Conclusion: These results suggest that a NS schedule causes circadian dysregulation of DNA repair genes and increases DNA damage – a primary hallmark of carcinogenesis – which may underlie the elevated cancer risk in NS workers.
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0026

TARGETED GENOME SEQUENCING IDENTIFIES MULTIPLE RARE VARIANTS IN CAVEOLIN-1 ASSOCIATED WITH OBSTRUCTIVE SLEEP APNEA

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Introduction: Obstructive sleep apnea (OSA) is a common disorder associated with increased risk for cardiovascular disease, diabetes, and premature mortality. There is strong clinical and epidemiologic evidence supporting the importance of genetic factors influencing OSA, but limited data implicating specific genes.
Methods: Leveraging high depth genomic sequencing data from the NHLBI Trans-Omics for Precision Medicine (TOPMed) program and imputed genotype data from multiple population-based studies, we performed linkage analysis in the Cleveland Family Study followed by multi-stage gene-based association analyses in independent cohorts to search for rare variants contributing to OSA severity as assessed by the apnea-hypopnea index (AHI) in a total of 7,708 European-Americans.
Results: We identified 21 non-coding rare variants in Caveolin-1 (CAV1) associated with lower AHI after accounting for multiple comparisons (P = 7.4×10-8). These non-coding variants together significantly contributed to the linkage evidence. Follow-up analysis revealed significant associations between increased CAV1 expression with lower AHI (P=0.024) and higher minimum overnight oxygen saturation (P=0.007).
Conclusion: Caveolin-1 is a membrane scaffolding protein that is essential in the formation of plasma membrane lipid rafts and mediates cholesterol trafficking; regulates several signaling molecules including transforming growth factor β (TGF-beta), Toll Like Receptor 4 (TLR4) and endothelial nitric oxide synthase (eNOS); with mutations implicated in disorders associated with OSA: pulmonary hypertension, diabetes, atherosclerosis, endothelial and cardiac dysfunction, and inflammation. Our results indicate that caveolin-1 also plays a significant role in OSA, with rare variants and higher CAV1 expression associated with lower AHI.
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RECIPROCAL MODULATION OF CORTICAL EXCITATORY AND INHIBITORY SYNAPSES BY WAKE-SLEEP HOMEOSTATIC STATE

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Introduction: A widely debated function of sleep involves a homeostatic program of down-regulation of excitatory synaptic strength following an overall increase during the preceding waking period, preserving however the previously existing synaptic weights associated with newly acquired memories. We tested this hypothesis by applying thorough statistical analysis of parameters of excitatory and inhibitory miniature postsynaptic currents (mEPSC/mIPSC) recorded ex vivo in mouse cortical pyramidal neurons at three characteristic wake/sleep stages.
Methods: Cingulate cortex coronal slices were obtained at fixed Zeitgeber time (ZT6, to control for circadian clock) from control C57BL6 (MEF2C f/f) mice subjected to 6h acute sleep deprivation (SD), recovery sleep =4hSD+2h(RS), or 6h control sleep (CS). mEPSCs and mIPSCs were recorded from functionally identified whole-cell patch-clamped pyramidal neurons in cortical layer 2/3 (L2/3). Statistical analysis of frequencies, amplitudes, and charge transfer rates of mEPSCs and mIPSCs was done using non-parametric Kruskal-Wallis multiple comparison test and K-means clustering test.
Results: mEPSC frequency (F) and charge transfer (CT) were significantly reduced for RS and CS compared to SD (F: -57%, -47%; CT: -64%, -55%). mEPSC amplitude (A) was significantly reduced for CS compared to SD (-15%). Two-centroid clustering test revealed that analyzed parameters of F, A and CT for SD condition were approximately evenly split between upper and lower range clusters, while the same parameters for RS and CS conditions revealed a pronounced redistribution (>75% lower-, <25% upper ranges). Wake/sleep state related changes of mIPSC parameters showed opposite pattern compared to excitatory synapses. All three parameters were increased in RS vs. SD (F: +63%, A: +7%, CT: +42%) and this difference reached significance levels in CS vs. SD (F: +88%, A: +24%, CT: +109%). Clustering analysis of mIPSC parameters revealed mostly stable distribution pattern between upper and lower ranges for all wake/sleep states.
Conclusion: Significant changes in excitatory/inhibitory balance in the frontal cortex is part of the homeostatic response upon transition from wakefulness to various phases of sleep. The excitatory component prevails during wakefulness, while the inhibitory component peaks during sleep.
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NETWORK ANALYSIS OF ADIPOKINES IN SLEEP DISORDERS AND METABOLIC DYSREGULATION

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Introduction: Adipokines are a growing group of secreted proteins that play important roles in metabolism. Accumulating evidence suggests that adipokines may mediate the close association between sleep disturbance and metabolic derangements. Due to the extensive crosstalk between adipokines and metabolic pathways, an integrated approach is required to better understand the significance of adipokines in sleep disorders and associated metabolic dysregulation. In the current study, we employed network analysis, a set of concepts and methods derived from graph theory, to obtain novel insights into the roles of adipokines in sleep disorders and associated metabolic dysregulation.
Methods: A network of six adipokines and their molecular targets is constructed based on current understanding of their roles in sleep and metabolic disorders using an adjacency matrix. The network is then visualized and analyzed using an open source platform Gephi to derive network-level metrics, including degree and centrality measures. These metrics are used to explore the relationship between sleep disturbance and associated metabolic dysregulation in several disease processes.