12 hours) are common in night shift worker, it may be that sleep initiation difficulties associated with circadian misalignment is masked by elevated fatigue or an increased homeostatic drive from prolonged wakefulness. These results may help guide decisions about the magnitude of phase shifts required (e.g., with light therapy) for the desired improvement in daytime sleep.
Support: Support for this study was provided to PC by the NHLBI (K23HL138166)

0008

SUVN-G3031, A HISTAMINE H3 RECEPTOR INVERSE AGONIST PRODUCES ROBUST WAKE PROMOTING AND ANTICATAPLECTIC ACTIVITY IN OREXIN KNOCKOUT MICE

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Introduction: Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, sleep paralysis, hallucinations, and in some cases episodes of cataplexy. Results from animal studies indicate the involvement of deficient orexin transmission in narcolepsy which can be circumvented by the activation of histaminergic neurons. SUVN-G3031 is a potent and selective histamine H3 receptor inverse agonist with hKi of 8.7 nM and shows less than 50% inhibition at 1 µM against 70 other targets. SUVN-G3031 exhibited excellent pharmacokinetic properties and brain penetration in preclinical species. Oral administration of SUVN-G3031 produces significant increase in histamine, dopamine and norepinephrine levels in the rat cortex. Long-term safety studies in animals have been successfully completed without any concern for further development of SUVN-G3031. In the present study, the effects of SUVN-G3031 were evaluated in orexin knockout mice, a reliable animal model of narcolepsy as a proof-of-concept study for the treatment of narcolepsy with and without cataplexy.
Methods: Male orexin knockout mice (10 - 15 weeks old, 25 - 35 g at the time of surgery) were implanted with telemetric device for simultaneous monitoring of electroencephalography (EEG) and electromyography. Animals were allowed surgical recovery of 3 weeks prior to EEG recording. Effects of SUVN-G3031 (3 and 10 mg/kg, *p.o.*) were evaluated during active period of animals.
Results: SUVN-G3031 produced significant increase in wakefulness with concomitant decrease in non-rapid eye movement sleep in orexin knockout mice. SUVN-G3031 also significantly decreased the number of cataplectic episodes in orexin knockout mice.
Conclusion: Results from the current preclinical study provide a strong basis for the utility of SUVN-G3031 for the treatment of narcolepsy with and without cataplexy. SUVN-G3031 is currently being evaluated in a Phase 2 study as monotherapy for the treatment of narcolepsy with and without cataplexy (ClinicalTrials.gov Identifier: NCT04072380).
Support: None

0009

ANTI-STREPTOCOCCAL ANTIBODIES IN CHINESE PATIENTS WITH TYPE -1 NARCOLEPSY

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Introduction: Narcolepsy type 1 (NT1) is considered to be an autoimmune disease, and streptococcal infection may be an environmental trigger. However, previous studies from Asian narcolepsy patients did not reveal elevated anti-streptolysin O [ASO]. The aim is to investigate whether large sample Chinese patients with NT1 have an increase in antistreptococcal antibody titers.

Methods: A total of 214 narcolepsy patients and 360 healthy controls were recruited. All patients were DQB1*0602 positive with clear-cut cataplexy or had low CSF hypocretin-1. Participants were tested for ASO and anti DNAse B [ADB]. These patients were divided into five groups according to disease duration, including 29 patients less than 3 months; 25 from 3 months to 1 year; 40 from 1 to 3 years; 61 from 3 to 10 years and 59 patients over 10 years. Comparison was also made between children and adults with age matched controls, respectively.
Results: There were no significant differences between patients and healthy controls in regard to both ASO ≥ 200 IU (19.2% vs. 16.9%, p = 0.50) and ADB≥480IU (9.8% vs. 10.3%, p = 0.86). For children narcolepsy patients, ASO positive rates(19.8% vs. 18%, p = 0.68) and ADB positive rates(10.4% vs. 12%, p = 0.72) had no differences compared to age matched controls. And no difference was observed in adult narcolepsy patients either, with ASO positive rates (18.5% vs. 13.8%, p = 0.39) and ADB positive rates (9.3% vs. 5.3%, p = 0.42) compared to age matched controls, respectively. ASO (ADB) positive rates had no significant differences among different disease duration groups(p= 0.55, 0.9).
Conclusion: It is indicated that positive rates of ASO and ADB were not significantly different between Chinese patients with NT1 and healthy controls, including recent onset cases and children.
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0010

FUNCTIONAL BRAIN CONNECTIVITY ALTERATIONS IN RESTLESS LEGS SYNDROME ARE MODULATED BY DOPAMINERGIC MEDICATION

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Introduction: Functional brain connectivity studies revealed alterations within thalamic, salience, and default mode networks in patients with restless legs syndrome. The objective of this study was to characterize functional connectivity and network topology in a large cohort of patients with restless legs syndrome compared to healthy controls, and to investigate the modulatory effect of dopaminergic treatment upon connectivity.
Methods: 82 patients with restless legs syndrome (untreated, n=30; on dopaminergic medication, n=42; on alpha-2-delta ligands as mono- or polytherapy combined with dopaminergic medication, n=10) and 82 individually age and gender matched healthy controls were studied with resting state functional MRI. Connectivity of twelve resting-state networks was compared with independent component analysis, and among 410 brain regions with graph theoretical modeling.
Results: Patients with restless legs syndrome showed significantly higher connectivity within salience (P=0.029), executive (P=0.001), somatomotor (P=0.050), and cerebellar (P=0.041) networks, as well as significantly (P<0.05) lower cerebello-frontal communication compared to healthy controls. Untreated patients had significantly (P<0.05) lower cerebello-parietal communication compared to healthy controls and connectivity between the thalamus and frontal regions were significantly increased in patients on dopaminergic medication compared to untreated patients and healthy controls (P<0.05).
Conclusion: Networks with higher intra-network connectivity (i.e. salience, executive, somatomotor, cerebellar) and lower between regions connectivity (i.e. cerebello-frontal, cerebello-parietal) in restless legs syndrome correspond to regions associated with attention, response inhibitory control, and processing of sensory information. Dopaminergic medication normalizes the altered cerebello-parietal communication and increases thalamic connectivity to the prefrontal cortex suggesting that these regions are associated with the emergence of symptoms in restless legs syndrome.
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0011

THE INFLUENCE OF OBSTRUCTIVE SLEEP APNEA SEVERITY AND SEX ON CEREBRAL PERFUSION

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Introduction: Obstructive Sleep Apnea (OSA) has been shown to initiate a pathological cascade negatively affecting the cardiovascular system, including cerebral circulation. There is limited data on OSA effects on regional brain function, though reduced global cerebral blood flow (CBF) has been observed among patients with OSA. However, there are few precise assessments. We hypothesized that regional CBF values are altered in OSA, and that sex influences the hypothesized relationship.
Methods: Participants from the NYU Center for Brain Health cohort (n=68; 57.4% female; mean age=66.32±6.84), representing cognitively healthy volunteers with OSA (AHI4% > 5/hr) and without, from several NIA-supported studies, completed evaluations including clinical, structural & functional high-resolution arterial spin labeling 3 tesla MRI scans. Hippocampal and temporal cortex CBF was assessed at baseline and after CO_2 challenge using a rebreathing protocol. Analyses were completed using one-way ANCOVA controlling for age and BMI.
Results: More men had OSA (82.8% vs 56.4%). Men without OSA showed a larger change in CBF after challenge in left (t=2.6, p=0.014) and right (t=2.4, p=0.021) hippocampus. Although the main analyses by severity level only boarded significance, pairwise comparisons indicated men with severe OSA (AHI4%>30/hr) exhibited a larger change in CBF after challenge in the hippocampus overall compared to those with mild OSA (AHI4%5–15/hr; p=0.015) and without OSA (p=0.017). Women with severe OSA showed a reduced change in CBF after challenge in the right hippocampus compared to those with mild (p=0.016), moderate (AHI4%16–29/hr; p=0.008), and without OSA (p=0.015).
Conclusion: This study suggests a possible differential effect of OSA severity and sex on regional CBF in response to a CO_2 challenge, specifically in the hippocampus. Further studies will examine cognitive consequences of these sex-specific hippocampal perfusion abnormalities in OSA.