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Late Breaking Abstracts

LBA 1

GABA neurons in the sublaterodorsal tegmental nucleus regulate REM sleep

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Introduction: The circuits that control REM sleep remain speculative. However, the sublaterodorsal tegmental nucleus (SLD) plays a well-documented role in controlling REM sleep, although it is unclear which type(s) of SLD neurons are involved. We previously showed, using both opto- and chemogenetic strategies, that glutamate SLD neurons play a central role in controlling both REM sleep and REM sleep atonia. But, published work indicates that GABA cells in the SLD are also involved in REM sleep control. Here, we used optogenetic strategies to determine if GABA SLD neurons function to control REM sleep.

Methods: To test the role of GABA SLD cells in REM sleep control, we optically manipulated them by driving AAV-mediated expression of eArch3.0 (an inhibitory opsin) in vGAT-Cre mice (n=10). Then, we bilaterally implanted optic fibers above the SLD, and implanted EEG and EMG electrodes to monitor sleep-wake states. In order to determine how GABA cells contribute to REM sleep, optical stimuli (i.e., green light pulses) were selectively delivered at REM sleep onset.

Results: First, we showed that eArch3.0 was preferentially expressed in GABA neurons, indicating that changes in REM sleep were mediated by GABA SLD cells. Second, we showed that inhibition of GABA SLD neurons immediately terminated episodes of REM sleep ($p<0.001$). Third, we showed that inhibition of GABA SLD neurons terminated REM sleep by promoting substantially longer periods of wakefulness ($p<0.01$), suggesting that GABA SLD neurons function to promote REM sleep.

Conclusions: Our loss-of-function data suggest that GABA neurons in the SLD are necessary to maintain REM sleep, and that silencing of these cells promotes wakefulness. However, it remains to be determined if activation of GABA SLD cells can trigger REM sleep. Our current findings, coupled with our previous work, suggests that both glutamate and GABA SLD neurons regulate REM sleep. Therefore, we propose that REM sleep is under the control of a local glutamate-GABA microcircuit that operates within the SLD.

LBA 2

Evening to morning increase in plasma tau levels following acute sleep loss in healthy young humans

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Introduction: Disrupted sleep is associated with an increased risk of Alzheimer disease (AD), and has been shown to increase cerebrospinal fluid levels of amyloid beta and tau. Our aim was to determine whether experimental sleep loss that mimics overnight shift work also alters diurnal levels of plasma-based biomarkers that are associated with Alzheimer disease.

Methods: In a randomized, 2-condition crossover study, 15 healthy young men participated in two standardized in-lab sessions with two different conditions during the second night: one night of normal sleep versus one night of overnight sleep loss. Levels of total tau and neurofilament light chain (NfL) were analyzed using ultrasensitive Single molecule array (Simoa) assays (Quanterix), in plasma samples obtained in the evening prior to, and in the morning after, each intervention.

Results: Acute sleep loss resulted in increased evening to morning levels of tau in plasma, which were significantly greater compared with the evening-to-morning change in the normal sleep condition (P=0.0062). However, no differences were found between the two conditions for the evening to morning change in plasma NfL levels (P=0.25).

Conclusion: Our exploratory study suggests that acute sleep loss results in increased plasma levels of tau, which has been proposed as a biomarker to assess subsequent risk of AD. Given that levels of NfL did not change as a result of acute sleep loss, this argues against acute neuroaxonal injury, and may instead be due to sustained neuronal activity, e.g. due to sustained neuronal activity during overnight wakefulness. Further studies are warranted to assess circadian modulation of these biomarkers, and the interplay with other lifestyle factors.
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LBA 3

Where to trim the hours, first or second half?

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Introduction: Sleep deprivation has been shown to have detrimental effects on health and cognitive performance. Here we compare the effects of reduced sleep on polysomnography (PSG), subjective adjective ratings, and neurobehavioral output in young healthy participants undergoing either an early sleep (ES) protocol or a late sleep (LS) protocol. These protocols were designed to test whether early or late short sleep provides better functioning in young adults.

Methods: We compared data obtained from two separate sleep deprivation protocols in which participants aged 20-30 (n=52) were subjected to 4hr sleep per night for three consecutive nights (ES: 11PM-3AM; LS: 3AM-7AM). PSG was used to record the electrophysiology of participants during wake and sleep periods. The recordings were scored by a sleep technologist. A visual analog scale displaying different adjectives describing moods such as "Happy," "Sleepy," was used to assess participants' subjective states every two hours during the wake periods throughout the two sleep deprivation protocols. The psychomotor vigilance task (PVT) was used to assess participants' vigilant attention during the waking hours. Mixed model analyses (SPSS) were used to account for inter-individual variations and assess differences from baseline for the metrics described.

Results: Although there were no differences in sleep electrophysiology, ES participants felt worse after deprivation, reporting feeling significantly more lonely ($p<0.001$) and less carefree ($p=0.007$). ES participants also performed worse on the PVT with significantly higher reaction time (lower reciprocal RT, $p=0.045$, lower reciprocal slowest 10% RT, $p=0.016$).

Conclusion: For healthy young adults, shortening sleep by staying up longer demonstrates better performance and mood outcomes than going to bed early and getting up after 4 hours. Further research is needed to explore the relationship between age, sex, and the timing of reduced sleep.

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LBA 4

Exquisite sensitivity of the human circadian system to light flashes

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Introduction: We have demonstrated previously that the human circadian clock can respond to a sequence of brief light flashes and that such responses can evoke changes in circadian phase that surpass those elicited from continuous light of the same intensity. The parameters of these light flashes, including their duration and intensity, were selected initially based on previous literature from rodents and continuous light exposure in humans. We here report on a systematic evaluation of these parameters and how they impact the circadian phase shifting of light flashes.

Methods: A group of healthy, young men and women (N=56) took part in two parallel 16-day studies. The first 14 days took place at home and were a circadian phase stabilization protocol in which participants maintained a regular sleep/wake cycle, as confirmed through actigraphy and sleep logs. The last two days occurred in a specialized time-isolation laboratory, during which the phase of the circadian pacemaker (salivary melatonin onset) was determined in constant routine conditions on evening 1 and 2; light exposure occurred between these two phase determinations on night 1. Light exposure consisted of 1 hour of a sequence of light flashes during enforced wake starting 2 hours after habitual bedtime. Flashes were presented every 15 seconds and varied either by duration (10 µsec → 10 sec, intensity fixed at 2200 lx) or intensity (3 lx → 9500 lx, duration fixed at 2 msec).

Results: Flash durations as brief at 10 µsec elicit significant phase shifts that are of similar magnitude to those observed after flash durations 6 log units longer (10 sec, i.e., 1 million times more light). Flash intensity exhibits a sigmoidal relationship with phase shifting, with a half-maximal shift observed at 8 lux and 90% of the maximal shift occurring after exposure to flashes as dim as 50 lux. None of the flash sequences caused acute suppression of melatonin.

Conclusion: When distributed as flashes, the human circadian system can be phase shifted by extraordinarily brief and dim light.

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