Sleep Homeostasis and Models of Sleep Regulation

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Abstract According to the two-process model of sleep regulation, the timing and structure of sleep are determined by the interaction of a homeostatic and a circadian process. The original qualitative model was elaborated to quantitative versions that included the ultradian dynamics of sleep in relation to the non-REM-REM sleep cycle. The time course of EEG slow-wave activity, the major marker of non-REM sleep homeostasis, as well as daytime alertness were simulated successfully for a considerable number of experimental protocols. They include sleep after partial sleep deprivation and daytime napping, sleep in habitual short and long sleepers, and alertness in a forced desynchrony protocol or during an extended photoperiod. Simulations revealed that internal desynchronization can be obtained for different shapes of the thresholds. New developments include the analysis of the waking EEG to delineate homeostatic and circadian processes, studies of REM sleep homeostasis, and recent evidence for local, use-dependent sleep processes. Moreover, nonlinear interactions between homeostatic and circadian processes were identified. In the past two decades, models have contributed considerably to conceptualizing and analyzing the major processes underlying sleep regulation, and they are likely to play an important role in future advances in the field.

Key words circadian process, homeostatic process, interaction, mathematical models, simulation, two-process model, slow-wave activity

Three basic processes underlie sleep regulation: (1) A *homeostatic* process mediating the rise of sleep propensity during waking and its dissipation during sleep; (2) a *circadian* process, a clocklike mechanism that is basically independent of prior sleep and waking and determines the alternation of periods with high and low sleep propensity; and (3) an *ultradian* process occurring within the sleep episode and represented by the alternation of the two basic sleep states, non-REM sleep and REM sleep.

Models have served to place these processes in the context of sleep regulation and to provide a conceptual framework for their analysis. Models of sleep have been extensively reviewed in 1992 (Borbély and Achermann, 1992). Here we provide an update of developments since that date. The paper focuses on the two-process model of sleep regulation, and particularly on its homeostatic facet. The model has continued to trigger experiments in which particular aspects of its tenet were subjected to experimental testing. Its persistent influence is mirrored in the rising trend of citations of the original two key papers (Borbély, 1982b; Daan et al., 1984) over the past 15 years (1983-1988: 165; 1989-1993: 216; 1994-1999: 320). Overviews of related developments are provided in a book chapter (Borbély and Achermann, 1999) and in two recent review articles (Beersma, 1998; Borbély and Tononi, 1998).

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ANTECEDENTS OF THE TWO-PROCESS MODEL AND DEVELOPMENTS UNTIL 1992

Our previous review summarizes the antecedents of the two-process model (Borbély and Achermann, 1992). They include the recognition of the relationship in the 1930s between EEG slow waves and sleep intensity, the documentation in the early 1970s that slow wave sleep is determined by the duration of prior wakefulness, and the first theoretical concept of Feinberg in 1974. The original version of the two-process model was established to account for sleep regulation in the rat (Borbély, 1980; 1982a) and was then applied to human sleep (Borbély, 1982b). It postulates that the homeostatic Process S rises during waking and declines during sleep and that it interacts with a circadian Process C. It is important to note that from the beginning, the time course of the Process S was derived from a physiological variable, EEG slow-wave activity. Subsequently, an elaborated, quantitative version of the model was established (Daan and Beersma, 1984; Daan et al., 1984), which predicted the timing of human sleep for a variety of different schedules. Achermann and colleagues elaborated the homeostatic facet of the model by incorporating the ultradian dynamics related to the non-REM-REM sleep cycle (Achermann, 1988; Achermann and Borbély, 1990; Achermann et al., 1990). In addition to the timing of sleep and waking, the time course of daytime vigilance could be accounted for by the interaction of a homeostatic and a circadian process. Also, this feature had been simulated in the quantitative version of the two-process model (Daan et al., 1984). Daytime alertness was simulated by a modified version of the two-process model in which sleep inertia was included ("three-process model"; Folkard and Åkerstedt, 1987, 1989, 1992; Åkerstedt and Folkard, 1990).

TWO-PROCESS MODEL: NEW DEVELOPMENTS

Table 1 summarizes the recent developments in modeling sleep homeostasis and circadian processes that are relevant for sleep.

Ultradian Dynamics and Parameter Estimation

In an elaborated version of the two-process model in which the ultradian dynamics were included, a parameter estimation was performed. To estimate the values of the model parameters, an optimization procedure was used in which empirical data from 26 nights of 16 subjects served as reference. A sensitivity analysis revealed the model to be quite robust to small changes (±5%) of the parameter values. The estimated parameter values were used to simulate data sets from three different experimental protocols in which the timing and duration of sleep were altered. A close fit was obtained between the simulated and empirical slow-wave activity (SWA) data, and even the occasional late SWA peaks during extended sleep ("resurgence of slow wave sleep") could be reproduced (Achermann et al., 1993).

Sleep Inertia

The three-process model was further elaborated (Åkerstedt and Folkard, 1997) and was used to develop an alertness nomogram (Åkerstedt and Folkard, 1995) and to predict sleep latency (Åkerstedt and Folkard, 1996a) and sleep duration (Åkerstedt and Folkard, 1996b). New experimental data were used to simulate the time course of sleep inertia by an exponential process and to estimate its time constant (Achermann et al., 1995; Jewett et al., 1999).

Interaction of S and C

One of the basic assumptions of the model is the independence of its two constituent processes. However, a possible feedback of S on C has been noted already in 1984 (Daan et al., 1984). The authors pointed out that the scheduling of sleep and waking may alter the timing of light exposure and thereby affect the phase of C. Also, the period of C can be affected by sleep-wake-related light exposure (Klerman et al., 1996). In the model proposed by Putilov (1995), Process S exhibits a circadian modulation. For specific variables, nonlinear interactions between a homeostatic and circadian component are revealed (Table 2).

Upper and Lower Threshold of the "Somnostat"

In the original model, the upper and lower thresholds were represented by skewed sinusoid functions (Daan et al., 1984). The wake (lower) threshold was estimated on the basis of experimental data. In a first step, the sleep (upper) threshold was assumed to be in parallel. In subsequent theoretical papers, it was pro-

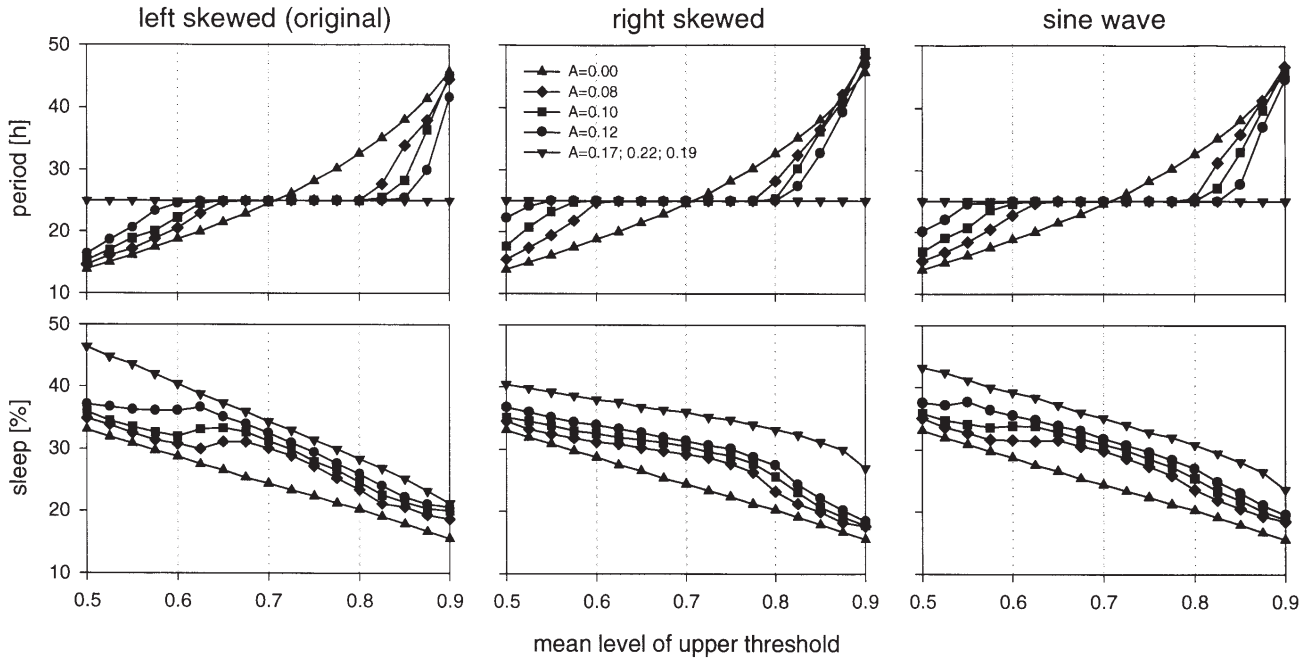

Figure 1. Internal synchronization and desynchronization. Simulations with the two-process model for different shapes of the thresholds. For various amplitudes (A) of the circadian process C, the mean level of the upper threshold was systematically varied. Resulting periods (average length of intervals between consecutive sleep onsets) and average sleep length as percentage of the corresponding period length are illustrated. Thresholds were left skewed as in the original model (Daan et al., 1984), right skewed, or represented by a sine wave. For A = 0.0 and A = 0.17 (left skewed), 0.22 (right skewed), or 0.19 (sine wave) no noise was applied; all other curves represent mean values of five simulations with noise (Daan et al., 1984).

posed that the skewness of one or both thresholds is opposite to the skewness originally proposed (Borbély et al., 1989; Achermann and Borbély, 1994). The simulations showed that during the regular waking episode, the circadian process counteracts the increasing sleep propensity of the homeostatic process and thereby maintains sleep propensity at a constant level. The antagonistic or opponent action between the two processes was postulated also by Edgar et al. (1993) on the basis of animal data. Also, the sleep latency data in the forced desynchrony protocol (Dijk and Czeisler, 1994, 1995) indicated that the skewness of the circadian thresholds of the somnostat is opposite to that assumed in the two-process model. Since one of the key features of that model was the simulation of internal desynchronization, we investigated if that feature can be still obtained for different shapes of the thresholds.

Simulations were performed with the original shape of the thresholds (left skewed), with both thresholds skewed in the direction opposite to that in the original model (right skewed), and with sine waves. A period of 25 h was assumed for Process C (Daan et al., 1984). For different amplitudes of C, the mean level of the upper threshold (H) was systematically varied (Fig. 1). Resulting periods (average length of intervals between consecutive sleep onsets) and average sleep length as a percentage of the corresponding period length are illustrated. For an amplitude of 0, the resulting period is only a function of the distance between the thresholds. An amplitude of 0.17 (left skewed), 0.22 (right skewed), or 0.19 (sine wave) is needed to achieve synchronization for the entire range over which the mean level of H is varied. These extremes set the boundaries for the observed patterns. Lowering the mean level of H leads first to a circabidian sleep-wake (S-W) pattern, then to internal desynchronization with longer periods of the S-W cycle than the period of C, followed by synchronization. A further reduction in the mean level of H results in internal desynchronization, with periods of the S-W cycle shorter than the period of C, which is followed by polyphasic S-W patterns. Internal desynchronization could be simulated with all three shapes of the thresh-

olds. The range of the mean level of H over which desynchronization is observed differs between the various thresholds. Also, the range over which synchronization with C is achieved as well as the percentage of sleep depend on the shape of C.

Since the period is calculated as the mean interval of consecutive sleep onsets, in some cases the resulting period is shorter than the estimate from a periodogram analysis. Nevertheless, the value provides an indication of the polyphasic pattern.

Model Equations

Since the various model equations were published in different papers, they are compiled in this article (for equations, see appendix).

With the exception of altering the shape of the thresholds, the equations of the original two-process model were not changed. The equations are reported in Daan et al. (1984) and in Achermann and Borbély (1994).

The equations of the elaborated version of the two-process model, in which the ultradian dynamics of SWA is modeled, are described in Achermann et al. (1993). The REM sleep trigger process was based on experimental data. This is the preferred approach for a quantitative simulation and a comparison with experimental data. To perform explorative simulations, the REM sleep trigger process may be replaced by the reciprocal interaction model of McCarley and Massaquoi (1986) as proposed in a composite model (Achermann and Borbély, 1992). The equations for SWA and S and their parameters basically do not differ between the two approaches. Only the scales of SWA and S are different. The main parameters that need to be adapted are initial conditions, the upper asymptote of S, and the lower asymptote of SWA.

EXPERIMENTAL EVIDENCE FOR HOMEOSTATIC AND CIRCADIAN PROCESSES

The basic assumptions of the two-process model, and in particular of its homeostatic facet of non-REM sleep regulation, have been subjected to extensive experimental verification. In addition, in new empirical approaches the concepts of the model have been used implicitly or explicitly in the design and data analysis (Tables 1 and 2).

Repeated Partial Sleep Deprivation

When sleep episodes were curtailed to 4 h for four nights, SWA in nonREM sleep increased by approximately 20% in the first night following sleep restriction, remained at this level in the subsequent three nights, and decreased immediately after the first recovery night (Brunner et al., 1993). The two-process model predicted this time course.

Effect of a Nap on Subsequent Sleep

The reduction of SWA during sleep by a preceding daytime nap has been further confirmed (Werth et al., 1996a). The level and initial buildup of SWA was reduced, and the declining trend over consecutive non-REM sleep episodes was attenuated. The time course of SWA could be closely simulated with the elaborated version of the two-process model. Some discrepancies in level and buildup of SWA were apparent. The study showed that homeostatic mechanisms can largely account for the dynamics of the sleep EEG under conditions of reduced sleep pressure. Another study based on the integrated amplitude of delta activity reached the same conclusion (Feinberg et al., 1992).

Sleep in Short and Long Sleepers

Homeostatic sleep regulation in habitual short and long sleepers was investigated during baseline conditions and after sleep deprivation (Aeschbach et al., 1996). The enhancement of SWA in non-REM sleep after sleep loss was larger in long sleepers (47%) than in short sleepers (19%). The two-process model of sleep regulation predicted this difference in the SWA response on the basis of the different sleep durations. The results indicate that short sleepers live under a higher “non-REM sleep pressure” than do long sleepers. However, the two groups do not differ with respect to the homeostatic sleep regulatory mechanisms.

Forced Desynchrony Protocol (Table 2)

The basic assumption of the two-process model is that its two constituent processes determine main

Table 1. New developments in modeling of sleep homeostasis and circadian processes since 1992.

Simulated Aspect or Elaborated Model	*Description*	*Simulations Performed*
"Original" two-process model		
Repeated partial sleep deprivation (Brunner et al., 1993)	Application of original two-process model.	Prediction of time course of SWA during repeated partial sleep restriction and recovery sleep.
Daytime vigilance (Achermann and Borbély, 1994, 1996)	Vigilance determined by an additive interaction of process S and C. Various shapes of C were used. Incorporation of sleep inertia.	Subjective alertness ratings in a forced desynchrony protocol, sleepiness ratings in a photoperiod experiment, and alertness during space missions.
Circadian modulation of Process S (Putilov, 1995)	Modification of two-process model: The homeostatic process (time constants and asymptotes) undergo circadian modulation. Process S may increase during sleep and decrease during wakefulness.	Baseline sleep, sleep derivation, and displaced sleep.
Sleep in short and long sleepers (Aeschbach et al., 1996)	Application of original two-process model.	Response to sleep loss in long and short sleepers could be predicted using the same time constants of S. Short sleepers have higher level of S than long sleepers.
Internal desynchronization (Nakao et al., 1997; Nakao and Yamamoto, 1998)	Interpretation of entrainment and internal desynchronization based on circle maps.	Simulation of sleep-wake patterns as a function of the distance between the thresholds. Calculation of bifurcation diagram.
Elaborated version of two-process model		
Ultradian variation of SWA (Achermann et al., 1993)	The change of S, not the level of S, corresponds to SWA. Continuous rise of S is offset by SWA. An REM sleep oscillator triggers the decline of SWA prior to REM sleep.	(1) Parameter estimation and simulation of independent datasets; (2) time course of SWA during normal sleep, after sleep deprivation, during extended sleep; (3) recurrence of SWA predicted on the basis of vigilance states.
Changes of SWA in response to sleep manipulations (Beersma and Achermann, 1995)	Application of above model with the same parameters.	Effects of changes in REMS latency on SWA.
Daytime nap (Werth et al., 1996a)	Application of above model with the same parameters.	Time course of SWA could be closely simulated; some discrepancies in level and buildup of SWA.
Combined models		
Composite model (Achermann and Borbély, 1992)	Combination of elaborated two-process model and limit cycle model for REM sleep regulation; incorporation of inertia.	Patterns of SWA and REM sleep; alertness.
Integrated model (Massaquoi and McCarley, 1992)	Limit cycle reciprocal interaction model for REM sleep regulation, incorporation of sleep homeostasis, and arousal events.	Patterns of SWA and REM sleep; spontaneous wake up.
Three-process model of alertness regulation (Åkerstedt and Folkard, 1995, 1996a, 1996b, 1997)	Extension to other variables.	Performance, sleep latency, and sleep length. Alertness nomogram for sleep-related safety risks.
Nonlinear interaction in model of alertness (Jewett et al., 1996; Kronauer et al., 1996)	Nonlinear interaction of homeostatic and circadian components. Only part of homeostatic component is exponential. Incorporation of sleep inertia.	Subjective alertness during sleep deprivation.
Circadian process		
Simulation of light effects on human circadian pacemaker (Klerman et al., 1996)	Kronauer model of the human circadian pacemaker (Kronauer, 1990).	Effects of single and triple light pulses on phase and amplitude; entrainment properties; effects of light intensity in forced desynchrony protocol; effect of self-selected sleep-wake schedules and associated light on free-running period.
Refinement of limit cycle oscillator (Jewett and Kronauer, 1998)	Refinement of model of Kronauer (1990) for accurate predictions of the effects of light on the human circadian pacemaker.	Phase/amplitude resetting after three-cycle bright-light stimulus.
Thermoregulatory model of sleep control (Nakao et al., 1995a, 1995b)	Thermoregulatory feedback control mechanism with modulation by two circadian oscillators. Homeostatic features of sleep rhythm generated by integration of heat load during waking.	Simulations under entrained conditions of biphasic sleepiness pattern, timing of sleep, and sleep deprivation.

NOTE: SWA = slow-wave activity (EEG power in the 0.75-4.5 Hz range).

Table 2. Experiments since 1992 that are related to the two-process model of sleep regulation.

Variable	*Homeostatic*	*Circadian*	*Interaction*	*Protocol*	*Reference*
Sleep					
SWA	+	–*		FD	Dijk and Czeisler, 1995; Dijk et al., 1997
	+	–	n.i.	CP	Aeschbach et al., 1997b
SFA	+	+	nonlinear	FD	Dijk and Czeisler, 1995
	+	+	n.i.	CP	Aeschbach et al., 1997b
Wakefulness during sleep	+	+	nonlinear	FD	Dijk and Czeisler, 1994
Sleep latency	n.i.	+		FD	Dijk and Czeisler, 1994
REM sleep	+	+	nonlinear	FD	Dijk and Czeisler, 1995
α activity in REM sleep	n.i.	+		FD	Dijk et al., 1997
	+	n.i.		SRD	Endo et al., 1998; Roth et al., 1999
Waking					
Psychophysiological variables					
Alertness	+	+	nonlinear	FD	Johnson et al., 1992; Dijk et al., 1992
Performance	+	+	nonlinear	FD	Johnson et al., 1992; Dijk et al., 1992
Mood	–	+		FD	Boivin et al., 1997
EEG power spectra					
δ and ϑ activity	+	+	n.i.	CR	Cajochen et al., 1995, 1998; Aeschbach et al., 1997a; Dumont et al., 1999
α activity	+	–	n.i.	CR	Aeschbach et al., 1997a; Dumont et al., 1999
σ activity	+	+	n.i.	CR	Aeschbach et al., 1997a; Cajochen et al., 1998; Dumont et al., 1999
β activity	+	–	n.i.	CR	Aeschbach et al., 1997a

NOTE: + = evidence for a significant component; – = no evidence for a significant component; n.i = not investigated; * = small circadian variation, partly due to circadian modulation of preceding sleep episode; SWA = slow-wave activity; SFA = activity in the spindle frequency range; FD = forced desynchrony; CR = constant routine with prolonged wakefulness; CP = sleep at different circadian phases; SRD = selective REM sleep deprivation; interaction = interaction between circadian and homeostatic components; it is nonlinear if amplitude of circadian component is sleep-wake dependent or homeostatic component is influenced by circadian phase.

aspects of sleep regulation. The original papers had shown that sleep patterns during various experimental protocols can be accounted for by the interaction of S and C (Borbély, 1982b; Daan et al., 1984). However, more direct and stronger evidence was obtained by the forced desynchrony paradigm. In its first applications to sleep, subjects were scheduled to a 28-h sleep-waking cycle (Dijk and Czeisler, 1994, 1995; Dijk et al., 1997). 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 to 24.2 h (Czeisler et al., 1999), the 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 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 EEG SWA was determined mainly by homeostatic (i.e., sleep-waking dependent) factors, whereas the REM sleep / non-REM sleep ratio depended on both homeostatic and circadian factors. This relationship confirms the main tenets of the two-process model. The postulated sleep-related disinhibition of REM sleep (Borbély, 1982b) was equally confirmed.

Waking EEG

In the first, qualitative version of the model, the rising part of Process S during waking was inferred from the initial and terminal level of S as derived from EEG SWA. In 1987, Torsvall and Åkerstedt reported wake-dependent components in the waking EEG. Recently, the waking EEG was used for delineating homeostatic and circadian processes (Table 2). Cajochen et al. (1995) demonstrated that power in the 6-9 Hz band exhibited a progressive rise during waking. In another study, power in the 12-25 Hz band was found to be determined by the interval of prior waking (Aeschbach et al., 1997a).

REM Sleep Homeostasis

In the first version of the model, REM sleep propensity was assumed to be determined by Process C in conjunction with the sleep-dependent Process S (Borbély, 1982b). Analysis of data obtained in the forced desynchrony protocol confirmed that the ratio of REM and non-REM sleep is determined by a circadian process (Process C) and that, similar to the postulate of the two-process model, a sleep-dependent disinhibition contributes to the increase of REM sleep in later parts of the sleep episode (Dijk and Czeisler, 1995).

One of the difficulties in modeling REM sleep regulation is that in contrast to non-REM sleep, there is no obvious marker of REM sleep intensity. If an intensity dimension of REM sleep is indeed not existent, then a rise in "REM sleep pressure" must manifest itself exclusively in an increased duration of REM sleep. Recent data showed a correlate of REM sleep propensity in the sleep EEG. Thus, repeated selective REM sleep deprivation gave rise to a reduction of alpha activity in REM sleep, an effect that dissipated over three recovery nights (Endo et al., 1998; Roth et al., 1999). This EEG variable has not yet been used for modeling REM sleep regulation.

Two different hypotheses accounting for the effects of selective REM sleep deprivation were advanced (Endo et al., 1998). The assumption of a strong homeostatic drive implies a dissipation of REM sleep propensity during waking, which would indicate that some aspects of wakefulness could functionally substitute REM sleep. In contrast, assuming a weak homeostatic drive would imply a prominent role of circadian factors as well as of the sleep-dependent disinhibition of REM sleep. The two hypotheses could be reconciled if the timing and maintenance of REM sleep were separately controlled.

Benington and Heller (1994) advanced the hypothesis that the homeostatic buildup of REM sleep propensity occurs during non-REM sleep.

Evidence for Use-Dependent, Local Sleep (Table 3)

According to the two-process model, Process S rises as a function of the duration of waking. Since waking activities entail an increase in brain metabolism as indexed by global cerebral blood flow (Braun et al., 1997), the wake-dependent increase in SWA may be a consequence of brain metabolism. In other words, the electrophysiological marker of Process S may be a consequence of increased brain activation. A logical consequence of this assumption would be that parts of the brain that have been more intensely activated exhibit a larger rise in Process S and a more intense "local sleep." Is it legitimate to regard sleep as a local brain phenomenon in addition to its global aspect? In a theoretical paper, Krueger and Obál (1993) proposed a local, use-dependent function of sleep.

Clear evidence for a regional differentiation of the sleep process was obtained in the dolphin, which is known to exhibit unihemispheric slow-wave sleep (Mukhametov et al., 1977). When the occurrence of slow-wave sleep was prevented in one hemisphere only, sleep rebound was limited to that hemisphere (Oleksenko et al., 1992). In humans, it was shown that unilateral activation of the somatosensory cortex enhanced SWA over the activated area during the first hour of sleep (Kattler et al., 1994). During normal sleep, an antero-posterior gradient of spectral power within the slow-wave frequency range prevailed during the first two non-REM-REM sleep cycles and then vanished (Werth et al., 1996b, 1997). This observation may indicate that the frontal areas of the cortex are particularly activated during waking activities and show a higher rise of Process S than other cortical areas. This interpretation is supported by the finding that after a partial non-REM sleep deprivation, SWA in the fronto-central derivation was increased more than in the centro-parietal derivation (Werth et al., 1998). During a 24-h constant routine, dissimilar dynamics were shown in the waking EEG where the rise of SWA in the frontal derivation was more prominent than in the occipital derivation (Cajochen et al., 1998).

The results in humans correspond to recent findings in animals. Thus, regional differences of EEG changes after sleep deprivation were observed in the rat (Schwierin et al., 1999). Moreover, Pigarev et al. (1997) reported that in the monkey, the electrophysiological concomitants of the initial sleep process do not occur synchronously over the entire cortex but involve first the association areas.

CONCLUDING REMARKS

The homeostatic facet of the two-process model was derived from the time course of SWA during nor-

Table 3. Experimental evidence for local and use-dependent aspects of sleep regulation.

Aspect	*Description*	*Reference*
Animal		
Unihemispheric slow-wave sleep rebound in dolphins	Dolphins do not exhibit deep slow-wave sleep in both hemispheres simultaneously. Selective deprivation of unihemispheric sleep gives rise to a unihemispheric slow-wave sleep rebound.	Oleksenko et al., 1992
Asynchronous development of sleep in monkey	The process of falling asleep does not occur synchronously in the entire brain.	Pigarev et al., 1997
Regional differences in rat EEG	Differential response to sleep deprivation in different derivations may reflect regional use-dependent features.	Schwierin et al., 1999
Human		
Selective activation of specific cortical area during wakefulness induces local EEG changes during sleep	Stimulation of the right (dominant) hand resulted in a shift of power in the non-REM sleep EEG toward the left hemisphere in central derivation situated over the somatosensory cortex. Effect was most prominent in the delta range and limited to the first hour of sleep.	Kattler et al., 1994
EEG topography during baseline sleep	Sleep-dependent hyperfrontality of SWA. In the initial two non-REM sleep episodes, power in the 2-Hz band was dominant at the frontal derivation. Antero-posterior gradient vanished in the second part of sleep episode.	Werth et al., 1996b, 1997
EEG topography after partial non-REM sleep deprivation	Deprivation induced increase of SWA higher in fronto-central derivation than in centro-parietal derivation.	Werth et al., 1998
Topographical difference in EEG power during wakefulness	Increase of SWA in wake EEG more prominent in frontal than occipital derivation.	Cajochen et al., 1998

NOTE: SWA = slow-wave activity.

mal sleep and after sleep deprivation. With elaborated versions of the model, it was possible to simulate SWA for various experimental paradigms. In view of the central role of slow waves, it is an important development that this facet of the sleep EEG could be related to events at the cellular level. The hyperpolarization of thalamocortical neurons during non-REM sleep is associated with fluctuations of the membrane potential in the range of EEG slow waves (Steriade et al., 1993, 1994; McCormick and Bal, 1997). During intermediate states of hyperpolarization, the fluctuations occur in the frequency range of sleep spindles, which are a hallmark of the superficial state of non-REM sleep. Recently, an even slower rhythm with a frequency below 1 Hz was described at the cellular level and then discovered also in the EEG (Steriade et al., 1993, 1994; Achermann and Borbély, 1997; Amzica and Steriade, 1997). Although EEG components other than SWA have not yet been used as physiological markers for sleep models, their sleep-wake dependent and circadian properties are being increasingly defined (Table 2). The expectation that the brain mechanisms underlying sleep homeostasis will be elucidated at the cellular and molecular level is reasonable in view of the recent advances. For example, adenosine was proposed as the promoter of SWA in response to an increased local energy demand in the brain (Benington and Heller, 1995). Moreover, the wake level of specific mitochondrial mRNA exceeded the sleep level by 20%-30% (Tononi and Cirelli, 1997). The beauty of the modeling approach is that it can serve as a guide of investigations on the macroscopic level of EEG and behavior as well as of analysis on the level of cellular and subcellular mechanisms.

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APPENDIX

The equations of the two-process model and its elaborated version including the ultradian dynamics of SWA are compiled in this appendix.

Two-Process Model (Daan et al., 1984):

Process S

$$S_t = \begin{cases} d\,S_{t-1}\,; d = e^{\frac{-\Delta t}{\tau_d}}\,(sleep) \\ 1 - r(1 - S_{t-1}); r = e^{\frac{-\Delta t}{\tau_r}}\,(wake) \end{cases}$$

S: homeostatic process, increasing during waking, decreasing during sleep; *d:* decay factor of *S; r:* rise factor of *S;* τ_d, τ_r*:* time constants; Δt*:* time step. Note: *S* is described by a recursive formulation (iteration); time steps indicated by indices *t*, *t* – 1.

Process C

$$C = A\begin{Bmatrix} 0.97\sin\left[\omega(t-t_0)\right] + 0.22\sin\left[2\omega(t-t_0)\right] + 0.07\sin\left[3\omega(t-t_0)\right] \\ +0.03\sin\left[4\omega(t-t_0)\right] + 0.001\sin\left[5\omega(t-t_0)\right] \end{Bmatrix}$$

$$\omega = \frac{2\pi}{\tau}$$

C: circadian process independent of sleep and waking; *A*: amplitude of skewed sine wave (sign determines direction of skewing); *t*: time; τ: period of *C*; t_0: defines the circadian phase at the beginning of the simulation.

For more realistic simulations in the timing of sleep and waking, noise is added to the thresholds (Daan et al., 1984).

Noise

$$n_t = \frac{1}{2}\left[n_{t-1} + N\,rand_t\right]$$

N: strength of noise; $rand_t$*:* normal distributed random number (mean = 0; standard deviation = 1); noise values are drawn at a fixed time interval (0.5 h).

Interaction

sleep initiation: if $S > H_m + C$
sleep termination: if $S < L_m + C$

H_m, L_m: mean level of upper (*H*) and lower (*L*) threshold, respectively.

Parameters:

τ_d = 4.2 h; τ_r = 18.2 h; Δt = 0.5 h; A = 0.12; τ = 24 h; t_0 = 8.6 h; H_m = 0.67; L_m = 0.17; N = 0.022.

Depending on the type of simulation, some of the parameters need to be changed (Daan et al., 1984).

Ultradian dynamics of SWA (Achermann et al., 1993; Achermann and Borbély, 1992):

Slow-wave activity (SWA)

$$\frac{d\mathrm{SWA}}{dt} = rc\,\mathrm{SWA}\left(1 - \frac{\mathrm{SWA}}{S}\right)\frac{S}{S_U} - fc_R\left(\mathrm{SWA} - \mathrm{SWA}_L\right)REMT(t) - fc_W\left(\mathrm{SWA} - \mathrm{SWA}_L\right)W(t)$$

REMT(*t*): REMS trigger signal (1 if activated, otherwise 0) derived from empirical data (Achermann et al., 1993) or from a REMS oscillator (Achermann and Borbély, 1992); *W*(*t*): wake trigger signal (1 if activated, otherwise 0) derived from empirical data (Achermann et al., 1993) or based on a composite model (Achermann and Borbély, 1992); *rc*: rise constant; fc_R: fall constant of SWA during activated REMT; fc_W: fall constant of SWA during activated *W*; SWA_L: lower asymptote of SWA; SWA(0): initial level of SWA at sleep onset; to mimic the noisy pattern of SWA, a noise term proportional to the level of SWA was introduced as an additive parameter ([1 + *n*(*t*)] SWA); *n*(*t*): noise, values drawn at fixed time interval of 1 min.

Process S

$$\frac{dS}{dt} = -gc\ \mathrm{SWA} + rs(S_U - S)$$

gc: gain constant; *rs:* rise rate of *S;* S_U*:* upper asymptote of *S;* *S*(0): initial level of *S* at sleep onset.

Parameters

rc = 0.283; fc_R = 0.236; fc_W = 1; *n*(*t*): normal distributed, mean = 0, standard deviation = 0.182; *gc* = 0.00835; *rs* = 0.0009167.

S and SWA scaled to fit empirical data (Achermann et al., 1993): SWA_L = 10.0%; SWA(0) = 46.8%; S_U = 564.1%; *S*(0) = 313.8 %; *S* and SWA scaled between 0 and 1 (Achermann and Borbély, 1992): SWA_L = 0.0177; SWA(0) = 0.083; S_U = 1; *S*(0) = 0.5563.

Depending on the type of simulation, some of the parameters or initial conditions need to be changed (Achermann et al., 1993; Achermann and Borbély, 1992).

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