



Late Breaking Abstracts

LBA 1

OPTOGENETIC STIMULATION OF MCH NEURONS INCREASES SLEEP

Konadhode RR², Pelluru D², Blanco-Centurion C², Zayachkivsky A⁴, Liu M², Uhde T², van den Pol AN³, Glen WW², Mulholland PJ², Shiromani PJ^{1,2}

¹Ralph H. Johnson VA Medical Center, Charleston, SC, USA, ²Medical University of South Carolina, Charleston, SC, USA, ³Department of Neurosurgery, Yale University School of Medicine, New Haven, CT, USA, ⁴Yale University School of Medicine, New Haven, CT, USA

Introduction: Wake and sleep states are tightly regulated by a distributed network of arousal and sleep neurons. There are many more arousal populations, whereas only the VLPO neurons are included in current models of sleep-wake regulation. There are likely to be other sleep neurons but these have proven difficult to identify. One such population is the melanin concentrating hormone (MCH) neurons. MCH neurons are active during sleep, but do they increase sleep when stimulated?

Methods: The gene for channelrhodopsin-2 was delivered (rAAV-MCH-ChR2 (H134R)-EYFP) into the hypothalamus of wild-type C57BL/6J mice. After 3 weeks, the baseline sleep was recorded for 48h (0Hz). Light stimulation (473nm) was given for 1min “on” and 4 min “off” for 24h and sleep was recorded. Each mouse was stimulated at one of the three frequencies (5, 10 and 30Hz) selected in random order. Stimulation was done at two circadian time periods: start of night (lights-off) or second half of day period.

Results: *In-vitro* slice studies confirmed that ChR2-EYFP neurons responded to 5, 10, 20 and 30Hz blue light stimulation. Sleep studies (n=14) determined that 10 and 30 Hz, but not 5hz significantly reduced length of wake bouts by 50%, shortened time to sleep onset and increased total time in non-REM and REM sleep during the circadian night period. Delta power, a measure of sleep intensity was increased during the sleep period. MCH stimulation had no significant effect on sleep during the day cycle. There was no effect of light stimulation in mice without ChR2 (n=7).

Conclusion: MCH neurons are candidate sleep neurons since the increase in sleep occurred during the animal's active period demonstrating that stimulation of MCH neurons can readily counteract a strong arousal signal. This could be potentially useful in sleep disorders where sleep needs to be triggered against a strong arousal drive.

Support: NIH grants MH055772, NS052287, NS079940, and Medical Research Service of the Department of Veterans Affairs

LBA 2

QUANTIFYING MYELIN PATTERNS AND HIGH DENSITY SLEEP EEG IN PRESCHOOL CHILDREN: INVESTIGATIONS OF BRAIN MATURATION AND FUNCTION

Kurth S¹, Deoni SC², Dean DC², Huber R³, Doucette M¹, Chevalier N⁴, Munakata Y⁴, LeBourgeois MK¹

¹Sleep and Development Laboratory, Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO, USA, ²Advanced Baby Imaging Laboratory, School of Engineering, Brown University, Providence, RI, USA, ³Child Development Center, University Children's Hospital Zurich, Zurich, Switzerland, ⁴Cognitive

Development Center, Department of Psychology, University of Colorado Boulder, Boulder, CO, USA

Introduction: Synaptic remodeling and white matter growth are essential for brain maturation. Sleep EEG slow-wave activity (SWA 1-4.5Hz) reflects gray matter changes and learning. Yet, it remains unknown how sleep is related to white matter development and functions assignable to these networks (eg. processing speed, PS). We used novel imaging tools to contrast myelin, sleep EEG and brain function in preschool children.

Methods: All-night high-density EEG was recorded in 16 children (2-6y, 9m). Typical EEG preprocessing was followed by EEG power (109 electrode mean) and topography (frontal-occipital ratio, FO) calculations. Using age-appropriate protocols, mcDESPOT MRI was obtained (n=13, non-sedated). Myelin-water-fraction (MWF) maps were calculated, normalized to custom pediatric templates, and smoothed (Gaussian kernel). PS (eye-tracking, touch screen, paper-pencil-tasks) and behavior (motor, language, visual reception) were quantified. Cluster analysis (Euclidean distance) and correlation matrices were calculated to examine variable proximity.

Results: MWF (ANOVA $p<0.05$) and SWA (FO $R=0.7$ $p=0.006$; power $R=0.5$ $p=0.04$), but not theta or spindle power increased across age. MWF and our selected EEG measures were not closely related. However, FO ($R=0.6-0.7$ $p=0.02-0.002$) and MWF ($R=0.5-0.7$ $p=0.02-0.05$) were related to PS and several behavior variables, while SWA was strongest associated with motor-related variables ($R=0.6$ $p=0.03$). Cluster analyses revealed proximity of several MWF sub-regions and confirmed relationships between FO-age-behavior, or SWA-motor variables. Neither spindle nor theta power were grouped with MWF, PS or behavior.

Conclusion: This first investigation of inter-relationships of EEG activity, brain function and myelination reveals that SWA and topography account for variability in brain function. Novel EEG tools in future analyses (coherence, traveling waves), which incorporate distant cortical synchrony, might be indicative for myelination. Despite recent suggestions that action potentials

trigger myelination, the role of sleep EEG activity in myelination must be investigated further, as sleep EEG measures may be crucial early biomarkers for neurodevelopmental disabilities.

Support: This work was supported by the University of Colorado Boulder (ML), the Swiss National Science Foundation (PBZHP3-138801 and PBZHP3-147180, SK) and the Institute of Cognitive Science at University of Colorado Boulder.

LBA 3

ASSOCIATION BETWEEN SLEEP DURATION AND INCIDENT DEMENTIA: THE FRAMINGHAM STUDY

Westwood AJ¹, Beiser A^{1,2,3}, Himali JJ¹, Au R^{1,3}, DeCarli C⁴, Wolf PA^{1,3}, O'Connor GT^{3,5}, Auerbach SH^{1,3}, Seshadri S^{1,3}

¹Department of Neurology at Boston University School of Medicine, Boston, MA, USA, ²Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA, ³Framingham Heart Study, Framingham, MA, USA, ⁴University of California at Davis, Sacramento, CA, USA, ⁵Department of Medicine at Boston University School of Medicine, Boston, MA, USA

Introduction: Sleep restriction and sleep-disordered breathing are known to negatively affect cognitive performance. In a cross-sectional observational analysis sleep duration did not show an association with cognition in women. This is the first study to relate sleep duration to brain volume and to the risk of incident AD.

Methods: Self-reported total hours of sleep was obtained from participants of the Framingham Study Original and Offspring cohorts (total N=2607, mean age 72 \pm 7 years, 57% women) between 1986-1990 and 1998-2001 respectively. Participants were followed prospectively for AD. Brain MRI and cognitive performance were assessed in Offspring (N=2306, mean age 62 \pm 9 years, 54% women) between 1999-2005. Hours of sleep were related to cross-sectional measures of brain volume and cognitive performance using linear regression and to risk of incident AD using Cox proportional hazards models.

Results: 177 persons developed incident AD in 10 years of follow-up. In multivariable analyses adjusted for apoE-, total homocysteine-, age-, sex-, and education, an abnormally prolonged reported sleep time (\geq 10 hours per night) was associated with lower total brain volume (β =-1.12, SE=0.42, p=0.007), worse performance on a Trails B task (β =-0.09, SE=0.03, p=0.002) and increased risk of AD (1.97 (95% CI 1.08-3.61), p=0.027). Additional adjustment for depression and polysomnogram-defined obstructive sleep apnea (respiratory disturbance index \geq 15), where available, did not alter these associations.

Conclusion: Abnormally prolonged sleep time was associated with smaller brain volume, poorer executive function and a greater risk for AD, independent of obstructive sleep apnea or depression. Sleep duration may be a marker of early neurodegeneration and hence, a useful clinical screen to identify those persons at higher risk for future cognitive impairment.

LBA 4

INSOMNIA SYMPTOMS AND RISK FOR FATAL ACCIDENTS: A PROSPECTIVE STUDY

Laugsand LE¹, Strand LB¹, Vatten LJ¹, Janszky I^{1,2}, Bjørngaard JH¹

¹Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway, ²Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden

Introduction: Only a few prospective studies investigated insomnia in relation to fatal accidents, and these studies assessed either only few aspects of insomnia or included only work-related accidents. There is also lack of larger prospective studies assessing the association of insomnia symptoms and fatal motor-vehicle accidents. We aimed to assess the prospective association between self-reported insomnia symptoms and the risk of fatal accidents in a large Norwegian cohort.

Methods: Baseline data on insomnia symptoms, including difficulty initiating sleep, difficulty maintaining sleep and having non-restorative sleep, socio-demographic data, shift-work, psychological distress, and alcohol intake, were collected from 54,402 men and women 20- 89 years of age who participated in the Nord- Trøndelag Health Study (HUNT) between 1995 and 1997. The cohort was followed for fatal from baseline through 2008. We used Cox proportional hazard models to assess the association of baseline insomnia symptoms with the risk of fatal accidents.

Results: A total of 235 fatal accidents and 58 fatal motor-vehicle accidents occurred during a mean follow-up of 11.3 years identified by the National Cause of Death Registry. There was a dose-dependent association between the number of insomnia symptoms and risk of fatal accidents. The multi-adjusted hazard ratios were 1.44 (0.62- 3.35), 2.47 (0.89- 6.83) and 8.87 (2.73- 28.76) for people with one, two, and three insomnia symptoms, compared to people with none of the symptoms (P for trend 0.001). The corresponding hazard ratios for fatal motor-vehicle accidents were 0.91 (0.22- 3.80), 2.32 (0.55- 9.74), and 11.03 (2.56- 47.42), respectively (P for trend 0.012).

Conclusion: Insomnia is associated with a markedly increased risk of both fatal accidents in general, as well as for fatal motor-vehicle accidents. Identifying persons with insomnia may be important in preventing fatal accidents.

LBA 5

TASIMELTEON TREATMENT ENTRAINS THE CIRCADIAN CLOCK IN TOTALLY BLIND INDIVIDUALS WITH NON-24 HOUR CIRCADIAN RHYTHMS AND SIGNIFICANTLY IMPROVES THE DURATION AND TIMING OF SLEEP

Lockley SW¹, Dressman MA², Xiao C², Fisher D³, Torres R², Lavedan C², Licamele L², Polymeropoulos MH²

¹Division of Sleep Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA,

²Vanda Pharmaceuticals Inc., Washington, DC, USA, ³P Less Than, San Francisco, CA, USA

Introduction: The majority of totally blind individuals exhibit non-24-hour circadian rhythms due to light signals not reaching the suprachiasmatic nucleus, resulting in Non-24-Hour Sleep-

Wake Disorder (Non-24). Tasimelteon is a novel circadian regulator in development for Non-24, a serious circadian disorder with no FDA-approved treatment.

Methods: Two phase III placebo-controlled studies in blind Non-24 patients assessed safety, efficacy and maintenance of effect of tasimelteon treatment (20mg/day). Circadian period was assessed from urinary 6-sulfatoxymelatonin (aMT6s) and cortisol. Clinical assessments included a Non-24 Clinical Response Scale (N24CRS), nighttime sleep, daytime naps and Clinical Global Impression of Change (CGIC).

Results: *Entrainment Study (SET)* (*n*=84): Tasimelteon entrained the circadian clock (aMT6s: 20.0 vs. 2.6%; cortisol: 17.5 vs. 2.6%), had more clinical responders on the N24CRS (23.7 vs. 0%), improved CGIC (2.6 vs. 3.4), increased sleep in the worst quartile of nights (LQ-nTST) (57 vs. 17 mins), decreased nap duration in the worst quartile of days (UQ-dTSD) (46 vs. 18 mins), and improved mid-point of sleep timing (MoST) (35 vs. 14 mins), compared to placebo (*p*<0.05).

Maintenance Study (RESET) (*n*=20): Tasimelteon-entrained patients were randomized to continued treatment or placebo. Tasimelteon maintained entrainment compared to placebo (aMT6s: 90 vs. 20%; cortisol: 80 vs. 20%). In treated patients, nighttime sleep (LQ-nTST) increased, and daytime sleep (UQ-dTSD) decreased, by 67 and 59 mins/day, respectively, and MoST increased by 36 mins/day (*p*<0.05).

Tasimelteon was safe and well-tolerated in both studies.

Conclusion: Tasimelteon entrained the circadian pacemaker in blind patients with Non-24, and caused significant clinical improvement in multiple measures of sleep, wake and global functioning. Discontinuation of tasimelteon abolished circadian entrainment, resulting in an hour less sleep each night and an hour more sleep each day. These studies demonstrate that tasimelteon is an effective circadian regulator, and that continued treatment is required to maintain entrainment and the resulting clinical benefits.

Support: Vanda Pharmaceuticals Inc. (ClinicalTrials.gov NCT01163032 and NCT01430754)

LBA 6

SAFETY AND EFFICACY OF UPPER AIRWAY STIMULATION IN TREATMENT OF OBSTRUCTIVE SLEEP APNEA

Strollo PJ¹, Soose RJ², Strohl KP³

¹Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, ²Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, ³Division of Pulmonary, Critical Care and Sleep Medicine, Case Western University School of Medicine, Cleveland, OH, USA

Introduction: Moderate to severe obstructive sleep apnea (OSA) is associated with significant health risks. Continuous positive airway pressure (CPAP) can mitigate these risks, although effectiveness is frequently compromised by inadequate adherence to treatment. We hypothesized that electrical stimulation of the hypoglossal nerve would restore upper airway patency and provide an alternative treatment option for OSA. The primary aim of this study was to determine the safety and efficacy of upper airway stimulation for treatment of OSA.

Methods: The design was a prospective, multicenter trial with randomized therapy withdrawal arm. The study enrolled participants with moderate to severe OSA who had failed or had not tolerated CPAP. All qualified participants underwent a screening polysomnographic (PSG) study, surgical consultation and drug-induced sleep endoscopy (DISE). Participants without complete concentric collapse at the retropalatal airway received an implanted neurostimulator (Upper Airway Stimulation system, Inspire Medical Systems, Minnesota). All implanted participants were followed for 12 months to collect adverse events. Therapy efficacy was evaluated by PSG and quality of life measures Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) at 12 months compared with baseline. The therapy withdrawal effect was evaluated by randomizing half of consecutive therapy responders at 12 months to one week of therapy suspension versus therapy maintenance followed by a PSG.

Results: 126 participants (21 females) received an implanted system. Average age was 54.5 ± 10.2 yrs and BMI was $28.4 \pm 2.6 \text{ kg/m}^2$. At 12 months, there was a significant reduction in the Apnea Hypopnea Index (AHI) from a median of 29.3 (IQR of 14.9) at baseline to 9.0 (IQR of 18.2) and the Oxygen Desaturation Index from a median of 25.4 (IQR of 17.1) to 7.4 (IQR of 17.0). The ESS and FOSQ also showed significant improvement from pre-implant to 12 months. The therapeutic effect of stimulation was also confirmed at 12 months with a significant increase in AHI in the therapy withdrawal arm vs. no change in the therapy maintenance arm.

Conclusion: Upper airway stimulation is effective for the treatment of moderate to severe OSA with clinically and statistically significant improvement in objective and subjective measurements of OSA severity.

Support: Inspire Medical Systems, Minnesota