Insomnia and the 2-Process Model of Sleep Regulation: Etiopathogenic Considerations

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This article summarizes the current state of knowledge regarding sleep regulatory mechanisms and describes how homeostatic and circadian principles are thought to interact to attain consolidated sleep episodes at night and consolidated episodes of wakefulness during the day. On the basis of these concepts, it is possible to distinguish 3 categories of possible causes of insomnia. These categories and ideas concerning the development of therapeutic strategies are presented, leading to the conclusion that sleep regulatory mechanisms are insufficiently explored in insomnia research.

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The fact that we do not know the functions of sleep constitutes a major problem for the diagnosis and treatment of insomnia. A complaint about severely disturbed sleep gives no clue as to which physiologic processes are impaired. Even knowing that chronic pain, for example, is the main cause of the sleep disturbance would be of little help, because if the pain cannot be treated, there is as yet no way to compensate for the consequences of the disturbed sleep resulting from the pain. However, even though the functions of sleep are unknown, knowledge of the regulatory mechanisms involved is increasing due to data obtained using an electroencephalogram (EEG).[1] This knowledge may sometimes yield additional insights into the pathologic processes and provide ideas for a therapeutic approach. The purpose of this article is to present an overview of the current view on sleep regulatory mechanisms using data from the EEG and to discuss the impact of this view on diagnosis and treatment of insomnia.

THE 2-PROCESS MODEL OF SLEEP REGULATION

The generally accepted global view on regulating the timing of sleep is that it results from an interaction between a homeostatic process and a circadian process.[2,3] The idea is that the "need for sleep" (subsequently referred to as *process S*) increases monotonically during prolonged wakefulness, while it decreases during deep non–rapid eye movement (NREM) sleep. In this way, process S is kept close to an average value, thereby demonstrating homeostatic regulation. The timing of the switch from wakefulness to sleep and vice versa is largely influenced by the subject. However, time of day is also a factor, preventing sleep-wake alternations from randomly drifting and occurring at unpredictable times, which would be disruptive since humans are active primarily during the day.

In the 2-process model, the influence of time of day is suggested to be a result of the impact of the circadian pacemaker, located in the suprachiasmatic nuclei of the hypothalamus. The circadian pacemaker is thought to regulate the level of 2 thresholds to process S: 1 for the transition from wakefulness to sleep and 1 for the transition from sleep to wakefulness (Figure 1).[3] The 2 oscillating thresholds are thought to run in parallel, and together they are called *process C*.

The 2-process model summarizes other influences on sleep regulation by proposing that conscious decisions exert an influence on the timing of sleep through short-lasting modifications of process C. Obviously, the same mechanisms that allow the engagement in activities to increase the level of vigilance, and thereby the level of process C, also apply to pain. More generally speaking, the concepts of the 2-process model of sleep regulation would apply only to insomnia if the set of influences on vigilance would also include those influences not under conscious control.

According to the structure of the 2-process model for the timing of sleep, pathologic sleep timing may result from (1) disturbances in process S, (2) disturbances of the circadian variation in process C, or (3) disturbances in the level of process C (which could also be considered disturbances in the regulation of vigilance).

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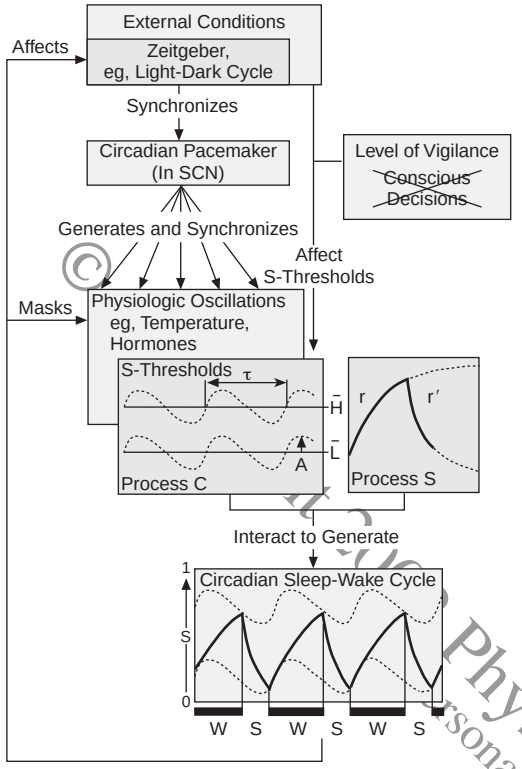
Figure 1. Scheme of the 2-Process Model of Sleep Regulation[a]



[a]Modified from Daan et al.[3] Abbreviations: A = amplitude, $\bar{H}$ = mean upper sleep threshold, $\bar{L}$ = mean wake threshold, Process C = oscillating thresholds of wakefulness to sleep and sleep to wakefulness, Process S = need for sleep, r and r′ = rate of change in need for sleep, S = sleep, SCN = suprachiasmatic nuclei, W = wake.
Symbol: τ = period of sleep-wake alternation.

EEG slow-wave activity (SWA) responds to changes in sleep timing in much the same way as would be expected for the rate of change of process S.[4,5] Thus, the 2-process model is not just a global theoretical framework. SWA data have been collected to specify the 2-process model in such a way that it can be used for quantitative predictions of specific experiments.[3] The fit between data and predictions in turn has served as a test for the quality of the 2-process model.[4,6–8]

The same, however, does not apply to process C. Until now, no physiologic process has been found to perfectly mimic the expected behavior of the thresholds. These thresholds have only been estimated indirectly from experiments with spontaneous sleep termination in healthy subjects.[3]

EEG SWA

In healthy adult subjects, sleep alternates in cycles of about 100 minutes between NREM sleep and rapid eye movement (REM) sleep. Successive NREM episodes tend to decrease in intensity; the acoustic threshold for awakening gradually decreases, which is paralleled by a gradual reduction in the amplitude of delta waves (oscillations in the 0.5–4.0 Hz range) in the sleep EEG.[9] Computer analysis of the sleep EEG can provide the quantification of the power of the delta waves, a measure proportional to the square of the amplitude of SWA. Dijk et al.[8,10] have demonstrated that SWA is a strictly regulated variable. Experimental disturbance of sleep for part of the night, in such a way that the subject did not wake up but continued sleeping with reduced SWA, revealed rebound SWA afterward. The magnitude of the rebound could be predicted from the loss of SWA during the experimental disturbance. This suggests that a certain "need" for SWA develops in the course of wakefulness, which is dissipated during sleep. Naps scheduled in the course of the day revealed increasing amounts of SWA at longer intervals of prior wakefulness,[7] which is consistent with this proposition.

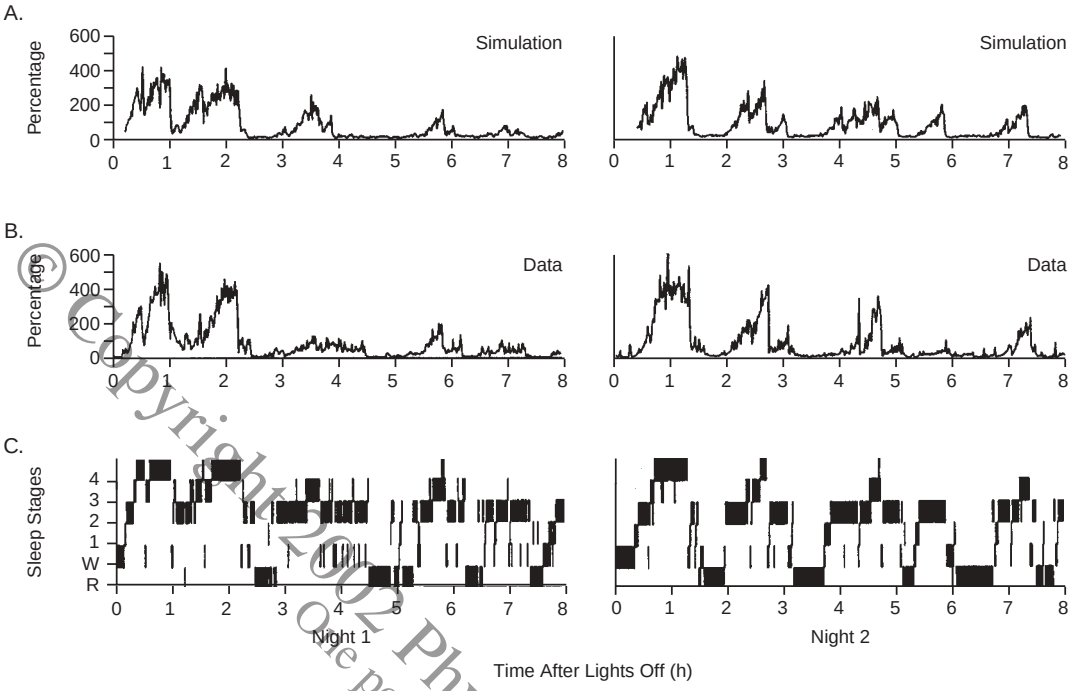
In subsequent studies,[11] the detailed course of SWA in sleep recordings of healthy subjects was quantified. The time it takes for SWA to rise to maximum values in each of the various NREM episodes was measured, and the levels to which SWA rises as well as the time it takes to get back to the low values during REM sleep and during EEG arousals were determined. This was done for sleep episodes scheduled at normal sleeping hours, but also after various amounts of sleep deprivation. A mathematical model was developed,[4] which was meant to predict the minute-by-minute course of SWA during sleep of healthy subjects from the measured sequence of wakefulness, NREM sleep, and REM sleep. Figure 2 shows some of the results. There is a reasonable correspondence between data and simulations, suggesting that major aspects of the mechanisms of SWA regulation are included in the mathematical model. What is also clear, however, is that the computer program needs to receive information about the timing of NREM sleep, REM sleep, and wakefulness. Unfortunately, as yet, the timing of sleep states cannot be predicted in sufficient detail.

Etiopathogenesis of Insomnia

As stated earlier, the 2-process model generates 3 categories of possible causes for insomnia: (1) disturbances in process S, (2) disturbances of the circadian variation in process C, and (3) disturbances in the regulation of vigilance. It is important to distinguish between these categories, because they probably require different treatment strategies.

Disturbances in process S. When disturbances in process S are the reason for insomnia, only 2 possible causes are considered: (1) the buildup of process S during wakefulness could be deficient, leading to sub-upperthreshold values of the need for sleep at the expected time of sleep onset and, hence, to sleep-onset insomnia, or (2) the decline of process S during sleep could be too fast, reaching the lower threshold earlier than desired and, hence, lead-

Figure 2. Simulation of Slow-Wave Activity (SWA) Profile (A), Empirical SWA (B), and Sleep Stages of 2 Nights of Sleep (C)[a]



[a]Adapted with permission from Achermann et al.[4] The SWA profiles were normalized with respect to the mean value of the first 7 hours of sleep.

ing to early morning awakening. Both options have been discussed in the context of sleep disturbances in depressive disorders[12,13] but not in other types of insomnia. Sleep deprivation, a way to increase process S to higher values, may also improve mood in most depressed patients.[14] However, the increase of process S in response to sleep deprivation is very similar in responding and nonresponding depressed patients, and the increase is also very similar to the increase of process S in healthy subjects.[15] Apparently, if a causal link exists between process S and mood, this does not hold for all depressed patients.

Disturbances of circadian variation (process C). When disturbances of the circadian variation of process C are the cause of insomnia, sleep is being attempted at the wrong internal time, such as with jet lag. Because the circadian window for consolidated sleep is very narrow in elderly people,[16] a disturbed-phase position of the circadian pacemaker in this population could be one of the causes of insomnia. Because circadian phase shifts can be induced by exposing someone to properly timed bright light, light therapy is a possible treatment.

Disturbances in other processes. Finally, when other processes, such as conscious decisions or increased levels of vigilance, are causing insomnia, process S and process C are only secondarily involved. They are changed in response to vigilance-induced wakefulness and/or accompanying altered light exposure.

CONCLUSION

Because increased levels of vigilance can affect the thresholds of process S and the phase angle of process C (through behavioral changes), it can be difficult to ascertain to which of the 3 categories of possible causes of insomnia a specific disorder belongs. To the best of my knowledge, this type of labeling has never been attempted. Nevertheless, the current mathematical formulation of the 2-process model of sleep regulation should allow for the distinction between these causes. For that purpose, a set of sleep EEGs recorded from a group of patients belonging to the diagnostic insomnia subgroup under study should be simulated according to the procedure described by Achermann et al.[4] Means and standard deviations of the resulting parameter values should be compared with those of an appropriate control group. Although it is uncertain whether the simulations will be sufficiently sensitive to detect small differences in the circadian phase, it is quite possible to attribute specific changes in other parameter values to specific sleep disorders. Because parameters of the 2-process model are linked to specific phenomena of SWA profiles, including rise time of SWA after sleep onset and decay time of SWA at the onset of arousals or REM sleep, the simulation of sleep profiles of diagnostic subgroups of insomnia may generate ideas explaining the cause of these sleep problems.

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