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FROM SLOW WAVES TO SLEEP HOMEOSTASIS: NEW PERSPECTIVES

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INTRODUCTION

Sleep is a regulated process. As early as 1937 electrophysiological concomitants of sleep regulation have been described. Blake and Gerard (9) reported that sleep intensity as specified by the arousal threshold is associated with the level of slow waves in the sleep EEG. Low-frequency high-amplitude activity typically predominates in the first part of sleep and then declines as sleep becomes shallower. Slow waves are exacerbated by sleep deprivation and decreased by excess sleep (see ref. 11 for early references). Kleitman was well aware of sleep regulation depending on prior sleep and waking, a facet that now is being referred to as sleep homeostasis (10, 13). In the beginning of the century, homeostatic sleep regulation was viewed in the context of humoral theories of sleep (30, p.351). It was assumed that sleep may be the result of the accumulation of end-products of metabolism or other substances (toxins) in the tissues. It is interesting to note that after presenting these theories extensively, Kleitman dismissed the concept for the following reason (30, p. 354):

'A strong argument against the toxin theories is that, on staying awake for several days, one does not get continuously sleepier but follows a periodic curve of greater sleepiness at night and lesser sleepiness in the daytime.'

We know now that these puzzling variations in sleep propensity can be accounted for by the interaction of two different processes.

Two-process model.

According to the two-process model (11, 19), sleep architecture and sleep propensity are determined by a history-dependent homeostatic process and a circadian process. The interactions between the two processes have been formalized in the model (see ref. 12 for a recent overview). The model, originally proposed to account for sleep regulation in the rat, postulates that a homeostatic process (Process S) rises during waking and declines during sleep. S interacts with a circadian process (Process C) that is independent of sleep and waking. The time course of Process S was derived from EEG slow-wave activity (SWA; spectral power in the 0.75-4.5 Hz band). Various aspects of human sleep regulation were accounted for first by a qualitative version of the model (11). Subsequently, an elaborated, quantitative version had Process S vary between two thresholds that are modulated by a circadian process (19). Diverse phenomena such as the recovery

from sleep deprivation, circadian phase-dependence of sleep duration, sleep during shift work, sleep fragmentation during continuous bedrest, and internal desynchronization in the absence of time cues could be successfully simulated. Achermann and colleagues elaborated the homeostatic facet of the model by incorporating the ultradian dynamics of SWA which is generated by the nonREM-REM sleep cycle (1, 2). Then a parameter estimation in conjunction with an optimization procedure was performed on a large data base (26 nights from 16 subjects; 3). A sensitivity analysis revealed the model to be robust to small changes of the parameter values. The parameter values estimated from the baseline set were then used to simulate independent data sets from three experimental protocols in which the timing and duration of sleep differed. A close fit was obtained between the simulated and empirical SWA data, and even the occasional late SWA peaks during extended sleep ('resurgence of slow wave sleep') could be reproduced. The relatively simple model based on the homeostatic Process S proved effective in accounting for the time course of SWA in a variety of paradigms. REM sleep was not yet incorporated in the model itself but introduced as an external parameter.

Simulation of sleep in short and long sleepers.

In a recent application of the model the global time course of SWA was simulated in habitual short and long sleepers (4). The study was designed to examine whether the large differences in sleep duration were due to different parameters in the sleep regulatory processes. The system was challenged by sleep deprivation. It turned out that one and the same model could predict the level of SWA for both baseline and recovery sleep. In accordance with the model, the enhancement of SWA after sleep loss was considerably larger in long sleepers (47%) than in short sleepers (19%). By restricting their sleep duration, short sleepers chose to live under a higher "non-REM sleep pressure" than long sleepers. However, the analysis demonstrated that there was no need to assume different time constants for the homeostatic Process S. Differences between the two groups were recently reported also for the wake EEG (7). Average power in the frequency range of theta – low alpha calculated for a 24-h waking episode was higher in short sleepers than in long sleepers. Since power in this frequency range is known to reflect sleep propensity, the results support the conclusion that short sleepers live at a higher level of 'sleep pressure'.

Simulation of animal sleep.

The homeostatic facet of the two-process model was used to simulate also animal data. In a simulation of rat sleep, Process S was assumed to decrease exponentially in nonREM sleep, and increase according to a saturating exponential function in waking and REM sleep (23). In a 96-h experiment SWA was calculated for consecutive 8-s epochs of a 24-h baseline period, a 24-h sleep deprivation period, and a 48-h recovery period. This extensive data set served as the basis for the simulation. After optimizing the initial value and the time constants of S, a close fit was obtained between the hourly mean values of SWA and Process S. In

particular, major changes of SWA could be reproduced such as the biphasic time course during baseline, the initial increase after sleep deprivation and the subsequent prolonged negative rebound.

A similar approach was recently taken for simulating sleep regulation in mice (28). After a parameter estimation based on baseline recordings, the effect of 6-h sleep deprivation on SWA was simulated and also here a good fit was obtained between empirical and simulated data.

In summary, it has been demonstrated that the homeostatic sleep process can be successfully simulated in both humans and animals.

Validation of the model by the forced desynchrony protocol.

The basic assumption of the two-process model is that two separate, constituent processes determine the main aspects of sleep regulation. For a long time it was difficult to test the model because the two facets could not be independently manipulated. The forced desynchrony protocol proved to be an ingenious paradigm for disentangling the two processes. Experiments were performed in which subjects were scheduled to a 28-h sleep-waking cycle (22). During one third of the cycle the lights were switched off and the subjects were encouraged to sleep. Since the free-running circadian rhythm has a period of 24.1-24.2 h (18), sleep episodes occurred at different circadian phases. The data showed that maximal sleep propensity coincided closely with the nadir of the circadian rectal temperature rhythm. The rising limb of rectal temperature was paralleled by a gradual decrease in sleep propensity, which reached its lowest level 16 hours after the temperature minimum. This phase corresponds to the habitual bedtime under entrained conditions. When sleep was initiated at this phase, sleep continuity during the following hours was high, whereas sleep initiation after the temperature minimum gave rise to disrupted sleep. An important result of this experiment was that changes in SWA could be largely accounted for by the homeostatic (i.e. sleep-waking dependent) factor, whereas the influence of the circadian rhythm was negligible. This result confirms the major tenet of the two-process model. In contrast to SWA, other EEG variables such as spindle frequency activity, and the REM sleep/nonREM sleep ratio were determined by both homeostatic and circadian factors. The sleep-related disinhibition of REM sleep was another result that confirmed a prediction of the initial version of the model (11).

Markers of sleep propensity in the waking EEG.

It has become increasingly apparent that sleep propensity is reflected in the waking EEG. In humans, power in the theta band is closely linked to the duration of waking (8, 44). However, in contrast to SWA in the sleep EEG, theta activity is not determined predominantly by homeostatic factors but also by the circadian rhythm. The changes of the homeostatic component have been approximated by a saturating exponential function (5, 6, 15). Interestingly, the time constant is similar to the one of Process S that was derived from the changes of SWA in the sleep EEG. This suggests that theta activity in the wake EEG and SWA in the sleep EEG

may be related, and may even represent two facets of a common underlying process. In support of this assumption, the rise rate of theta power during prolonged waking exhibited a positive correlation with the increment of SWA in the first nonREM sleep episode between baseline and recovery sleep (22a). Could theta activity in the waking EEG reflect a sleep-like recuperative process that occurs during the wake state? This possibility will require experimental scrutiny.

In animals, SWA is the index of sleep propensity in the wake EEG (14, 24, 28). Thus a rat subjected to 24-h sleep deprivation exhibits a rising level of slow waves even though it is active and engaged in different behaviors (14, 24). Again the question of a possible functional significance arises. It is conceivable that the small increment of SWA in recovery sleep between 12-h and 24-h sleep deprivation (39), is due to the compensatory action of slow waves during waking. The failure to analyze the wake EEG precluded the recognition of slow waves in prolonged sleep deprivation experiments (34). The moderate rebound of slow waves during recovery sleep was puzzling and appeared not to support the tenets of the two-process model. However, by disregarding major changes in the wake EEG only a partial picture is obtained which is prone to erroneous interpretations. If a partial compensation of a sleep debt may occur during waking, it is impossible to perform a prolonged total sleep deprivation. For investigating sleep regulation it is therefore mandatory to analyze the EEG during both sleep and waking.

Slow-wave activity and sleep continuity.

Slow waves are a marker of sleep homeostasis. However, are they actually associated with the sleep process or do they represent mere epiphenomena? In animals and humans, sleep is not continuous but is repeatedly interrupted by brief awakenings. Sleep continuity can be quantified by determining the frequency of such short waking episodes. Animal studies showed a close correlation between SWA and sleep continuity (24, 28, 40). This correlation was present even during the phase of 'negative rebound' in which SWA declines below baseline, and which follows upon the initial positive rebound (23, 24).

A wake-like process during hibernation?

Some rodents are capable of lowering periodically their metabolism and entering into a prolonged sleep-like state. Hibernating species such as the ground squirrel reduce their body temperature to a level that is just above the freezing point. However, the hibernation period is not maintained throughout the winter season but is periodically interrupted by brief euthermic episodes. The Djungarian hamster exhibits a milder form of hypometabolism. On some winter days it enters daily torpor for several hours, its body temperature declining to the level of room temperature. Since natural sleep is associated with a slight decline of metabolism and body temperature, it is informative to compare it to the more prominent states of hypometabolism. Studies yielded two unexpected observations (20, 21, 45): First, animals emerging from hibernation spent a large part of their euthermic episode in sleep. Second, sleep exhibited a high initial level of SWA, similar to

recovery sleep after sleep deprivation. Moreover, the enhancement of SWA was related to the duration of the episode spent in hibernation or daily torpor. This indicates that hypometabolic states are functionally more closely related to waking than to nonREM sleep because they appear to give rise to a sleep debt. Thus the reduction of metabolism does not arrest the process that underlies the enhancement of slow wave propensity.

Sleep as a local, use-dependent process.

In addition to its global aspect, sleep may have also a local facet. The hypothesis of a use-dependent regional modulation of sleep was examined in an experiment in which the cortical projection area of the dominant hand was selectively activated during the waking hours preceding sleep (29). The sleep EEG recorded from the central lead overlying the somatosensory cortex exhibited a shift in power towards the contralateral side during the first hour of sleep. Such changes were significant in the low-frequency range and were restricted to the central derivation.

A regional facet of sleep could be expected to emerge also during normal sleep since cortical areas are involved to a varying extent in waking activities. A regional analysis of the sleep EEG showed a prevalence of slow waves at frontal EEG derivations during the initial part of sleep, a regional difference that vanished as sleep progressed (46, 47). This finding may indicate that a putative recuperative process of sleep of which slow waves are a marker, occurs at a higher rate in frontal areas than in other areas. This interpretation is consistent with reports that a sleep deficit impairs primarily high-level cognitive skills which depend on frontal lobe function (25, 26).

Sleep homeostasis as a key for identifying antecedents of sleep.

Sleep-like behavioral states are not a prerogative of vertebrates but exist also in invertebrates (e.g. moth, bee, crayfish) (38). However, it is fairly recent that the regulatory aspects of sleep have been utilized to explore the evolution of sleep. In analogy to sleep deprivation in mammals, two invertebrate species, the scorpion and the cockroach, were "rest-deprived" by keeping the animals active for several hours (41, 42). Both species exhibited an increase in rest episodes after these manipulations. The results are consistent with an early appearance of homeostatic regulatory mechanisms that compensate excessive activity by a prolonged sleep-like resting state. In recent experiments, Drosophila (27, 37) and honey bees (36) were subjected to rest-deprivation. Also in these insects a 'rest rebound' was observed.

The experimental approach that is based conceptually on mammalian sleep homeostasis, can be extended to investigate changes at the molecular genetic level. Techniques such as subtractive hybridization and differential display can be employed to determine, at least in principle, all the genes that modify their expression between sleep and waking (33, 35). When a rat was either spontaneously awake or sleep deprived for a few hours, the expression of c-fos, NGFI-A and other immediate early genes was high in cortex, hippocampus, and other brain regions (17, 31,

32). In a systematic survey of gene expression in the brain of sleeping and waking animals using differential display it was found that waking is associated with levels of mitochondrial mRNA that are higher than in sleep by 20-30% (16, 43). This is a large change considering that these mRNAs are expressed ubiquitously and at high levels. It is possible that this increase may represent a local regulatory response of mitochondria. Studies are in progress to see whether the changes in gene expression observed in Drosophila (37) can be compared to those identified in mammals.

CONCLUSION

Since Kleitman's classic sleep studies, considerable advances were made in our understanding of sleep. Nevertheless, its basic mechanism and function remains little understood. A useful approach has been to deduce the major regulatory properties of sleep from the response of SWA, a salient sleep EEG variable, to various experimental challenges. The two-process model served as a conceptual framework. Due to the recent spectacular progress in elucidating the generation of circadian rhythmicity, attention has shifted away from sleep homeostasis. Some have advocated emulating in sleep research the research strategy that had proved successful in rhythm research. However, this advice may be questionable in view of the fact that sleep processes have a much higher degree of complexity than circadian rhythms. Circadian factors appear to act merely as modulators of sleep processes and are not involved in their basic generating mechanism. Sleep homeostasis persists even in the absence of circadian rhythmicity (13).

One of the aspects that are in common to sleep and circadian rhythm research, is the search for homologies on a molecular genetic level between simple organisms and mammals. Can sleep-like processes be identified in species that emerged early in evolution and will they be ultimately found to be present even within a single cell as has been the case for circadian rhythmicity? According to Kleitman (30, p. 346) Pavlov has anticipated this possibility in 1935:

To a member of the audience who wondered why such an important function as sleep should not have a center, Pavlov repeated: "It is very simple. Inhibition and sleep exist in every cell. Why then should there be a special group of cells?"

Now, in the beginning of a new century, we are approaching this problem on a somewhat similar avenue with the help of molecular genetics, a field whose explosive development and huge significance in neuroscience could not have been imagined by either of the two pioneers.

SUMMARY

EEG slow waves are the epitome of deep nonREM sleep. The level of slow-wave activity (SWA; defined as spectral power in the 0.5-4.5 Hz band) in the initial part of sleep is determined by prior sleep and waking, and thereby represents a marker

of a homeostatic sleep regulating process (Process S). Models based on SWA were successful in simulating sleep architecture in a variety of experimental protocols. SWA is an exceptional sleep variable in that it is little influenced by circadian phase and variations of the photoperiod. There is recent evidence that it is not waking per se but the absence of sleep, which engenders a rise in sleep propensity. Thus animals emerging from the hypometabolic states of hibernation or daily torpor exhibit an increase in SWA akin to sleep deprivation. Recent human studies showed SWA to be a marker of a local, use-dependent facet of sleep. Selective activation of specific cortical areas during waking enhanced SWA over the activated region during sleep. A frontal predominance of power in the 2-Hz band was documented in the initial part of a normal sleep episode. Sleep homeostasis may be a valuable concept for exploring the evolutionary origin of sleep. Thus 'rest homeostasis' has been demonstrated in invertebrate species, and the search for homologies of rest and sleep on a molecular genetic level has begun. Conceptualizing and characterizing sleep as a regulated process may eventually shed light on its function.

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