PRINCIPLES AND PRACTICE OF

Sleep Medicine

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Sleep Homeostasis and Models of Sleep Regulation

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The level of electroencephalographic (EEG) slow wave activity (SWA) is determined by the duration of prior sleep and waking. SWA is a marker of nonrapid eye movement (NREM) sleep intensity and may serve as an indicator of NREM sleep homeostasis. Power in the range of sleep spindles (spindle frequency activity, SFA) shows in part an inverse relationship to SWA. This observation can be accounted for by neurophysiological data. Thalamocortical neurons exhibit oscillations in the range of sleep spindles at an intermediate level of hyperpolarization (corresponding to superficial NREM sleep), and slow oscillations at a high level of hyperpolarization (corresponding to deep NREM sleep). Although the homeostatic NREM sleep process is largely independent of circadian factors, it interacts with the circadian rhythm of sleep propensity.

The two-process model of sleep regulation is based on the homeostatic process S and the circadian process C. Advanced versions of its homeostatic part can simulate the SWA pattern for a variety of experimental schedules. Essential aspects of the model have been validated by results from forced desynchrony protocols. Other models include the two-oscillator model, the reciprocal interaction models, and combined models. The incorporation of rapid eye movement (REM) sleep homeostasis is still at an early stage.

There is recent evidence for a local, use-dependent facet of sleep regulation. This concept is derived from unihemispheric sleep experiments in marine mammals, and from studies revealing specific regional effects in the sleep EEG of humans. The modeling approach could be extended to local sleep.

Three basic processes underlie sleep regulation: (1) a homeostatic process determined by sleep and waking; (2) a circadian process, a clock-like mechanism defining the alternation of periods with high and low sleep propensity and being basically independent of sleep and waking; and (3) an ultradian process occurring within sleep and represented by the alternation of the two basic sleep states—nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. This chapter focuses on "sleep homeostasis." *Homeostasis* has been defined as "the coordinated physiological processes which maintain most of the steady states in the organism."[1] The term *sleep homeostasis*[2] refers to the sleep-wake–dependent aspect of sleep regulation, as homeostatic mechanisms counteract deviations from an average "reference level" of sleep. They augment sleep propensity when sleep is curtailed or absent, and they reduce sleep propensity in response to excess sleep.

The interest in modeling the processes underlying sleep regulation has increased over the past decade. In the research briefing report of the Institute of Medicine,[3] a panel of leading North American experts in basic sleep research recommended that "the homeostatic and circadian influences need to be integrated into a single functional model that can describe both the timing of sleep and its quality." Models help delineate the processes involved in the regulation of sleep and thereby offer a conceptual framework for the analysis of existing and new data.

HOMEOSTATIC REGULATION OF SLEEP

Electroencephalographic Slow Wave Activity: A Physiological Indicator of NREM Sleep Homeostasis

Slow-Wave Sleep and Slow Wave Activity. NREM sleep is not a homogeneous substate of sleep, but can be subdivided according to the predominance of electroencephalographic (EEG) slow wave activity (SWA). The percentage of slow waves (frequency, 0 to 2 Hz; minimum peak-to-peak value, 75 μV) is the major criterion for scoring human NREM sleep into the stages 2, 3, or 4.[4] Stages 3 and 4 are commonly referred to as slow-wave sleep (SWS). However, the conventional sleep scoring method is inadequate for a quantitative analysis, because the sleep stages are based on rather general and arbitrary criteria. Presently, EEG parameters can be assessed by computer-aided methods of signal analysis. One of the most important functional EEG parameters will be referred to as "slow wave activity." It is equivalent to "delta activity" and encompasses components of the EEG signal in the frequency

range of approximately 0.5 to 4.5 Hz as obtained by spectral analysis (e.g., see reference 5).

Slow Oscillations (Less Than .1 Hz). Recently, a novel low-frequency component with a mean peak value of 0.7 to 0.8 Hz was identified in the power spectrum of NREM sleep.[6,7] Its frequency corresponded to the 0.7- to 0.9-Hz oscillation that has been reported in the sleeping cat[8] (see: Relationship to Neurophysiology). This slow component had been obscured in previous studies of the human sleep EEG owing to the attenuating effect of EEG amplifiers in the low-frequency range. The typical decline in delta activity from the first to the second NREM sleep episode was not present at frequencies below 2 Hz. Periodicity at even lower frequencies was identified. Thus the occurrence of sleep spindle activity showed a 4-sec periodicity[6,9] and slow waves tended to recur at 20- to 30-sec intervals.[6]

Slow Waves and Sleep Intensity. It was recognized as early as 1937 that sleep intensity is reflected by the predominance of slow waves in the sleep EEG.[10] Subsequent studies confirmed that the responsiveness to stimuli decreases as EEG slow waves become more predominant.[11] Under physiological conditions, this EEG parameter can be regarded therefore as an indicator of "sleep depth" or "sleep intensity." This statement applies not only to human beings but also to animals.

Global Time Course of Slow Wave Activity During Sleep. Figure 29–1 illustrates the conventionally scored sleep stages and SWA of a young subject. Note that SWS provides a rough indication of the prevalence of SWA. However, this EEG parameter shows a rather continuous rise from sleep onset to stage 4, a change that is only grossly reflected by the stepwise transitions of the sleep stages. In general, the measure derived directly from the EEG signal shows the variations of the NREM-REM sleep cycle and the fluctuations within NREM sleep episodes in much greater detail than the sleep profile. Moreover, the EEG parameter lends itself to a quantitative analysis from which inferences can be made regarding the underlying processes.

It is a plausible assumption that "sleep need" is high during the initial part of the sleep episode and gradually declines with the progression of sleep. In

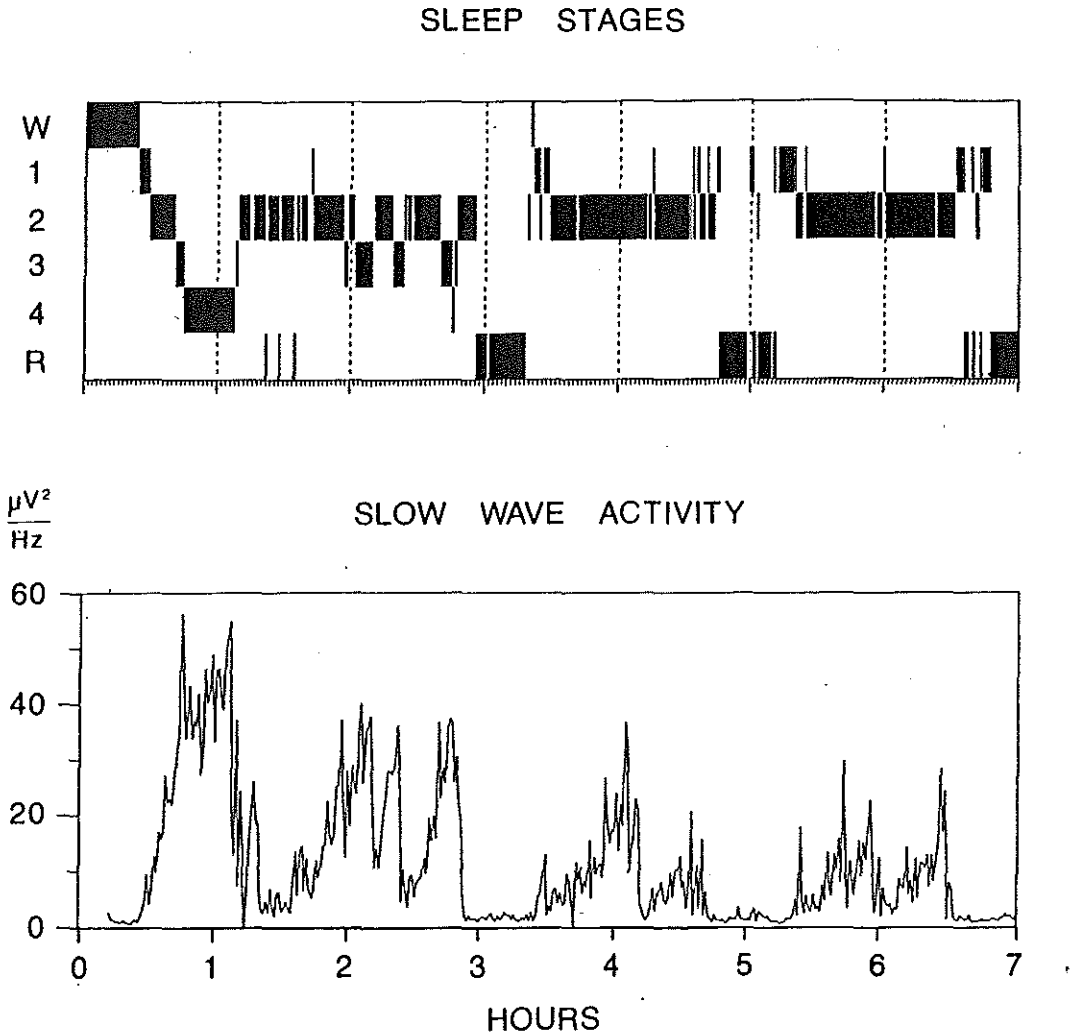

Figure 29–1. Sleep stages and slow wave activity. Sleep stages were scored for 30-sec epochs, slow wave activity (i.e., mean power density in the 0.75- to 4.5-Hz band) was calculated for 1-min epochs. (Modified from Achermann P, Borbély AA. Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics. Hum Neurobiol. 1987;6:203–210.)

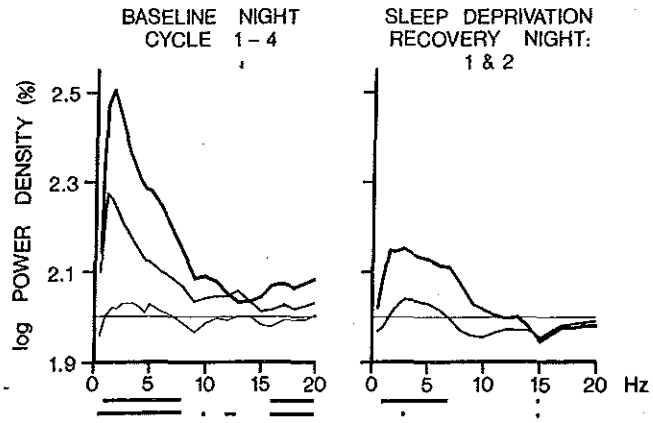

Figure 29–2. *Left,* Changes of relative spectral power density over the first four NREM-REM sleep cycles of a baseline night (N = 8; curves for consecutive cycles indicated by decreasing thickness of lines). In each frequency bin the data are expressed relative to the value in the fourth cycle (100%; horizontal line). *Right,* Effect of sleep deprivation (40.5 h waking) on spectra of the sleep electroencephalogram. In each bin, the values of the first two recovery nights are plotted relative to the baseline night (100%). The upper and lower horizontal bars below the abscissa indicate for the left part significant differences between cycle 1 and 2, and between cycle 2 and 3, respectively, and for the right part between recovery 1 and baseline, and between recovery 2 and baseline, respectively. (Modified from Borbély AA, Baumann F, Brandeis D, et al. Sleep deprivation: effect on sleep stages and EEG power density in man. Electroencephalogr Clin Neurophysiol. 1981;51:483–493.)

accordance with this notion, it has been reported in early studies that both the arousal threshold and the predominance of slow waves in the EEG were high in the initial part of sleep and then progressively decreased.[10] Thus SWS, the high-intensity part of NREM sleep, appeared to be a good candidate for a physiological indicator of sleep homeostasis. The predominance of SWS in the early part of the sleep episode was confirmed in subsequent studies.[11–13]

All-night spectral analysis of the sleep EEG made it possible to quantify SWA and to delineate its time course during sleep.[5] Its mean value per cycle plotted for consecutive NREM-REM sleep cycles showed a monotonic decline over the first three cycles.

Figure 29–2 (left) shows the changes of mean EEG power density over four cycles for the frequency range between 0.25 and 20 Hz. The values of each bin are expressed relative to the reference level of cycle 4 (100%). Note that although the largest changes occur in the low delta range, they encompass frequencies up to the theta band.

Nap Studies. The analysis of daytime naps is useful for assessing the level of SWA after various durations of waking. The observation that the naps taken later in the day contained more SWS than naps taken early in the day[14] has been recently confirmed.[15] In a detailed study of daytime naps scheduled at 2-h intervals throughout the day, direct evidence for a monotonic rise of SWA was obtained.[16–18]

If naps reverse the rising trend of slow wave propensity, a reduction of SWA in the subsequent nighttime sleep can be expected. This prediction was borne out by the results of several experiments.[19–24] When the duration of nighttime sleep was shortened, SWA in a subsequent morning nap was enhanced.[25, 26]

Effect of Sleep Deprivation. It has been repeatedly shown that partial or total sleep deprivation gives rise to increased SWS in the recovery night (see reference 27 for a review of the older literature). Webb and Agnew[13] presented compelling evidence that SWS increases as a function of prior waking. The quantitative assessment of SWA by all-night spectral analysis revealed that a night without sleep (i.e., 40.5 h of wakefulness) resulted in an enhancement of this EEG parameter during recovery sleep.[5] Figure 29–2 (right) illustrates the changes of power density in the two recovery nights relative to the baseline level (100%). In the first recovery night, the largest increase was present in the low delta range, the part of the spectrum undergoing the largest changes in the course of baseline sleep (see Fig. 29–2, left).

Figure 29–3 depicts the global trend as well as the ultradian dynamics of SWA over successive NREM-REM sleep cycles. The prolongation of the waking period causes a prominent rise of SWA during recovery sleep. A declining trend over three to four cycles is evident in both records. Note that the peaks are at a steady low level during last four cycles of recovery sleep.

The enhancement of SWA by sleep deprivation was confirmed in several studies[28, 29] (for references before 1992, see reference 30). The extent of the increase was shown to be a function of the duration of prior waking.[18, 31]

Intranight Rebound After Selective Slow Wave Deprivation. The propensity of SWA does not necessarily steeply decline during sleep but may persist at an elevated level if the occurrence of SWS is prevented. Thus a slow wave suppression by acoustic stimuli during the first 3 h of sleep resulted in a prominent rise of SWA after discontinuation of the stimuli[32] (see also reference 33 for a related study). In another study, daytime sleep episodes with and without SWS deprivation were compared.[34] The experimental suppression of SWS during an interval corresponding to 90% of the undisturbed episode resulted in an increased accumulation of SWS and an extension of sleep duration. Taken together, the results indicate that slow waves are not merely an epiphenomenon of sleep but reflect major sleep-regulating mechanisms.

Ultradian Dynamics of Slow Wave Activity and Spindle Frequency Activity

Buildup of Slow Wave Activity Within NREM Sleep Episodes. Not only the mean level and the peak of SWA is determined by the duration of prior waking and sleep but also the rise rate within single NREM sleep episodes.[35–37] It is evident from Figures 29–3 and 29–4 that the rise rate of SWA decreases over the first three episodes both under baseline conditions and during recovery from sleep deprivation. In addition, the effect of prolonged waking manifests itself in a steeper

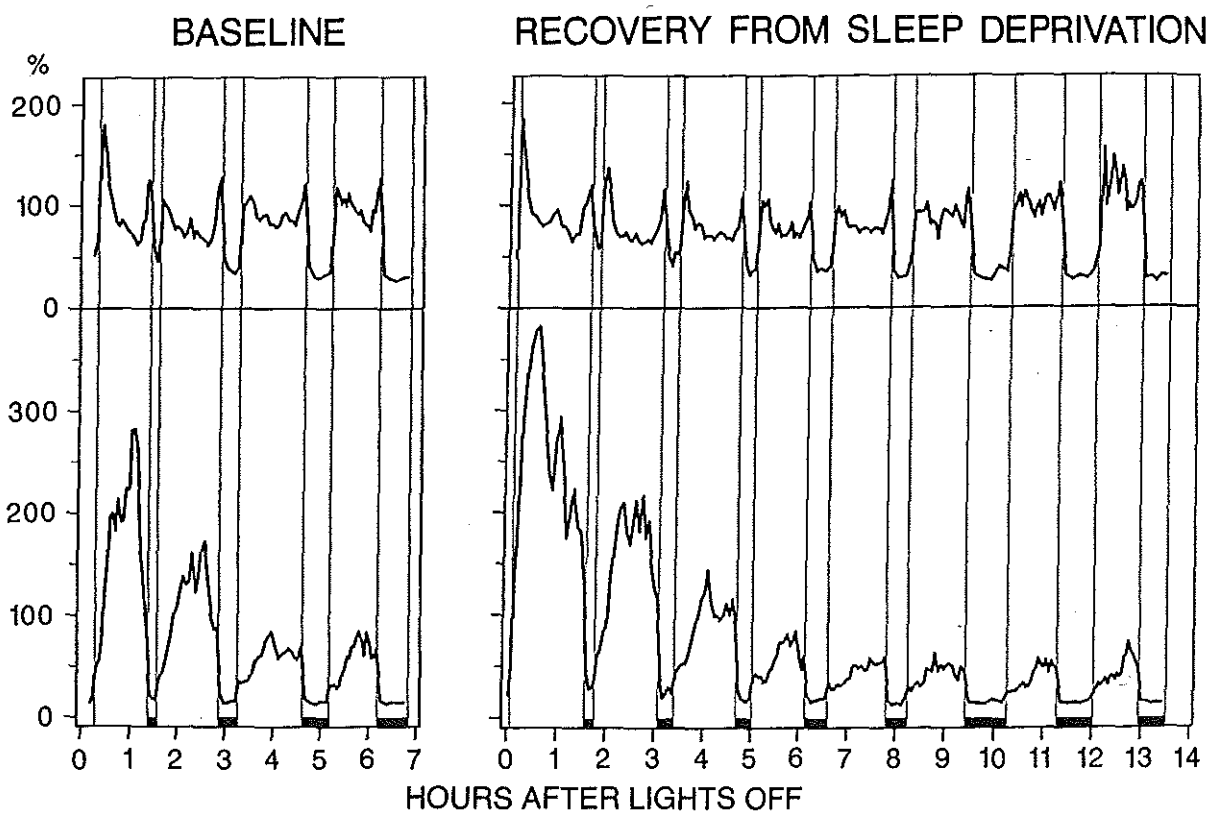

Figure 29–3. Time course of slow wave activity (power density in the 0.75- to 4.5-Hz band; lower curves) and activity in the spindle frequency range (13.25- to 15.0-Hz; upper curves) recorded under baseline conditions and after sleep deprivation (36 h of wakefulness). The NREM sleep episodes were divided into 20 equal parts, the REM sleep episode into five equal parts. The curves represent mean percentile values (N = 8 except for cycle 8 of recovery sleep where N = 6) and have been expressed relative to the mean slow wave activity level in baseline NREM sleep (100%). The mean timing of REM sleep episodes is delimited by vertical lines and horizontal bars above the abscissa. (Reanalysis of the data from Dijk DJ, Brunner DP, Borbély AA. Time course of EEG power density during long sleep in humans. Am J Physiol. 1990;258:R650–651, by D. Aeschbach.)

buildup (of SWA) within the episodes[28, 29, 37] (see Fig. 29–4).

Slow Wave Activity and Spindle Frequency Activity. The term *spindle frequency activity* (SFA) is used to denote the power density in the frequency range of sleep spindles (12 to 15 Hz). There is a close correspondence between this measure and measures based on the occurrence of sleep spindles.[28]

The time courses of SWA and SFA differ in several respects. The global declining trend of SWA is not present in the spindle frequency range. Within NREM sleep episodes, SFA shows a bimodal pattern with an initial and a terminal peak. This gives rise to a U-shaped curve within the episode and a partly inverse relationship to SWA[28, 38–43] (see Fig. 29–3). This inverse relationship becomes less prominent with age.[44] Within the 12- to 15-Hz range, low-frequency (12 to 13 Hz) and high-frequency (14 to 15 Hz) activity exhibited opposite circadian variations.[40, 45, 46] These results support the notion that there are at least two different types of spindles (see also references 47 through 50).

Sleep spindles in the 13- to 14-Hz band are remarkable because of their high intrahemispheric and interhemispheric coherence.[51, 52] This raises the question whether this episodic, high-coherence activity is of functional significance for sleep and whether sleep spindles may represent carrier frequencies upon which some relevant information is modulated (see reference 51 for a further discussion).

Relationship to Neurophysiology. In recent years it has become increasingly evident that the typical oscillations in the sleep EEG are closely associated with cellular changes at the level of thalamic and cortical neurons.[53–58] The progressive hyperpolarization of thalamocortical neurons that occurs during the progression from waking to deep NREM sleep[59] results in fluctuations in the membrane potential, which are initially in the frequency range of sleep spindles and then in the range of delta waves.[53, 54, 56, 60] Synchronized oscillations appear to arise from the progressive recruitment of neurons, and their spontaneous cessation from a hyperpolarization-activated cation conductance.[61] The oscillations at the neuronal level are associated with corresponding changes in the EEG. The progressive hyperpolarization of thalamocortical neurons after sleep onset[59] provides an explanation for the predominance of SFA in the initial phases of NREM sleep, which give way to slow waves as sleep progresses.[28, 38] These changes occur more rapidly when sleep pressure is high[28, 29, 39] and are retarded when sleep pressure is reduced.[24]

In 1993 a new type of slow oscillation was reported

to occur in the thalamocortical system.[53–55] Its frequency (less than 1 Hz) was lower than that of the delta rhythm (1 to 4 Hz). This slow oscillation originating in cortical networks consisted of rhythmical depolarizing components separated by prolonged (0.2 to 0.8 sec) hyperpolarizations,[55] which grouped the thalamically generated spindles and the delta waves in slowly recurring sequences.[53, 55, 62] Long-lasting hyperpolarizations were associated with prolonged depth positive waves in the cortical EEG. Recently, a novel low-frequency component with a mean peak value of 0.7 to 0.8 Hz was identified in the power spectrum of NREM sleep.[6, 7] Its frequency corresponded to the 0.7- to 0.9-Hz oscillation that has been reported in the sleeping cat.[8] The important role of gamma oscillations in sleep is increasingly recognized and is studied both at the level of neurons[7, 8, 63] and the EEG.[64–66] Taken together, the new developments indicate that not only the sleep-related changes but also the mechanisms underlying sleep homeostasis will be open for investigation at the cellular level.

NREM vs REM Sleep Homeostasis

Effect of NREM Sleep Pressure on REM Sleep Homeostasis. During recovery from total sleep deprivation, SWS and EEG SWA exhibit an immediate rebound, whereas the increase in REM sleep is delayed to subsequent nights or is not present at all. Selective REM sleep deprivation augments "REM sleep pressure," which is manifested by the increasing number of interventions required to prevent REM sleep episodes (for the older literature, see references in Borbély[27]). However, the occurrence of a REM sleep rebound during recovery sleep is either inconsistent[67] or smaller than expected on the basis of the deficit.[68] This may suggest that REM sleep is not as finely regulated as SWS. However, this notion is contradicted by recent partial sleep deprivation studies. A REM sleep deprivation in the first 5 h of sleep induced a REM sleep rebound in the subsequent 2.25 h.[69] A curtailment of sleep duration during 2 or 4 nights, which induced a substantial REM sleep deficit, was followed by a REM sleep rebound in the 2 recovery nights.[70, 71] In these experiments, the REM sleep rebound occurred at a time when slow wave pressure was either low at the end of sleep[69] or was much less increased than "REM sleep pressure."[70, 71] These results also suggest that REM sleep is finely regulated but that the manifestation of REM sleep homeostasis is hampered by an elevated slow wave pressure.

Effect of REM Sleep Pressure on the REM Sleep EEG. An electrophysiological indicator of an intensity dimension of human REM sleep, comparable to SWA in NREM sleep, has not been identified. The density of rapid eye movements is not associated with REM sleep pressure[72] but is inversely related to slow wave propensity.[24, 29, 73–75] In a recent selective REM sleep experiment, power in the alpha band was reduced in the REM sleep EEG during recovery sleep.[68, 68a] This effect was most pronounced in the first recovery night and then gradually subsided. A progressive and persistent attenuation of alpha activity in REM sleep has been ob-

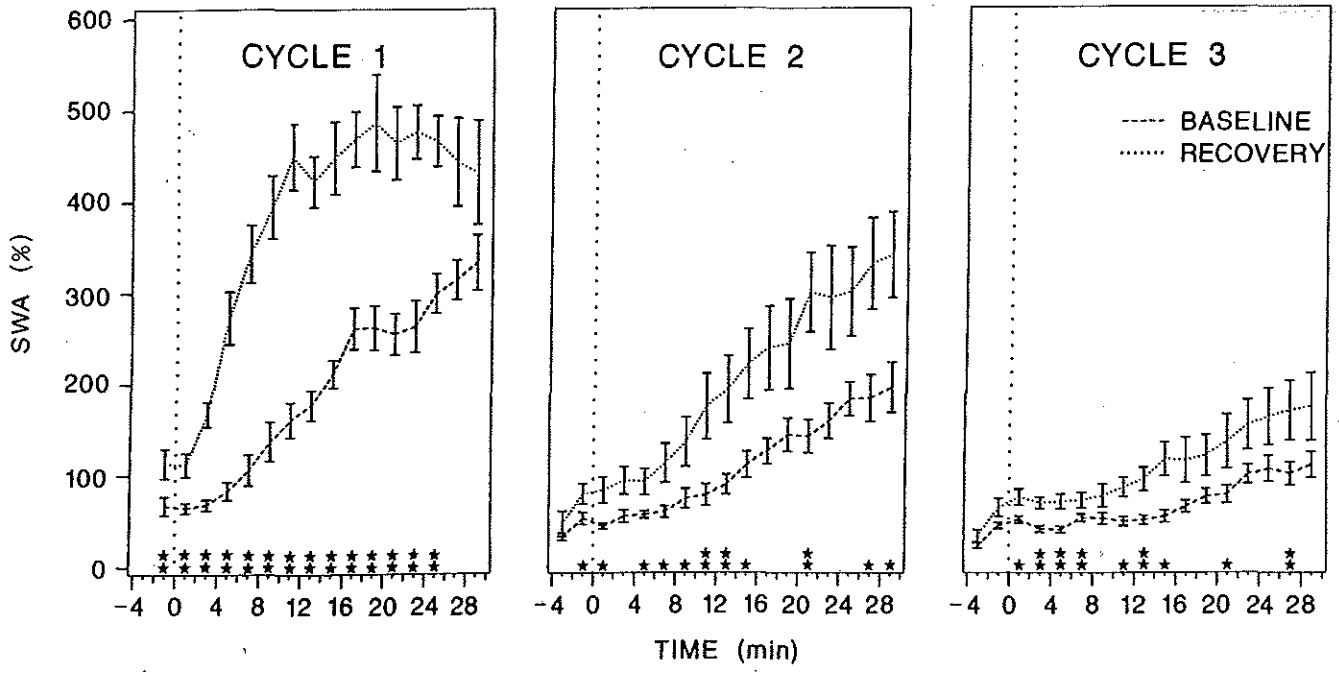

Figure 29–4. Buildup of slow wave activity (power density in the 0.75- to 4.5-Hz range) during the first 30 min of NREM sleep episodes 1, 2, and 3 for baseline conditions and after sleep deprivation (36 h of wakefulness). The data are expressed relative to the mean slow wave activity in the baseline sleep episode (100%). Mean values with standard errors (N = 9). Interrupted vertical lines delineate beginning of NREM sleep episode. Asterisks indicate significant differences between baseline and recovery nights (*P <.05; **P <.01; paired t-test on log-transformed values). (From Dijk DJ, Brunner DP, Borbély AA. Time course of EEG power density during long sleep in humans. Am J Physiol. 1990; 258:R650–651.)

served previously during recovery from total sleep deprivation,[5] as well as in a 4-day partial sleep deprivation protocol that induced a preferential deficit in REM sleep.[71] Therefore, alpha activity in REM sleep seems to be inversely related to REM sleep pressure. This conclusion is supported by a forced desynchrony study where the circadian rhythm of alpha activity in REM sleep and the REM sleep fraction of total sleep showed an inverse relationship.[46]

Effect of REM Sleep Pressure on the NREM Sleep EEG. In accordance with the notion of a mutual inhibitory interaction of the factors controlling SWA and REM sleep,[27] not only REM sleep is inhibited by "slow wave pressure," but also SWA by REM sleep pressure. Thus there was a significant reduction in the low-frequency activity of the NREM sleep EEG during selective REM sleep deprivation,[69] an observation that was also made in a recent animal experiment.[76] Also, the rise in REM sleep pressure induced by partial sleep deprivation suppressed the typical low-delta peak in the NREM sleep spectrum.[70, 71] However, this effect was not seen after selective REM sleep deprivation.[68]

Independence and Interactions of Homeostatic and Circadian Processes

There is evidence that homeostatic and circadian facets of sleep regulation can be independently manipulated and therefore may be controlled by separate mechanisms. Thus, throughout a 72-h sleep deprivation period, the subjective alertness ratings continued to show a prominent circadian rhythm.[77] Conversely, in a study in which the phase of the circadian process (as indexed by body temperature and plasma melatonin) was shifted by bright light in the morning, the time course of SWA remained unaffected.[78]

A powerful experimental paradigm is the forced desynchrony schedule in which the homeostatic and circadian facet of sleep can be separately analyzed. In this protocol, subjects were scheduled to a 28-h sleep-wake cycle.[45, 46, 79] During one third of the cycle the lights were off and the subjects were encouraged to sleep. Because under these experimental conditions the free-running circadian rhythm has a period of 24.18 h,[80] the sleep episodes occurred at different circadian phases. The data showed that sleep propensity was at the maximum when the circadian rhythm of rectal temperature was at the minimum. Sleep propensity gradually decreased on the rising limb of the rectal temperature rhythm and reached the minimum 16 h after the temperature minimum. This phase corresponds to the habitual bedtime under entrained conditions. When sleep was initiated at this phase, sleep continuity was high. In contrast, poor sleep continuity was observed when sleep was initiated after the temperature minimum.

The analysis of the data showed that SWA was determined mainly by homeostatic (i.e., sleep-waking dependent) factors, whereas the REM/NREM sleep ratio depended on both homeostatic and circadian factors. Furthermore, a previously postulated sleep-related inhibition of REM sleep[27] was confirmed by the results of the forced desynchrony study. Not only was the timing of sleep shown to be governed by the interaction of a homeostatic and a circadian process, but also the changes in daytime vigilance.

MODELS OF SLEEP REGULATION

Models help delineate the processes involved in the regulation of sleep and thereby offer a conceptual framework for the analysis of existing and new data. A synopsis of the major models discussed in this chapter is provided in Table 29–1 (see also references 30, 81, and 81a).

Two-Process Model and Related Models

The relationship between SWS and the duration of prior waking has been documented by Webb and Agnew[13] and placed into a theoretical framework by Feinberg.[82] The two-process model, originally proposed to account for sleep regulation in the rat,[2, 83] postulates that a homeostatic process (process S) rises during waking and declines during sleep, and interacts with a circadian process (process C) that is independent of sleep and waking (Fig. 29–5*A*). The time course of the homeostatic variable S was derived from EEG SWA. Various aspects of human sleep regulation were addressed in a qualitative version of the two-process model.[27] An elaborated, quantitative version of the model was established in which process S varied between an upper and a lower threshold that are both modulated by a single circadian process[84, 85] (Fig. 29–5*B*). This model was able to account for such diverse phenomena as recovery from sleep deprivation, circadian phase dependence of sleep duration, sleep during shift work, sleep fragmentation during continuous bed rest, and internal desynchronization in the absence of time cues.[85]

The two-process model triggered numerous experimental studies to test its predictions and was recently used to predict the response of habitual short and long sleepers to sleep deprivation.[29] It was concluded that short sleepers live under a higher NREM sleep pressure than long sleepers, and that the two groups do not differ with respect to the homeostatic regulatory mechanisms.

In a later version of the model (proposed by Beersma et al.[16] and Dijk et al.[32] and formalized by Achermann and Borbély[86]) it is the change of S, and not its level, which is proportional to the momentary SWA. The elaborated model addressed not only the global changes of SWA as represented by process S, but also the changes within NREM sleep episodes. The magnitude of the intranight rebound after selective SWS deprivation in the first 3 h of sleep was in accordance with the prediction.[86]

A further elaborated version of the model was subjected to an optimization procedure.[87] In general, a close fit was obtained between the simulated and em-

Table 29–1. MODELS OF SLEEP REGULATION AND CIRCADIAN RHYTHMS

Designation	Assumption	Description/Comment
Two-Process (S-C) Model and Related Models		
Two-process model[27, 84, 85, 89, 91]	Sleep propensity in humans is determined by a homeostatic process S and circadian process C; the interaction of S and C determines the timing of sleep and waking	Time course of S is derived from EEG slow wave activity; phase position and shape (skewed sine wave) of C are derived from sleep duration data obtained at various times of the 24-h cycle
Model of ultradian variation of slow wave activity[86–88, 122]	Derived from the two-process model; the level of S determines the buildup rate and the saturation level of slow wave activity within NREM sleep episodes	In contrast to the original two-process model, the change of S, not the level of S, corresponds to slow wave activity; a REM sleep oscillator triggers the decline of slow wave activity prior to REM sleep
Three-process model of the regulation of sleepiness and alertness[123–127]	Sleepiness and alertness are simulated by the combined action of a homeostatic process, a circadian process, and sleep inertia (process W); extension to performance, sleep latency, and sleep length	Parameters are derived from rated sleepiness during sleep-wake manipulations; time constant of the homeostatic process is similar to process S in the two-process model[85]; alertness nomogram for sleep-related safety risks
Rhythmostat model of the timing of sleep[128]	Modification of two-process model: the homeostatic process undergoes a circadian modulation	In contrast to the original two-process model, slow wave activity may increase during sleep and decrease during wakefulness; there are also differences with respect to the effects of naps
Two-Oscillator (x-y) and Related Models		
Original x-y model: predominant effect of light on y[95]	Two Van der Pol oscillators x and y affecting each other by "velocity"-type coupling; larger effect of x on y than y on x	"Strong" (x) circadian oscillator controlling core body temperature, REM sleep, cortisol; "weak" (y) circadian oscillator controlling the sleep-wake cycle
Revised x-y model: predominant effect of light on x[129, 130, 130a]	Van der Pol oscillator for x; cumulative effect of light; circadian modulation of sensitivity to light	Simulation of light effects on the human circadian pacemaker
Thermoregulatory model of sleep control[131, 132]	A thermoregulatory feedback control mechanism with modulation by two circadian oscillators; homeostatic features of sleep rhythm are generated by integration of heat load during waking	Simulations under entrained conditions of biphasic sleepiness pattern, timing of sleep, and sleep deprivation
Reciprocal Interaction Models of the NREM-REM Sleep Cycle		
Reciprocal interaction model[96]	NREM-REM sleep cycle generated by two coupled cell populations in the brainstem with self-excitatory and self-inhibitory connections according to the Lotka-Volterra model	Simulation of data: discharge rate of cholinergic FTG (or LDT and PPT) cells in cat; the role of postulated cell populations in the control of REM sleep, and their interactions have undergone revisions[97, 133]
Limit cycle reciprocal interaction model: original version[98, 99]	NREM-REM sleep cycle generated by the reciprocal interaction of two coupled cell populations (REM-on and REM-off)	Main features of previous model are maintained, but assumption of a stable limit cycle oscillation that is independent of initial conditions; introduction of a circadian term, which determines mode of approach to the limit cycle
Limit cycle reciprocal interaction model: extended versions[100]	As above; incorporation of sleep homeostasis and arousal events	Assumption of first-order decay dynamics for the arousal system; arousal as a stochastic process

EEG, electroencephalogram; FTG, gigantocellular tegmental field; LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus.

pirical SWA data and their time course (see Fig. 29–5C). In particular, the occurrence of late SWA peaks during extended sleep could be simulated. The simulations demonstrated that the model can account in quantitative terms for empirical data and predict the changes induced by the prolongation of waking or sleep. This version of the model was recently used to simulate the dynamics of SWA in an experimental protocol with an early evening nap[24] and the effect of changes in REM sleep latency on the time course of SWA.[88]

It had been already mentioned that the forced desynchrony protocol allows assessment of the interactions between the homeostatic (sleep-waking dependent) and circadian (sleep-waking independent) facets of sleep regulation and thereby testing of the essential parts of the two-process model. In accordance with its basic assumption, SWA, the marker of process S, was shown to be determined largely by homeostatic factors, whereas the REM sleep fraction of sleep was determined by both homeostatic and circadian factors.[45] This result corresponds to the propositions of the initial version of the model.[27] Also, the postulated sleep-re-

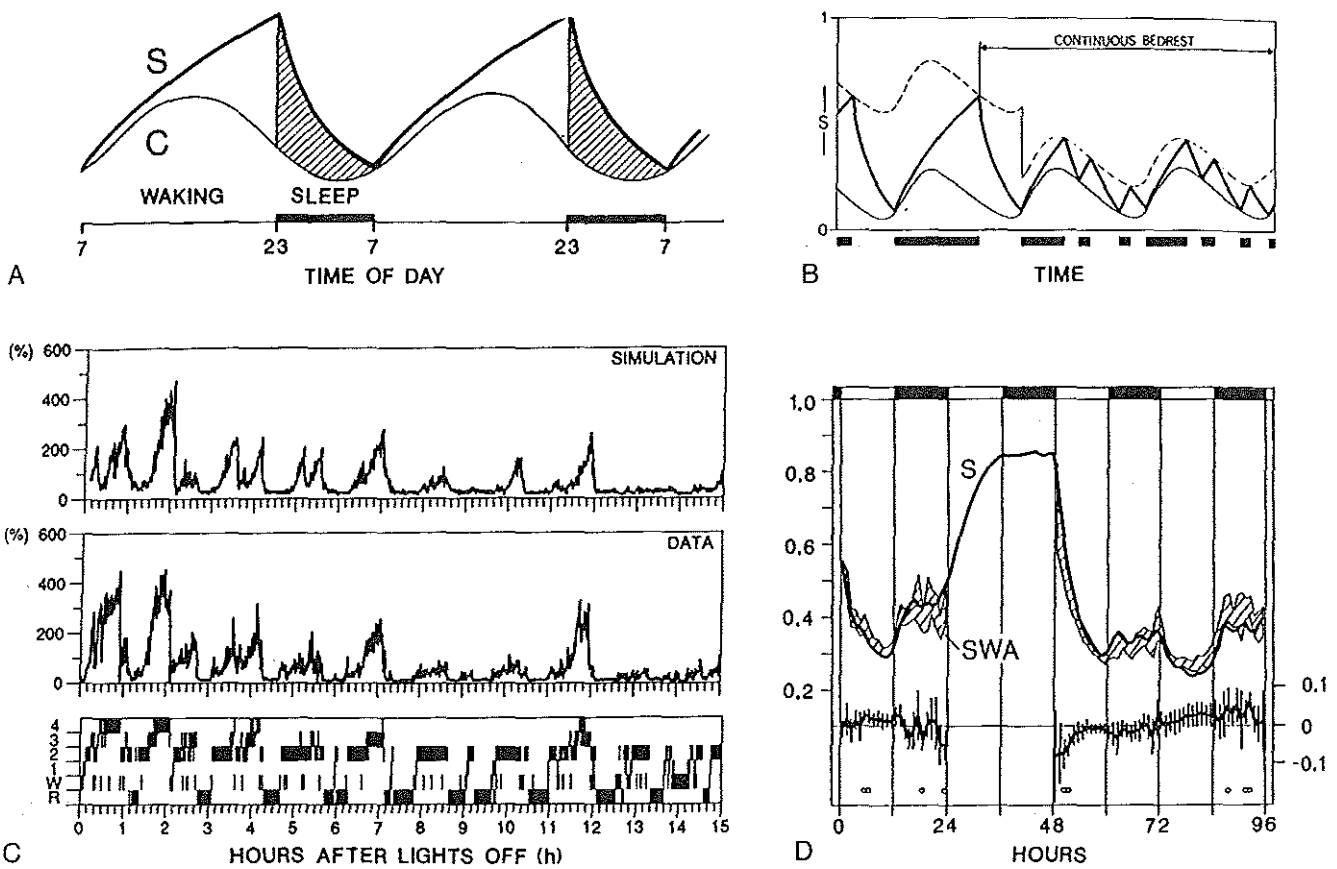

Figure 29–5. Two-process model of sleep regulation. *A*, Time course of homeostatic process S and circadian process C. S rises during waking and declines during sleep. The intersection of S and C defines time of wake-up. (Modified from Borbély AA. A two process model of sleep regulation. Hum Neurobiol. 1982;1:195–204.) *B*, Quantitative two-threshold version of the two-process model. Process S oscillates between upper and lower thresholds that are modulated by the circadian process C and determine the times of onset and termination of sleep, respectively. Due to the reduced arousal level, the upper threshold is lowered in a continuous bed rest schedule, giving rise to a polyphasic sleep-wake cycle. (From Daan S, Beersma DGM, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol. 1984;246:R161–178.) *C*, Simulated slow wave activity (*top*), empirical slow-wave activity (*middle*), and sleep stages (*bottom*) of an extended sleep episode. Empirical and simulated values of slow wave activity were standardized with respect to the mean value of the first 7 h of sleep. Values are plotted for 1-min intervals. (Modified from Brain Research Bulletin, Vol 31, Achermann P, Dijk DJ, Brunner DP, et al. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. 97–113, Copyright 1993, with permission from Elsevier Science.) *D*, Process S and empirical slow wave activity (SWA; 0.75 to 4.0 Hz) in the rat. Simulated process S (continuous line) and confidence interval (95%; n = 9) of slow wave activity in nonrapid eye movement sleep (hatched area) are superimposed for a 96-h period (baseline day, 24-h sleep deprivation, 2 recovery days). Lower curve shows mean differences (±2 SEM) between the linearly transformed SWA and S. SWA was expressed as a percentage of the mean baseline value (100%) and then linearly transformed. The ordinate denotes units of S. Intervals in which SWA and the simulation differed significantly from each other are indicated by circles below the difference curve ($P < .05$; two-tailed paired *t*-test). Black horizontal bars on top delineate the 12-h dark periods. (Modified from Franken P, Tobler I, Borbély AA. Sleep homeostasis in the rat: simulation of the time course of EEG slow-wave activity [published erratum appeared in Neurosci Lett. 1991;132:279]. Neurosci Lett. 1991;130:141–144.)

lated inhibition of REM sleep was confirmed by the results of the forced desynchrony study. Finally, the data analysis showed that not only the timing of sleep but also the changes in daytime vigilance are governed by the interaction of processes S and C, as simulated by Daan et al.[85] The rising homeostatic sleep pressure during waking seems to be compensated by the declining circadian sleep propensity.[85, 89–91] Conversely, during sleep the rising circadian sleep propensity may serve to counteract the declining homeostatic sleep pressure, thereby ensuring the maintenance of sleep.[79]

Although the two-process model originated from animal data,[2, 83] it was elaborated for human sleep. A quantitative simulation of NREM homeostasis was performed in the rat[92, 93] (see Fig. 29–5*D*). SWA determined in nine rats for consecutive 8-sec epochs of a 24-h baseline period, a 24-h sleep deprivation period, and a 48-h recovery period[94] served as the database for the simulation. As in the original human version of the model, process S was assumed to decrease exponentially in NREM sleep, and increase according to a saturating exponential function in waking. Unlike in the human model, an increase of S was assumed to occur also in REM sleep. After optimizing the initial value of S as well as its time constants, a close fit was obtained between the hourly mean values of SWA in NREM sleep and process S. In particular, the typical changes of SWA such as its biphasic time course during base-

line, its initial increase after sleep deprivation, and the subsequent prolonged negative rebound could be reproduced.

Two-Oscillator Model

A model based on the two circadian oscillators x and y has been proposed by Kronauer et al.[95] The model attempted to describe general features of the circadian system rather than focus specifically on the regulation of sleep and waking. The main problem with the different versions of the two-oscillator model is that the homeostatic aspect of sleep regulation is not addressed, and that additional assumptions are required to account for the effects of sleep deprivation.

Reciprocal Interaction Models

Reciprocal interaction models account for the cyclical alternation of NREM sleep and REM sleep. A distinctive feature of this class of models is that they evolved from neurophysiological data obtained in animals.[96] Although the original anatomical and physiological assumptions had to be modified,[97] the postulate that the NREM-REM sleep cycle is generated by the reciprocal interaction of two neuronal systems has been maintained. The original proposition of a Lotka-Volterra type of interaction was later transposed to humans, and further elaborated into the limit cycle reciprocal interaction model.[98–100]

Combined Models

Attempts were made to integrate various concepts into a combined model. Achermann and Borbély[101] regarded the models of various authors as "modules," which were linked into a combined model. Although its properties need to be further examined, the first simulations showed that it is feasible to incorporate homeostatic, circadian, and ultradian factors regulating nighttime sleep and daytime sleep propensity in a single model. Similarly, in the most recent extension of the limit cycle reciprocal interaction model,[100] homeostatic, circadian, and ultradian processes have been combined.

PERSPECTIVES

Processes and Models

The main characteristics of the homeostatic and the circadian facet of sleep regulation are summarized in Table 29–2. The major difference consists in the dependence of the former on prior sleep and waking, and in the sleep-wake–independent property of the latter. Sleep intensity of NREM sleep as indicated by SWA is the hallmark of a homeostatically regulated process, whereas the REM sleep fraction of sleep, as well as total sleep time, is the factor that is markedly influenced by the circadian phase. Nevertheless, the latter are also subject to a homeostatic regulation. The brain site in which the sleep-related circadian rhythms are generated is known to be the suprachiasmatic nuclei. By contrast, the neurobiological substrate of sleep homeostasis is still unknown. Neither the brain sites nor the mechanisms underlying homeostatic sleep regulation have been specified. Although this chapter deals with sleep regulation, it is pertinent to mention that a homeostatic process is reflected also in the waking EEG. Thus power in the theta and alpha range was shown to be enhanced after total[102] or partial sleep deprivation.[71] The rise in power during sustained wakefulness in a constant routine protocol occurred according to a saturating exponential function.[103]

Whereas models have focused on NREM sleep homeostasis, on the interaction of NREM and REM sleep, and on the circadian oscillator, REM sleep homeostasis has been largely ignored. In the context of a recent selective REM sleep deprivation experiment,[68] two salient observations were made, which were difficult to reconcile. On the one hand, REM sleep deprivation necessitated a dramatic rise in the frequency of interventions during the night to prevent this sleep state. On the other hand, there was a modest rise in the number of interventions across the three consecutive deprivation nights and the 40% REM sleep rebound in

Table 29–2. HOMEOSTATIC AND CIRCADIAN FACETS OF SLEEP REGULATION

	Homeostatic	Circadian
Influence of prior sleep and waking	Yes	No
Influence of the circadian phase	No	Yes
Sleep parameters most prominently affected	NREM sleep intensity (physiological correlate: EEG slow wave activity)	REM sleep fraction of sleep cycle; total sleep time
Nonsleep correlates	Unknown	Core body temperature; plasma level of certain hormones (e.g., melatonin, cortisol)
Regulatory structure in the brain	Not yet identified	Suprachiasmatic nuclei
Effect of lesioning the suprachiasmatic nuclei	Still operational	Disrupted
Effect of scheduled intensive light exposure in humans	Time course of slow wave activity not affected	Evidence for phase shift

EEG, electroencephalogram.

the first recovery night did by no means compensate for the amount of REM sleep lost. Two hypotheses were advanced. In the first, it is assumed that the homeostatic drive is strong, which is reflected by the dramatic rise in interventions during the deprivation nights. Waking may in part substitute for REM sleep, thereby accounting for the moderate night-to-night increase in interventions and the small REM sleep rebound. According to the second hypothesis, the homeostatic drive for REM sleep is weak and the rising trend in the number of interventions is attributed to circadian factors as well as to a sleep-dependent disinhibition of REM sleep propensity. This hypothesis could explain the limited savings from one night to the other as well as the modest rebound. Franken[104] proposed, on the basis of animal studies, that the initiation and maintenance of REM sleep could be controlled by separate processes and that the former may be accounted for by a rise in REM sleep propensity during NREM sleep, as postulated by Benington and Heller.[105] Further experiments are required to resolve this issue.

In conclusion, models help delineate the regulating processes underlying such a complex and little-understood phenomenon as sleep, and thereby offer a conceptual framework for the analysis of existing and new data. The major models have already inspired a considerable number of experiments. This approach has become particularly attractive by the possibility of using quantitative physiological measures in human beings for testing the predictions of a model. Thus EEG SWA represents the key parameter in the investigation of NREM sleep homeostasis, while the "unmasked" core body temperature and plasma melatonin are valuable indicators of the circadian process. Another positive feature of the modeling approach is the fact that the regulatory processes postulated are not restricted to a single species but probably represent basic mechanisms that are typical of mammalian sleep.[106]

Sleep: A Local, Use-Dependent Brain Phenomenon?

Recently, the question arose whether sleep represents a global or a local brain process. The observations that the dolphin does not exhibit deep SWS in both hemispheres simultaneously, and that the selective deprivation of unihemispheric sleep gives rise to a unihemispheric SWS rebound[107] shows that the sleep process is not necessarily present in the entire brain. There is recent evidence from studies in monkeys that the process of falling asleep may not occur synchronously in the entire brain.[108] Two hypotheses were advanced which imply that regional increases in neuronal activity and metabolic demand during wakefulness may result in selective changes in EEG synchronization of these neuronal populations during NREM sleep.[109, 110] Benington and Heller[110] proposed that adenosine, which is released upon increased metabolic demand via facilitated transport by neurons and glia cells throughout the central nervous system (CNS), promotes slow EEG potentials. Thus a use-dependent, local mechanism would underlie the sleep deprivation–induced changes in the sleep EEG. There is evidence from microdialysis studies that the adenosine level in the brain rises during waking and declines during sleep.[111]

The tenet of a local, use-dependent increase of sleep intensity was tested by investigating whether a local activation of a particular brain region during wakefulness affects the EEG recorded from the same site during sleep.[112] An intermittent vibratory stimulus was applied to the left or right hand during the 6-h period prior to sleep to activate the contralateral somatosensory cortex. Stimulation of the right (dominant) hand resulted in a shift of power in NREM sleep EEG toward the left hemisphere. This effect was most prominent in the delta range, was limited to the first hour of sleep, and was restricted to the central derivation situated over the somatosensory cortex (Fig. 29–6, right). Finally, a recent topographical study revealed a sleep-dependent hyperfrontality of SWA, which varies in the course of sleep.[47, 48] Thus in the initial two NREM sleep episodes, the power in the 2-Hz band was dominant at the frontal derivation, whereas in the second part of sleep the anteroposterior gradient vanished (Fig. 29–6, left). Recent experiments have shown that a sleep deficit impairs primarily high-level cognitive skills, which depend on frontal lobe function.[113, 114] Patients with lesions of the prefrontal cortex suffer from deficits that include distraction by irrelevant stimuli, diminished word fluency, flat intonation of speech, impaired divergent thinking, apathy, and childish humor.[115] Subjects foregoing sleep exhibit similar symptoms. Therefore, it may be more than a coincidence that the prevalence of slow waves is maximal at frontal EEG derivations in the initial part of sleep. This finding is consistent with the notion that the sleep process may occur in a topographically graded manner by involving preferentially those neuronal populations that have been most activated during waking. It could be speculated that the progressive anteroposterior shift in power in the low-frequency range reflects a high "need of recovery" in frontal parts of the cortex, which seem to exhibit the largest activity during wakefulness.[116] In the framework of the two-process model, the results may indicate that process S declines in the anterior region of the brain at a steeper rate than in posterior regions and that therefore the homeostatic NREM sleep-regulating process may exhibit regional differences. Experiments involving a specific manipulation of daytime activity are required to test this possibility.

Neurochemical and Genetic Facets

This chapter has focused on the homeostatic mechanisms of sleep derived largely from EEG variables and which gave rise to models describing the regulatory aspects. It is evident, however, that sleep homeostasis must have a neurochemical substrate and that possibly genetic mechanisms may be causally involved. The putative implication of adenosine has been mentioned. Another promising lead is the association of growth

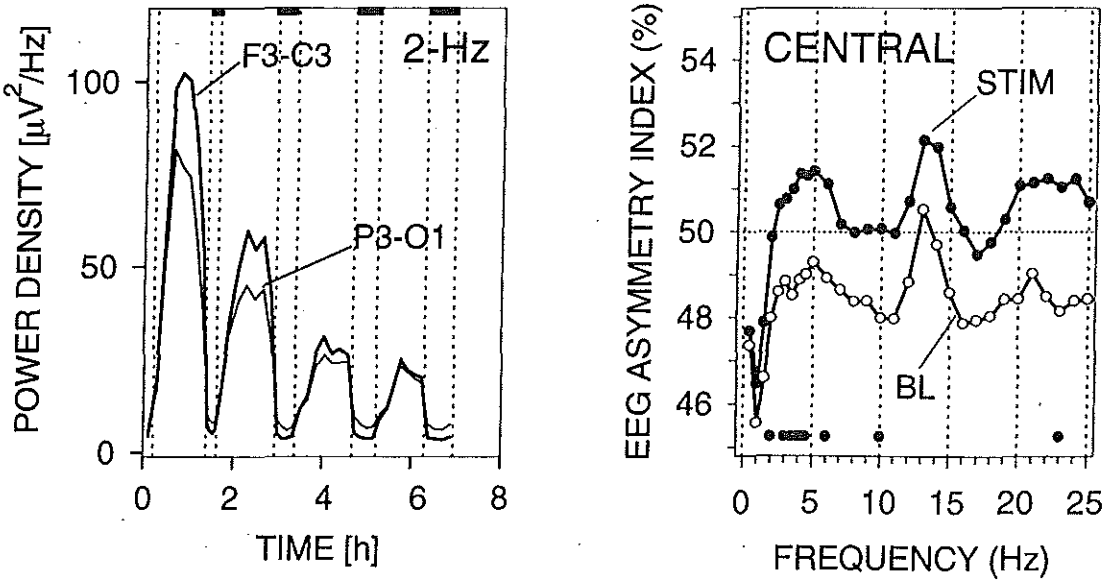

Figure 29–6. Regional differences in the sleep electroencephalogram (EEG). *Left*, Slow wave activity in the 2-Hz bin recorded from the frontocentral (F3-C3; *thick line*) and the parieto-occipital (P3-O1; thin line) derivation. Power density at the anterior site is higher in the first two NREM sleep episodes, but the difference vanishes in the last two episodes. Mean values (N = 20 subjects; 34 nights). Individual NREM sleep episodes were subdivided into seven equal intervals, REM sleep episodes into four intervals, and the time between lights-off and sleep onset was represented as one interval. Data were aligned with respect to sleep onset (cycle 1) or with respect to the first occurrence of stage 2 after a REM sleep episode (cycles 2–4). REM sleep is indicated by horizontal black bars at the top. (Modified from Werth E, Achermann P, Borbély AA. Brain topography of the human sleep EEG: antero-posterior shifts of spectral power. Neuroreport. 1996;8:123–127.) *Right*, Interhemispheric asymmetry index (100* [power in the left derivation]/[power in left and right derivation]) of the central derivation in NREM sleep during the first hour of sleep. An index larger than 50% indicates that power under baseline condition (BL) and after right-hand stimulation (STIM) is larger in the left hemisphere than in the right hemisphere. Circles above the abscissa indicate significant differences from baseline (paired *t*-test, $P < .05$). (Adapted from Kattler H, Dijk DJ, Borbély AA. Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. J Sleep Res. 1994;3:159–164.)

hormone (GH) release with SWS, and the evidence that the activation of GH–releasing hormone (GHRH) controls both these factors.[117] Pharmacological agents acting as GH secretagogues (e.g., gamma-hydroxybutyrate[118] and ritanserin[119]) enhance SWA. The question to be resolved is whether it is the homeostatic sleep–regulating mechanism itself that is affected by these agents.

Another approach to uncovering the basic substrates of sleep is derived from the observation that the activity of neuromodulatory systems, which project diffusely to the reticular formation subsides during sleep and that thereby the pathways mediating the phosphorylation of transcription factors and the induction of immediate early genes become ineffective.[120] This change may represent an essential cellular signature of sleep (see reference 120). A link to energy metabolism is suggested by the recent finding that the level of mitochondrial messenger RNAs (mRNAs) that are transcribed and translated into subunits of respiratory enzymes is considerably higher during waking than during sleep.[121] In conclusion, the identification of cellular and genetic correlates of sleep regulation may open the possibility of performing in vitro experiments (i.e., brain slices or cell cultures) to investigate the basic mechanisms of sleep.

Acknowledgments

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