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Models of sleep regulation in mammals

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SUMMARY A brief overview of models on the regulation of sleep/waking or rest/activity is provided. Applications of the two-process model are illustrated in two species: The homeostatic facet of the model (Process S) was used to quantitatively simulate sleep in the rat and guinea pig. The model parameters were estimated for rat sleep by an optimization procedure. A close correspondence between the time course of slow-wave activity and Process S was obtained for both species under baseline conditions. Whereas in the rat a close fit was obtained also for the recovery period from sleep deprivation, some discrepancies were present in the guinea pig. It is concluded that the concept of sleep homeostasis that has been elaborated and formalized in the two-process model for human sleep, can also be applied to simulate sleep in other mammals.

KEYWORDS guinea pig, rat, sleep homeostasis, two-process model

Several models have been developed to simulate certain aspects of the circadian rest/activity pattern (e.g. Daan and Berde 1978; Kronauer 1987; Carpenter and Grossberg 1987). In these models it has been implicitly assumed that sleep corresponds to rest, and waking to activity. None of the models has addressed the polyphasic pattern which is typical for sleep in animals. A model of the NREM–REMS cycle was established on the basis of electrophysiological recordings in the cat (McCarley and Hobson 1975).

The structure and regulation of sleep are similar in many mammalian species including humans. Thus sleep occurs predominantly during a specific portion of the 24-h cycle, NREMS and REMS alternate in a cyclic manner, and both substates show a compensatory response to a selective deprivation. Other invariant features that have been recognized more recently, include the following: (1) In nocturnal (e.g. rat, hamster) and diurnal (e.g. chipmunk) mammals with a clear 24-h sleep/wakefulness rhythm, EEG slow-wave activity (SWA; power density in the 0.75–4.0 Hz band) in NREMS is high at the beginning of the major sleep period and then declines. On the other side, in animals with a relatively even 24-h distribution of sleep and waking (e.g. cat, rabbit, guinea pig), the distribution of SWA is rather uniform (Tobler and Scherschlicht 1990; Tobler *et al.* 1990a, b). (2) Sleep deprivation (SD) enhances SWA in several mammalian species (human, cat, rabbit, rat, Syrian hamster, Siberian chipmunk and guinea pig) (Borbély *et al.* 1981, 1984; Tobler and Jaggi 1987; Dijk and Daan 1989; Tobler and Scherschlicht 1990; Tobler *et al.* 1990a, b; Lancel *et al.* 1991). (3) The polyphasic pattern that is a typical feature of sleep in most mammals, is seen also in humans under enforced bedrest (Campbell and Zulley 1985; Tobler 1989) and at early stages of development (Kleitman and Engelmann 1953).

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Homeostatic and circadian aspects of sleep regulation have been simulated in the two-process model (Borbély 1982b; Daan *et al.* 1984). Although the model had originated from animal data (Borbély, 1980, 1982a), its elaborated versions were developed for human sleep. The similarity of the structure and regulation of sleep in humans and other mammals prompted us to examine whether the model could be extended to simulate animal sleep.

Already in the first quantitative version of the two-process model, a polyphasic sleep/wake pattern was simulated by narrowing the interval between the two thresholds delimiting Process S (Daan *et al.* 1984). The application of this concept led to the qualitative simulation of the effects of methamphetamine on the rest/activity patterns in intact rats and in rats with lesions of the suprachiasmatic nuclei (Ruis *et al.* 1990). A qualitative simulation of the time course of S was performed with rat data based on spectral analysis of the EEG (Trachsel 1988; Borbély *et al.* 1989). A satisfactory simulation of empirical SWA was obtained for the light period, but not for the dark period. The latter problem was attributed to a circadian 'disturbance' factor interfering with the intraepisodic buildup of SWA during the activity period

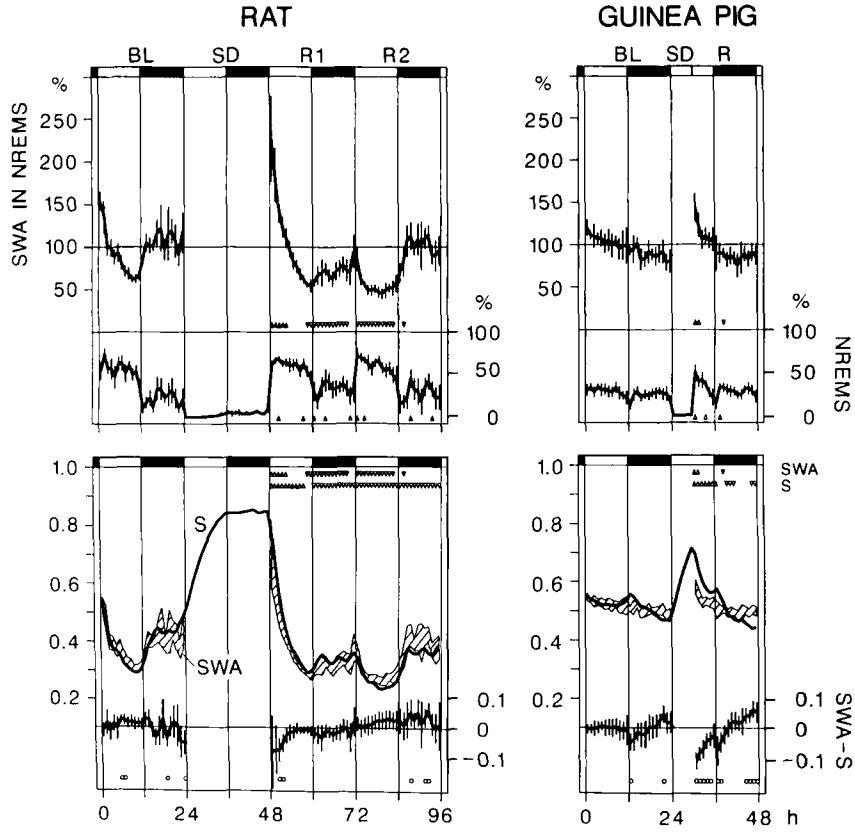

Figure 1. Upper panels: Time course of EEG slow-wave activity in NREMS (SWA; mean power density in the 0.75–4.0 Hz range; upper curve) and percentage of NREMS for 4 days (rat) and 2 days (guinea pig). Curves connect mean values (±2 SEM; $n = 9$ in both species) of 1-h intervals plotted at interval midpoints. SWA is expressed as percentage of the mean baseline value (=100%). In the recovery period, significant differences from corresponding baseline intervals are indicated by triangles below the curves ($P < 0.05$; two-tailed paired t-test). Triangles pointing downward or upward indicate the direction of deviation from baseline.

Lower panels: Confidence interval (95%) of EEG SWA (linearly-transformed) in NREMS (hatched area), mean simulated Process S (S, thick line) of experimental days and mean differences (±2 SEM) between the linearly-transformed SWA and S (lower curve). SWA was expressed as a percentage of the mean baseline value (=100%) and then linearly transformed. The ordinate denotes units of S. In the recovery period significant differences from corresponding baseline intervals are indicated by triangles above the curves ($P < 0.05$; two-tailed paired t-test). Intervals in which SWA and the simulation differed significantly from each other are indicated by circles below the difference curve ($P < 0.05$; two-tailed paired t-test; $n = 9$). Black horizontal bars on top delineate the 12-h dark periods (rat data adapted from Franken *et al.*, 1991b).

(Borbély *et al.* 1989). Recently, we performed a quantitative simulation of NREMS homeostasis in the rat (Franken *et al.* 1991b). SWA determined in 9 rats for consecutive 8-s epochs of a 24-h baseline period, a 24-h SD period, and a 48-h recovery period (Franken *et al.* 1991a) served as the data base for the simulation. As in the original human version of the model, Process S was assumed to decrease exponentially in NREMS, and increase according to a saturating exponential function in waking (Fig. 1, lower, left panel). Unlike in the human model, an increase of S was assumed to occur also in REMS. After optimizing the initial value of S as well as its time constants, a close fit was obtained between the hourly values of SWA in NREMS and Process S. In particular, the typical changes of SWA such as its biphasic time course during baseline, its initial increase after SD and the subsequent prolonged negative rebound could be reproduced.

We have tested the model on another species. The changes of SWA in the guinea pig were simulated by using the same parameter values as for the rat data. The data base consisted of 8-s SWA values of 9 guinea pigs which were recorded for a 24-h baseline period, a 6-h SD period, and a 18-h recovery period (Fig. 1, right panels). In contrast to the rat, the vigilance states were evenly distributed over the 24 h. As expected, the time course of SWA in the guinea pigs did not vary significantly either in the light or in the dark period (Tobler *et al.*, in prep.). A significant increase of SWA during recovery from SD was present also in this species. In comparison to the effect of 6-h SD in the rat (Tobler and Borbély 1990), the increase of SWA was markedly smaller in the guinea pig. The simulated and empirical values showed a close correspondence for the baseline condition but a discrepancy was present for the recovery period. The global time course of SWA could be simulated, but the magnitude of the changes induced by the SD were overestimated. The performance of the model may be improved by an estimation of the parameters for the guinea pig instead of transposing them from the rat. We conclude that the homeostatic facet of the two-process model is able to account for the global time course of SWA in various mammals.

REFERENCES

Borbély, A. A. Sleep: circadian rhythm versus recovery process. In: M. Koukkou, D. Lehmann, J. Angst (Eds) *Functional States of*

the Brain: their determinants. Elsevier, Amsterdam, 1980: 151–161.

Borbély, A. A. Sleep regulation: circadian rhythm and homeostasis. In: D. Ganten, and D. Pfaff, (Eds) *Current Topics in Neuroendocrinology. Vol. 1: Sleep. clinical and experimental aspects*. Springer, Berlin, 1982a: 83–103.

Borbély, A. A. A two-process model of sleep regulation. *Hum. Neurobiol.*, 1982b, 1: 195–204.

Borbély, A. A., Achermann, P., Trachsel, L. and Tobler, I. Sleep initiation and initial sleep intensity: interactions of homeostatic and circadian mechanisms. *J. Biol. Rhythms*, 1989, 4: 149–160.

Borbély, A. A., Tobler, I. and Hanagasioglu, M. Effect of sleep deprivation on sleep and EEG power spectra in the rat. *Behav. Brain Res.*, 1984, 14: 171–182.

Borbély, A. A., Baumann, F., Brandeis, D., Strauch, I. and Lehmann, D. Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroenceph. Clin. Neurophysiol.*, 1981, 51: 483–493.

Campbell, S. and Zulley, J. Ultradian components of human sleep/wake patterns during disentrainment. In: Schulz H. and Lavie P. (Eds) *Experimental Brain Research, Suppl. 12; Ultradian rhythms in physiology and behavior*. Springer-Verlag, Berlin, 1985: 234–254.

Carpenter, G. A. and Grossberg, S. The non-parametric influence of light on mammalian circadian rhythms. *Lect. Math. Life Sci.* 1987: 151–203.

Daan, S. and Berde, C. Two coupled oscillators: simulations of the circadian pacemaker in mammalian activity rhythms. *J. Theor. Biol.*, 1978, 70: 297–313.

Daan, S. Beersma, D. G. M. and Borbély, A. A. Timing of human sleep: Recovery process gated by a circadian pacemaker. *Am. J. Physiol.*, 1984, 246: R161–R178.

Dijk, D. J. and Daan, S. Sleep EEG spectral analysis in a diurnal rodent: Eutamias sibiricus. *J. Comp. Physiol. A*, 1989, 165: 205–215.

Franken, P., Dijk, D. J., Tobler, I. and Borbély, A. Sleep deprivation in the rat: Effects of electroencephalogram power spectra, vigilance states, and cortical temperature. *Am. J. Physiol.*, 1991a, 261: R198–R208.

Franken, P. Tobler, I. and Borbély, A. Sleep homeostasis in the rat: simulation of the time course of EEG slow-wave activity. *Neurosci. Lett.* 1991b, 130: 141–144.

Kleitman, N. and Engelmann, T. G. Sleep characteristics of infants. *J. Appl. Physiol.*, 1953, 6: 269–282.

Kronauer, R. E. Temporal subdivision of the circadian cycle. *Lect. Math. Life Sci.*, 1987: 63–120.

Lancel, M., Van Riezen, H. and Glatt A. Effects of circadian phase and duration of sleep deprivation on sleep and EEG power spectra in the cat. *Brain Res.*, 1991, 548: 206–214.

McCarley, R. W. and Hobson, J. A. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. *Science*, 1975, 189: 58–60.

Ruis, J. F. Buys, J. P. Cambras, T. and Rietveld, W. J. Effects of T cycles of light/darkness and periodic forced activity on methamphetamine-induced rhythms in intact and SCN-lesioned rats: explanation by an hourglass-clock model. *Physiol. Behav.* 1990, 47: 917–929.

Tobler, I. Napping and polyphasic sleep in mammals. In: D. F. Dinges and R. J. Broughton (Eds) *Sleep and alertness: chronobiological, behavioral, and medical aspects of napping*. Raven Press, New York, 1989: 9–30.

Tobler, I. and Borbély, A. A. The effect of 3-h and 6-h sleep deprivation on sleep and EEG spectra of the rat. *Behav. Brain. Res.*, 1990, 36: 73–78.

Tobler, I. and Jaggi, K. Sleep and EEG spectra in the Syrian hamster (Mesocricetus auratus) under baseline conditions and following sleep deprivation. *J. Comp. Physiol. A*, 1987, 161: 449–459.

Tobler, I. and Scherschlicht, R. Sleep and EEG slow-wave activity in the domestic cat: effect of sleep deprivation. *Behav. Brain Res.*, 1990, 37: 109–118.

Tobler, I., Franken, P. and Scherschlicht, R. Sleep and EEG spectra in the rabbit under baseline conditions and following sleep deprivation. *Physiol. Behav.*, 1990, 48: 121–129.

Tobler, I., Dijk, D. J. and Borbély, A. A. Comparative Aspects of sleep regulation in three species. In: Horne, J. A. (Ed.) *Sleep '90*. Pontenagel Press, Bochum, 1990: 349–351.

Trachsel, L. *Schlafregulation der Ratte: EEG-Analyse physiologischer und pharmakologischer Aenderungen und Computersimulationen*. PhD thesis, Diss ETH Nr. 8606, Zürich (CH) 1988: 101–119.

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