Late Breaking Abstracts

LBA 1

STATE DEPENDENT CHANGES IN ADENOSINE IN THE RODENT HIPPOCAMPUS RELIES ON GLIOTRANSMISSION

Blutstein T, Schmitt LI, Haydon PG

Department of Neuroscience, Tufts University School of Medicine, Boston, MA USA

Introduction: Normal and enforced wakefulness is correlated with an increase in extracellular adenosine in brain regions such as the basal forebrain. This increase is thought to contribute to the homeostatic sleep response as well as to sleep-deprivation induced memory deficits. However, it has yet to be determined if similar changes in adenosine occur in the hippocampus, a region known to be important for learning and memory. Using a transgenic mouse model which specifically impairs gliotransmitter release via the inducible astrocytic expression of a dominant negative SNARE (dnSNARE) protein, our lab has previously shown that gliotransmission is necessary for the accumulation of sleep pressure and contributes to the impairment of memory consolidation following sleep deprivation in an A1R dependent manner.

Methods: Here, we pair adenosine and inosine biosensors *in vivo* with EEG/EMG recordings to measure real time state-dependent changes in hippocampal adenosine in wild-type and dnSNARE mice.

Results: In wild-type animals (n=4), during the first 5min of wakefulness (combined spontaneous and enforced), there is a 121.2 +/-21.3 nM increase in hippocampal adenosine relative to the concentration at the transition. This rise in adenosine is detected within 30 seconds. In dnSNARE animals (n=5) extracellular adenosine decreases by 94.5 +/-93.2 nM following the transition to wakefulness. In the 5 min following the transition to NREM sleep, adenosine decreases in both wild-type (66.6 +/- 47.1 nM) and dnSNARE animals (96.5 +/- 248.7 nM). A brief sleep deprivation (30min) produces a dramatic increase in adenosine in wild-type animals (300.7 +/- 125.5 nM) that is absent in dnSNARE.

Conclusion: Here, we measure for the first time rapid changes in adenosine in the hippocampus in response to sleep-wake transitions and sleep deprivation that relies on functional gliotransmission. These findings may provide insight into the role of astrocyte derived adenosine in normal hippocampal function and sleep deprivation induced deficits in hippocampus-dependent memory.

Support: This work was supported by a postdoctoral National Research Service Award to T.B. (MH091883) and an RO1 to P.G.H. (NS037585).

LBA 2

PROLONGED TREATMENT OF COMPLEX SLEEP APNEA SYNDROME WITH CONTINUOUS POSITIVE AIRWAY PRESSURE VERSUS ADAPTIVE SERVOVENTILATION – A PROSPECTIVE RANDOMIZED STUDY

Morgenthaler TI[1], Kuzniar TJ[2], McLain W[3], Wolfe L[4], Fry J[5], Goldberg R[6], Rahangdale S[7]

[1]Center for Sleep Medicine, Mayo Clinic, Rochester, MN, USA, [2] Department of Internal Medicine, 4th Clinical Military Hospital, Wrocław, Poland, [3]SleepMed, Columbia, SC USA, [4]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [5]Center for Sleep Medicine, Chestnut Hill Hospital, Philadelphia, PA, USA, [6]Sleep HealthCenters, Pheonix, AZ, USA, [7]NorthShore University HealthSystem, Evanston, IL, USA

Introduction: Prior studies show that adaptive servoventilation (ASV) is initially more effective than CPAP for patients with complex sleep apnea syndrome (CompSAS), but choosing therapies has been controversial because residual central breathing events may resolve over time on less expensive chronic CPAP therapy in many patients. We conducted a multicenter, randomized, prospective trial comparing clinical and polysomnographic outcomes over prolonged treatment of patients with CompSAS with CPAP versus ASV.

Methods: Qualifying patients meeting criteria for OSA on diagnostic polysomnography but with a central apnea index ≥ 10 on best CPAP were randomized to either CPAP or ASV (ResMed VPAP Adapt™) treatment and then titrated to determine optimal settings. Clinical and polysomnographic measures were obtained at baseline and after 90 days of therapy.

Results: We randomized 66 patients (33 to each treatment arm, age 59.2 ± 12.9 years, BMI 35.0±8.0, ESS 10±5, 9.1% with CHF, 13.6% using chronic opiates). At baseline, diagnostic AHI was 37.7±27.8 (CAI = 3.2±5.8) and best CPAP AHI was 37.0±24.9 (CAI 29.7±25.0). After second-night treatment titration, the AHI on ASV was 4.7± 8.1 (CAI=1.1 ±3.7) and 14.1 ± 20.7 (CAI=8.8 ±16.3) on CPAP (AHI, $p=0.0003$; CAI, $p<0.0001$). Follow up was standardized, and at 90 days, the ASV vs. CPAP AHI was 4.4±9.6 vs. 9.9±11.1 ($p=0.0024$) and CAI was 0.7 ±3.4 vs. 4.8±6.4 ($p<0.0001$), respectively. In the intention-to-treat analysis, success (AHI<10) at 90 days of therapy was achieved in 89.7% vs. 64.5% of patients treated with ASV and CPAP, respectively ($p=0.0214$). Compliance, changes in ESS and SAQLI were not significantly different between treatment groups.

Conclusion: ASV was more reliably effective than CPAP in relieving CompSAS. Only two thirds of patients succeeded with CPAP, while nearly 90% succeeded with ASV. Since both methods produced similar symptomatic changes, it is unclear if this polysomnographic

effectiveness may translate into other desired outcomes.

Support: Supported by a grant from ResMed Corp

LBA 3

TOTAL SLEEP DEPRIVATION REDUCES RESTING STATE PCC-HIPPOCAMPUS CONNECTIVITY

Fang Z, Zhu S, Hu S, Detre JA, Goel N, Basner M, Dinges DF, Rao H

Center for Functional Neuroimaging and Unit for Experimental Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

Introduction: Sleep deprivation (SD) degrades multiple neurocognitive functions, including attention and memory. Previous neuroimaging literature has mainly focused on the attenuation effects of SD on task-induced brain activation, while the neural mechanisms by which SD impairs brain at resting state remain largely unknown. Recent studies using resting state fMRI found reduced functional connectivity (FC) between regions in the default mode network (DMN) and its anti-correlated network (ACN) after total or partial SD. In this study, we examined the effects of one night of acute total SD as well as two nights recovery sleep on resting state functional connectivity.

Methods: Seventeen healthy adults (9 female, age 22-48 yrs) were scanned three times between 7-9am on a Siemens 3T Trio scanner at resting state using a standard EPI sequence. All subjects underwent the three scans in a fixed order: a first scan at baseline (BS) after normal sleep, the second scan during SD, and a third scan after two nights of recovery sleep (RS). The core DMN node, the posterior cingulate cortex (PCC), was selected as the seed region for FC analyses. Data were analyzed by SPM8 and REST toolbox.

Results: The FC analyses of all three scans clearly detected both DMN and ACN. However, no significant effects of SD on DMN or ACN connectivity were found. Instead, we observed significantly reduced connectivity between PCC and bilateral hippocampus for SD compared to both BS and RS, while no such differences were found between BS and RS.

Conclusion: This study did not replicate the previous findings that SD reduced connectivity between DMN and ACN nodes, but revealed that SD reduced resting PCC-hippocampus connectivity. Our results extend the previous finding that SD impairs hippocampal connectivity during episodic memory encoding to resting state, and support the crucial role of sleep for memory consolidation.

Support: Supported in part by NIH Grants R01 HL102119, CTRC UL1RR024134, and P30 NS045839; and the PENN ITMAT-TBIC Pilot Project.

LBA 4

EFFICACY AND SAFETY OF SUVOREXANT, A DUAL OREXIN RECEPTOR ANTAGONIST, IN PATIENTS WITH PRIMARY INSOMNIA: RESULTS FROM TWO PIVOTAL TRIALS

Herring WJ[1], Connor K[1], Ivgy-May N[1], Snavely D[1], Snyder E[1], Liu K[1], Krystal AD[2], Roth T[3], Michelson D[1]

[1]Merck, Whitehouse Station, NJ, USA, [2]Duke University Hospital, Durham, NC, USA, [3]Henry Ford Hospital, Detroit, MI, USA

Introduction: Night-time administration of orexin receptor antagonists is hypothesized to dampen orexin-mediated wakefulness, facilitating sleep. Suvorexant, an investigational orexin receptor antagonist, was effective and well-tolerated in an initial 4-week proof-of-concept study in patients with Primary Insomnia. Here we report results from two 3-month confirmatory trials.

Methods: Two randomized, double-blind, placebo-controlled, 3-month trials in patients with primary insomnia. Two dose regimens were evaluated in each trial; one comprised 40mg for patients 18-64 years and 30mg for patients ≥65 years, the other comprised 20mg for patients 18-64 years and 15mg for patients ≥65 years.. Efficacy was assessed by patient self-report of total-sleep-time (sTST), time-to-sleep-onset (sTSO), and wake-after-sleep-onset (sWASO), as well as by polysomnographic endpoints of Latency-to-onset-of-Persistent-Sleep (LPS) and Wake-After-persistent-Sleep-Onset (WASO).
Results: The number of patients randomized was 1021 in Trial-1 and 1019 in Trial-2. In Trial-1, the 40/30mg regimen of suvorexant was significantly superior to placebo on the patient-report and polysomnographic endpoints at Months 1 and 3. Mean differences from placebo in change from baseline at 3 months were: sTST = 19.7min, sTSO = -8.4min, sWASO = -6.9min, LPS = -9.4min, WASO = -22.9min. The results for the 40/30mg regimen of suvorexant were similar in Trial-2, except that the effect on LPS at 3 months was not significant, likely due to high placebo response. Mean differences from placebo in change from baseline at 3 months were: sTST = 25.1min, sTSO = -13.2min, sWASO = -8.9min, LPS = -3.6min, WASO = -29.4min. In both trials, the magnitude of improvement seen for some endpoints was dose-related. Both dose regimens of suvorexant were generally well-tolerated and without evidence of clinically important rebound or withdrawal on discontinuation.

Conclusions: Suvorexant improved sleep onset and maintenance over a 3-month treatment period in two pivotal Phase 3 trials, without evidence of clinically important rebound or withdrawal effects following discontinuation.

Support: Merck

LBA 5

HEALTH EFFECTS OF POOR SLEEP: AN INVESTIGATION OF NEW ONSET MENTAL ILLNESS IN RELATION TO SLEEP PATTERNS IN THE MILLENNIUM COHORT STUDY

Gehrman P[1], Seelig AD[2], Boyko EJ[3], Jacobson IG[2], Hooper T[4], Smith B[2], Ulmer CS[5], Gackstetter GD[6], Crum-Cianflone NF[2], Smith TC[2]

[1]Department of Psychiatry, Penn Sleep Center, University of Pennsylvania, Philadelphia, PA, USA, [2]Department of Deployment Health Research, Naval Health Research Center, San Diego, CA, USA, [3]Seattle Epidemiologic Research and Information Center, Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA, [4]Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, Bethesda, MA, USA, [5]Durham VA and Duke University Medical Centers, Durham, NC, USA, [6]Analytic Services, Inc. (ANSER), Arlington, VA, USA

Introduction: Poor sleep is common in military populations. Longitudinal studies in civilian population have found that poor sleep is a risk factor for new-onset mental illness, but this has

not been examined in military cohorts. Population-based studies are needed to determine how poor sleep affects the health of US military service members.

Methods: Using self-reported data from the Millennium Cohort Study collected from 2001-2008, we evaluated the association of baseline sleep duration and insomnia symptoms on the development of new-onset mental illness among deployers. Participants (n=15,204) completed assessments before and after deployment to Iraq or Afghanistan. Multivariable modeling techniques were used to estimate the odds of developing a mental illness, including posttraumatic stress disorder (PTSD), depression, and anxiety syndrome, while adjusting for relevant covariates including combat experience.

Results: Insomnia symptoms and short sleep duration were significantly associated with the development of new-onset PTSD and anxiety syndrome (all *P*-values <0.01). Trouble sleeping, but not sleep duration, was significantly associated with new-onset depression following deployment (*P* <0.01). The risk associated with insomnia symptoms was second in magnitude only to combat, with odds ratios ranging from 1.8 to 4.4.

Conclusion: Pre-deployment poor sleep is a significant risk factor for developing new-onset mental illness post-deployment. The degree of risk conferred by insomnia symptoms is substantial. Given that poor sleep is potentially modifiable, a focus on improving sleep patterns and encouraging healthy sleep habits is recommended to improve the health and well-being of service members.