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ARC GENOTYPE MODULATES SLOW WAVE SLEEP FOLLOWING TOTAL SLEEP DEPRIVATION

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Introduction: The activity-regulated cytoskeleton associated protein (ARC) gene is an immediate early gene that is involved in synaptic plasticity. Recent evidence from a rodent model suggests that Arc may also be involved in sleep homeostasis. However, little is known about the molecular mechanisms regulating the sleep homeostat. In humans, sleep homeostasis is manifested by a marked increase in slow wave sleep (SWS) following acute total sleep deprivation (TSD). There are large, trait individual differences in the magnitude of this SWS rebound effect. We sought to determine whether a single nucleotide polymorphism (SNP) of the ARC gene is associated with individual differences in SWS rebound following TSD.
Methods: 64 healthy normal sleepers (ages 27.2 ± 4.8y; 32 females) participated in one of two in-laboratory TSD studies. In each study, subjects had a baseline day with 10h sleep opportunity (TIB 22:00–08:00) which was followed by 38h TSD. The studies concluded with 10h recovery sleep opportunity (TIB 22:00–08:00). Baseline and recovery sleep were recorded polysomnographically and scored visually by a trained technician. Genomic DNA was extracted from whole blood. The ARC c.*742 + 58C>T non-coding SNP, rs35900184, was assayed using real-time PCR. Heterozygotes and T/T homozygotes were combined for analysis. The genotype effect on time in SWS was assessed using mixed-effects ANOVA with fixed effects for ARC genotype (C/C vs. T carriers), night (baseline vs. recovery), and their interaction, controlling for study.
Results: The genotype distribution in this sample – C/C: 41; C/T: 17; T/T: 6 – did not vary significantly from Hardy-Weinberg equilibrium. There was a significant interaction between ARC genotype and night ($F_{1,62}=7.27$, $p=0.009$). Following TSD, T allele carriers exhibited 47.6min more SWS compared to baseline, whereas C/C homozygotes exhibited 62.3min more SWS compared to baseline. There was no significant difference in SWS between genotypes at baseline ($F_{1,61}=0.69$, $p=0.41$).
Conclusion: ARC T allele carriers exhibited an attenuated SWS rebound following TSD compared to those homozygous for the C allele. This suggests that the ARC SNP is associated with trait individual differences related to sleep homeostasis, and may thus influence molecular mechanisms involved in long-term memory.
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SELF-REPORTED SLEEP EFFICIENCY AND DURATION ARE ASSOCIATED WITH SYSTEMIC BIOENERGETIC FUNCTION IN COMMUNITY-DWELLING ADULTS

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Introduction: Sleep is important for aging, health, and disease, but its cellular role in these outcomes is poorly understood. Basic research suggests that disturbed and insufficient sleep impair mitochondrial bioenergetics, which is involved in numerous aging-related chronic conditions. However, the relationship between sleep and bioenergetics has not been examined in humans. We examined associations of self-reported sleep with systemic bioenergetic function in peripheral blood mononuclear cells (PBMCs) of community-dwelling adults.
Methods: N = 43 adults (79% female) ages 48–70 (M = 61.63, SD = 5.99) completed the Pittsburgh Sleep Quality Index (PSQI) from which key components of sleep (satisfaction, alertness, timing, efficiency, and duration) were calculated. Participants provided blood samples from which PBMCs were isolated and measured for bioenergetics using extracellular flux analysis. Associations of sleep components with bioenergetic parameters, including the Bioenergetic Health Index (BHI), were examined.
Results: In bivariate analyses, lower sleep efficiency was associated with lower maximal respiration, spare capacity, and BHI (ps < 0.05). Longer sleep duration was associated with lower BHI ($p < 0.01$) and later sleep timing was associated with higher basal respiration, ATP-linked respiration, maximal respiration, spare capacity, and non-mitochondrial respiration (ps < 0.05). After adjustment for age, sex, and body mass index, lower sleep efficiency ($\beta = 0.52$, $p < 0.01$) and longer sleep duration ($\beta = -0.43$, $p < 0.01$) were associated with lower BHI.
Conclusion: Self-reported indices of sleep efficiency and duration are related to systemic bioenergetic function in humans, suggesting a possible cellular pathway linking sleep to health.
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ASSOCIATION BETWEEN OBJECTIVE SLEEP DURATION AND DNA METHYLATION IN ADOLESCENTS

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Introduction: Insufficient sleep and circadian misalignment are highly prevalent in adolescents and have been associated with physical and mental health disorders. Several genome wide association studies (GWAS) in adults have identified genes that may be involved in the regulation of sleep and circadian traits. However, little is known regarding the epigenetic basis and significance of short sleep duration in adolescence, a critical developmental period.
Methods: To investigate the association between objective sleep duration, as measured by 9-hour in-lab polysomnography (PSG), and DNA methylation in GWAS-informed sleep-related genes, data from 263 adolescents of the Penn State Child Cohort (12-23y, 55.9% male, 23.2% racial/ethnic minorities) were analyzed. Using DNA extracted from peripheral leukocytes, epigenome-wide and GWAS-informed single nucleotide resolution of DNA methylation in cytosine-phosphate-guanine (CpG) sites and surrounding regions were obtained. Multivariable-adjusted linear regression models assessed the association between PSG sleep duration and site-specific methylation levels. Covariates in these models included sex, age, race/ethnicity, body mass index percentile, and psychoactive medication use (i.e., stimulants, anti-depressants, anxiolytics, sedatives, and/or anti-psychotics). P-values were adjusted using the Benjamini & Hochberg method to correct for false discovery rate and, thus, q-values are reported.
Results: PSG sleep duration was associated with differential methylation at 162 intragenic sites in the epigenome-wide analysis with a $q<0.05$. In GWAS-informed analysis, five genes were associated with altered DNA methylation, by which shorter PSG sleep duration was associated with hypermethylation in MAD1L1 ($q=0.02$), MAP2K1 ($q=0.03$), and RBM19 ($q=0.01$) and with hypomethylation in Brain Enriched Guanylate Kinase Associated (BEGAIN; $q=0.0005$) and SLC39A8 ($q=0.02$).

Conclusion: Objective sleep duration in adolescents is associated with altered DNA methylation in genes previously identified in adult GWAS of sleep and circadian traits. Importantly, our data also provides evidence for a potential epigenetic link between objective short sleep duration and genes involved in postsynaptic density (BEGAIN), circadian regulation (MAP2K1/RBM19) as well as internalizing (MAD1L1) and psychotic (SLC38A8) disorders.

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