Does the SCN Regulate More Than Sleep Timing?

Comment on Easton A et al. The suprachiasmatic nucleus regulates sleep timing and amount in mice. *SLEEP* 2004; 27(7):1307-18.

Martha U. Gillette, PhD

Department of Cell and Structural Biology, University of Illinois at Urbana-Champaign and University of Illinois College of Medicine

PRINCIPLES THAT GOVERN SLEEP REGULATION HAVE SEEMED UNCOMPLICATED—sleep comes when we are weary, and during a predictable time of the 24-hour cycle, at nighttime for you and me. Observation of the natural world emphasizes the ubiquity of these two basic features of sleep regulation. Early studies that probed sleep regulation suggested that two discrete brain systems converge in generating sleep observed. From them, Borbely and colleagues developed the two-process model, which posits that sleep is regulated by process "C", which patterns the occurrence of sleep and vigilance states with respect to the circadian cycle, and by process "S", a homeostatic drive that builds up during the active phase and is discharged by restorative qualities of sleep.[4,5] Sleep deprivation, which effectively extends the active phase beyond the normal set-point for sleep, increases pressure on the recovery phase, prolonging it without commensurate effects on circadian timing. Thus, the circadian system (C) has been thought only to gate the occurrence of the recovery process (S).[5] Since these mathematical models were proposed, considerable supportive evidence has accumulated both in humans and animals.[6,9,24]

Whereas the recovery process of sleep involves multiple brain sites, control of the circadian process resides only in one locus, the suprachiasmatic nucleus (SCN) of the hypothalamus.[23] Discrete lesions of the paired SCN, alone, abolish patterned occurrence of a host of metabolic, endocrine, and physiological processes that subserve daily rhythms of behaviors.[17,22] The cycle of sleep and wakefulness is among the circadian rhythms profoundly disrupted by SCN lesion, with attendant redistribution of sleep.[14,18] The SCN possesses endogenous near-24-hour timekeeping ability,[20] such that transplants of SCN tissue can restore circadian rhythms to SCN-lesioned hosts.[21] Hence, the SCN has become recognized to be the pacemaker or clock that generates temporal circadian organization of processes within the brain and body and synchronizes them to occur appropriately during day and night. Based upon damage:deficit relationships, the SCN has been determined to be the source of the circadian timing signal(s) for the occurrence and consolidation of sleep and wakefulness.

This timing function of the SCN in sleep regulation has been accepted widely for some time, however, recent studies suggest that this role may be defined too narrowly. A decade of progress in cracking the SCN's timekeeping code has revealed that the near-24-hour rhythm emerges from dynamic feedback loops of transcription-translational events involving a limited number of 'clock genes' essential to timekeeping.[15] Mutant and transgenic organisms bearing targeted alterations or disruptions in essential clock elements have proven to be powerful models for probing the role(s) of specific genes in SCN function, and the processes it regulates. Mice with genetic alterations for different clock genes exhibit predicted changes in the temporal patterning and consolidation of sleep/wakefulness.[13,19,25] However, they also show a range of changes in other sleep parameters, including sleep amount or intensity, depending on the gene and the conditions. Clock genes are expressed not only in the SCN, but in other brain regions, as well. Whether these changes in sleep parameters are caused by altered SCN function or action at other brain sites remains to be determined.

A significant new study by Easton et al.[11] revisits the issue of selectivity of the SCN regulatory signal by testing the hypothesis that the SCN may regulate aspects of sleep *beyond* timing of sleep/wake consolidation. The authors carefully evaluated baseline sleep and recovery from sleep deprivation in intact *vs.* SCN-lesioned C57Bl/6J mice. SCN lesion resulted in increased baseline NREM sleep, and caused attenuated NREM sleep increase after sleep deprivation, but had no effect on NREM sleep EEG delta power after sleep deprivation. While these mice had an altered waking:NREM sleep ratio, they exhibited no change in REM sleep regulation. This is remarkable because of the general notion that especially REM sleep expression is governed by circadian factors. They conclude that the SCN/clock genes influence various aspects of the sleep-wake cycle, including total sleep time, even while having no effect on the sleep homeostatic process as defined by NREM delta power in the EEG. The significance of this change in baseline amount of sleep is unresolved, but may reside in the alteration of SCN influence on sleep processes. However, the issue of what constitutes a change in homeostasis is not simple.[8] The implications of this study need to be examined by dose-response studies that further characterize the sleep homeostat.

In aggregate, this study of sleep in SCN-lesioned mice together with the changes reported previously in sleep parameters of mice with altered clock genes raise the provocative possibility that the influence of the SCN on sleep may be broader than is appreciated presently. The most noteworthy finding by Easton et al.[11] is that the SCN may influence not only timing but also the amount of baseline sleep. Previously, Edgar et al.[12] reported an increase in total sleep time in SCN-lesioned squirrel monkeys. From this, they concluded that the SCN primarily promotes wakefulness, and, since previously no increase in total sleep time had been reported after SCN lesion in rodents, they predicted a

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Address correspondence to: Martha Gillette, PhD, University of Illinois at Urbana – Champaign, Department of Cell & Structural Biology, B107 Chemistry & Life Sciences Lab, 601 S. Goodwin Avenue, Urbana, IL 61801, Phone: (217) 244-1355, Fax: (217) 333-4561, Email: mgillett@uiuc.edu

difference between the role of the SCN in sleep regulation between primates and rodents. Rather, the present study supports greater similarity of SCN function. Further, these data together with those of Mistlberger et al.[16] and Dijk et al.[10] indicate that the SCN may promote sleep at one time of day and wakefulness at another, potentially via a changing balance of output signals. This could have significant impact if circadian rhythmicity interacts with relative homeostatic sleep pressure in regulating sleep propensity.[8] Additionally, emerging evidence indicates that communication between the circadian system and sleep may be bidirectional. The SCN receives signals from brain stem and basal forebrain regions critical to sleep regulation, which may provide direct feedback concerning the states of sleep/wakefulness and degree of sleep loss.[1-3,7] In view of the rapidity of reports of new relationships between the SCN and sleep processes, we would do well to push on to determine the extent and level(s) (molecular/genetic to anatomical) of links between the circadian clock and the range of aspects of homeostatic sleep-wake characteristics. By taking a broad view of the possible convergences, we anticipate discovery of new linkages between the SCN and sleep.

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