Late Breaking Abstracts

LBA 1

HOME SLEEP DURATION AND GLYCEMIA IN LEAN AND OBESE ADOLESCENTS

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Introduction: Self-inflicted behaviorally mediated sleep restriction is rampant among adolescents, who may sleep as little as 6.4 hours on weeknights. In adults, chronic sleep restriction increases type 2 diabetes risk and experimental sleep restriction causes acute insulin resistance and glucose intolerance. Pediatric studies have associated short sleep with insulin resistance, but have not examined *home* sleep duration's influence on post-prandial glucose metabolism. We report on a pilot study examining relationships between home sleep and dynamic glucose and insulin homeostasis in adolescents.

Methods: 10 adolescents (age 13-18 years, Tanner 2-5) underwent oral glucose tolerance test (OGTT), anthropometrics, overnight polysomnogram, and home sleep assessment via actigraphy and sleep diaries. Continuous variables were analyzed by correlation analysis. Linear regressions examined associations between home sleep duration and metabolic outcomes, controlling for weight.

Results: We found significant negative associations between home sleep duration (actigraphy) and weight (r=-0.63, p=0.049) and OGTT 90-minute glucose (r=-0.66, p=0.036). Trends emerged towards associations between sleep duration and waist circumference (r=-0.60, p=0.086), fasting insulin (r=-0.59, p=0.074) and insulin resistance measures, i.e. homeostasis model assessment of insulin resistance (HOMA-IR: r=-0.56, 0.091), and whole-body insulin sensitivity index (higher values denote greater insulin sensitivity: r=+0.56, p=0.091). Linear regression analysis revealed that sleep duration was the primary predictor of 90-minute glucose (R^2 change=0.44, p=0.036) and that body weight was not a significant predictor.

Conclusions: In this pilot study, the first to our knowledge to examine potential interrelationships between home sleep duration and dynamic insulin and glucose homeostasis in adolescents, significant negative relationships between home sleep duration and both weight and post-challenge glucose levels were identified, and trends towards negative associations between

home sleep duration and both central obesity and insulin resistance were present. Our early results point towards an association between sleep and glucose/insulin homeostasis in adolescents that may be independent of body weight.

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LBA 2

OPTOGENETIC INHIBITION OF BASAL FOREBRAIN PARVALBUMIN GABA NEURONS SUPPRESSES CORTICAL ACTIVATION FROM BOTH GAMMA BAND AUDITORY STIMULATION AND HYPERCARBIA-INDUCED AROUSALS FROM SLEEP

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Introduction: We hypothesized that basal forebrain (BF) parvalbumin GABA (pvGABA) neurons form a key final common pathway for cortical activation from both sensory and visceral stimuli. We used the 40 Hz auditory steady state response (ASSR) as sensory stimuli and measured the resulting activation of cortical gamma band oscillations (GBO, ~40 Hz). Visceral stimuli were hypercarbia (10% CO2), to model obstructive sleep apnea and its cortical activation and arousal from sleep.

Methods: For optogenetic inhibition, we bilaterally injected a viral vector (AAV-FLEX-ArchT-GFP) with the proton pump ArchT and a green fluorescent protein marker (GFP) into the BF of parvalbumin (PV)-Cre mice (n=12), and histologically verified transduction. Inhibition was induced by 532 nM bilateral laser illumination preceding and during the 500ms ASSR or 30s hypercarbia stimuli and was compared with no illumination in the same animal.

Results: Projections of BF pvGABA neurons to frontal cortex was confirmed by GFP-labeled fiber tracing. Auditory Stimuli: In each of 8 successfully transduced mice, ArchT inhibition during wakefulness of BF PV cells attenuated ASSR-elicited GBO (binomial $p<0.01$). Overall, ArchT inhibition reduced FFT power near 40 Hz from no-inhibition mean of 1.88±0.4 to 1.22±0.2 microvolts-squared. Moreover, preliminary data indicated a 23% reduction in arousals from NREM by loud white noise sounds (30 dB>background). Hypercarbia: With bilateral ArchT BF PV inhibition, NREM EEG arousal latencies with hypercarbia in 5 mice were significantly increased (6.5±0.8s without ArchT, 13.1±1.7s with ArchT, paired t-test, $p=0.002$), an increase of 101.5%. Additionally, under control conditions, arousals occurred at a mean ambient CO2 level of 6.3±0.6%, but when bilateral ArchT BF PV inhibition was applied, the CO2 level for arousal was significantly increased to 8.2±0.8% (paired t-test, $p=0.025$).

Conclusion: Inhibition of BF pvGABA neurons confirms their key role in cortical activation from both sensory (auditory) and visceral (respiratory) stimuli.

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LBA 3

NON-VISUAL EFFECTS OF LIGHT ON MOOD THROUGH THE MELANOPSIN PATHWAY IN SEASONAL DEPRESSION

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Introduction: Individual differences in the effect of light on mood, mediated by retinal subsensitivity, may explain seasonal affective disorder (SAD). Previously we found reduced retinal melanopsin cell responding in SAD (post-illumination pupil response, PIPR). However, the effect of light exposure prior to testing the PIPR could be significant given differential light exposure in SAD, and has not yet been studied.

Methods: Participants include 33 individuals with SAD (84% Female; age *M*=38.4, *SD*=13.6), and 17 controls (73% Female; age *M*=34.1, *SD*=12.8). The PIPR was assessed in summer and winter. Light exposures (1 sec) were 15.78nm full width half-maximum (FWHM 632.9nm) and 22.68nm FWHM (467.7nm) and 13.5 log Photons/cm^2/s retinal irradiance accounting for age-related blue light absorption. Light exposure in the days prior to testing was measured using actigraphy.

Results: Total photons on the day of PIPR testing accounted for significant variation in PIPR values in SAD but not controls. Blue total photons accounted for the greatest proportion of variance in PIPR (R^2=0.318, β=0.39, p=0.013), and remained a predictor (R^2 change=0.14, p=0.013) when controlling for gender, chronotype, and time since wake. Furthermore, the PIPR was lower in SAD compared to controls (F(1,50.5)=6.34, p<0.05) and lower in evening chronotypes (F (1,53.2)=13.7, p<0.001) even when including group, season, gender, age, testing time, and wake time.
Conclusion: These data are the first to link light exposure and the PIPR in SAD. We speculate that low light levels in SAD trigger downstream changes in mood and behavior, and that the link between light and SAD may be mediated by the PIPR.

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LBA 4

EFFICACY AND SAFETY OF ORAL ADX-N05 FOR THE TREATMENT OF EXCESSIVE DAYTIME SLEEPINESS IN ADULTS WITH NARCOLEPSY: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Introduction: ADX-N05 (N05) is a unique wake-promoting agent with dopaminergic and noradrenergic activity that is being evaluated for the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy.

Methods: This double-blind, placebo-controlled, parallel-group, multicenter study evaluated safety and efficacy of N05 over 12 weeks in subjects aged 18-70 years with an ICSD-2 diagnosis of narcolepsy. Subjects were randomized to once-daily placebo (n=49) or N05 (n=44). Doses of N05 were 150 mg/day weeks 1-4 and 300 mg/day weeks 5-12. Co-primary efficacy endpoints were change from baseline to last assessment in average sleep onset latency (SOL) on the Maintenance of Wakefulness Test (MWT) and Clinical Global Impression-Change (CGIC). Secondary endpoints included change from baseline at weeks 4 and 12 on the Epworth Sleepiness Scale (ESS).

Results: Week 4 changes from baseline were significantly greater with N05 150 mg relative to placebo: increased MWT SOL (9.5 minutes vs 1.4 minutes; $P<0.0001$), CGIC improvement (80% vs 51%; $P=0.0066$) and decreased ESS scores (5.6 points vs 2.4 points; $P=0.0038$). At week 12, following 8 weeks of 300 mg, N05 resulted in greater improvement from baseline than placebo on MWT SOL (12.8 minutes vs 2.1 minutes; $P<0.0001$), ESS (8.5 points vs 2.5 points; $P<0.0001$), and proportion of patients with CGIC improvement (86% vs 38%; $P<0.0001$). Three subjects (6.8%) in the N05 group discontinued due to adverse events (AEs). The most common AEs with N05 vs placebo were headache (16% vs 10%), nausea (14% vs 6%), diarrhea (11% vs 6%), insomnia (14% vs 2%), decreased appetite (14% vs 0%) and anxiety (11% vs 0%). Two serious AEs (conversion disorder, acute cholecystitis) in the N05 group were considered probably unrelated to N05.

Conclusion: At doses of 150-300 mg/day, N05 was well-tolerated and significantly improved objective and subjective symptoms of EDS in adults with narcolepsy.

Support: This study was supported by Aerial BioPharma.