Circadian and Homeostatic Sleep Regulation: Measuring Clock - Homeostat Interactions

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Sleep is regulated by homeostatic and circadian processes [1]. In mammals, homeostatic sleep pressure is reflected by electroencephalogram (EEG) slow-wave activity (SWA, EEG power density between ~1 and 4 Hz) in undisturbed non-rapid eye movement (NREM) sleep. In all mammalian species investigated until now, not only the amount of sleep, but also SWA in NREM sleep increases after sleep deprivation. In several species a dose-response relationship between waking duration and subsequent SWA has been established and in humans taking an afternoon nap a predictable decrease in the nocturnal NREM sleep SWA was observed. Mathematical models predicting this phenomenon have been successfully applied in humans, rats and mice [2,3].

The circadian process is controlled by an endogenous pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus [4]. This pacemaker is thought to provide the sleep homeostat with a circadian framework. The circadian clock has a molecular basis for generating electrical activity rhythms in the SCN. This electrical neuronal activity can be recorded in vivo in freely moving animals [5]. Kept in constant conditions, this activity is high during the subjective day, the part of the animals rhythm that normally falls in the light period, and low during the subjective night.

Whether homeostatic and circadian regulation of sleep work independent or interact closely has been subject of many discussions. Homeostatic responses in sleep persist after circadian rhythmicity has been abolished by SCN lesioning,[6,7] and the circadian process can be manipulated by light in the morning without changing SWA [8]. It has, therefore, long been assumed that the timing of sleep is regulated independent from the need for sleep. However, more recent data indicate that there may be a continuous interaction between sleep homeostasis and the circadian clock. [9,10].

To get as close as possible to both processes, we set out to record both signals simultaneously in vivo in rats. All experiments were performed under the approval of the Animal Experiment Committee of the Leiden University Medical Center according to the Dutch law on animal experiments. The animals were equipped with electrodes recording EEG and EMG, to determine vigilance states and SWA in NREM sleep, together with electrodes recording SCN neuronal activity. Before the experiments, the animals were kept in constant darkness for at least a week, to exclude direct influences of light on behaviour, and all signals were recorded simultaneously on the same computer. In addition, drinking behaviour was recorded to obtain an estimate of rest-activity behaviour.

From baseline recordings it became clear that SCN neuronal activity changed under influence of vigilance state changes. Activity was increased during waking and REM sleep and decreased during NREM sleep. In addition, there was a clear negative correlation between EEG SWA and SCN neuronal activity. Suppression of SWA by slow-wave deprivation resulted in increased SCN neuronal activity, whereas REM sleep deprivation resulted in decreased activity. Total sleep deprivation caused the predicted increase in SWA during subsequent NREM sleep, and simultaneously a long term suppression of SCN neuronal activity. The latter lasted as long as the increase in SWA needed to recover [11,12].
Neuronal activity in the SCN clearly depended on the vigilance state of the animals, and deeper NREM sleep was accompanied by lower SCN neuronal activity. The data suggest an interaction between sleep homeostatic mechanisms and the circadian clock in which the clock receives continuous information about the status of the homeostatic process. Our present work is concentrating on possible consequences of this interaction on the

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circadian system, particularly when homeostatic sleep pressure is increased due to sleep loss. Sleep deprivation seems to diminish this functioning, as it was shown that the circadian clock phase shifting response to light is attenuated in sleep deprived animals [13,14]. With our techniques we are trying to resolve the neurophysiological mechanism behind this phenomenon and to investigate whether this can be reversed by pharmacological means.

1. Daan, S., Beersma, D.G.M., Borbely, A.A. (1984) Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol* **246**, R161-R178.

2. Yasenkov, R., Deboer T. (2012) Circadian modulation of sleep in rodents. *Progress in Brain Res* **199**, 203-218.

3. Deboer, T (in press) Behavioral and electrphysiological correlates of sleep and sleep homeostasis. *Curr Top Behav Neurosci.*

4. Meijer, J.H., Rietveld, W.J. (1989) Neurophysiology of the suprachiasmatic circadian pacemaker in rodents. *Physiol Rev* **69**, 671-707.

5. Meijer, J.H., Watanabe, K., Schaap, J., Albus, H., Detari, L. (1998) Light responsiveness of the suprachiasmatic nucleus: long-term multiunit and single-unit recordings in freely moving rats. *J Neurosci* **18**, 9078-9087.

6. Mistlberger, R.E., Bergmann, B.M., Waldenar, W., Rechtschaffen, A. (1983) Recovery sleep follwing sleep deprivation in intact and suprachiasmatic nuclei lesioned rats. *Sleep* **6**, 217-233.

7. Tobler, I., Borbely, A.A., Groos, G. (1983) The effect of sleep deprivation on sleep in rats with suprachiasmatic lesions. *Neurosci Lett* **42**, 49-54.

8. Dijk, D.J., Beersma, D.G.M., Daan S. (1989) Bright morning light advances the human circadian system without affecting NREM sleep homeostasis. *Am J Physiol* **156**, R106-R111.

9. Edgar, D.M., Dement, W.C., Fuller, C.A. (1993) Effect of SCN-lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci* **13**, 1065-1079.

10. Achermann, P., Borbely, A.A. (1994) Simulation of daytime vigilance by the additional interaction of a homeostatic and a circadian process. *Biol Cybern* **71**, 115-121.

11. Deboer, T., Vansteensel, M.J., Detari, L., Meijer, J.H. (2003) Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci* **6**, 1086-1090.

12. Deboer T., Detari, L., Meijer, J.H. (2007) Long term effects of sleep deprivation on the mammalian circadian pacemaker. *Sleep* **30**, 257-262.

13. Mistlberger, R.E., Landry, G.J., Marchant, E.G. (1997) Sleep deprivation can attenuate light-induced phase shifts of circadian rhythms in hamsters. *Neurosci Lett* **238**, 5-8.

14. Challet, E., Turek, F.W., Laute, M, Van Reeth, O. (2001) Sleep deprivation decreases phase-shift responses of circadian rhythms to light in the mouse: role of serotonergic and metabolic signals. *Brain Res* **909**, 81-91.