HYPOTHALAMIC SLEEP-PROMOTING MECHANISMS: COUPLING TO THERMOREGULATION

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INTRODUCTION

Kleitman's monograph, Sleep and Wakefulness (22), contains two chapters concerned with aspects of the relationship between body temperature and sleep. Included is a summary of Kleitman's own work as well as a review of other studies on the relative roles of lying down vs sleep onset in the fall of core temperature that normally accompanies sleep onset. He reaches the conclusion that both processes contribute to a fall in body temperature. This work has stood the test of time. Another chapter focused on the 24-hour rhythmicity in body temperature, particularly its development in normal and pathological children. He noted that abnormalities in circadian sleep-wake regulation were accompanied by abnormalities in circadian temperature rhythmicity. This work anticipated the strong interest in the interaction of sleep and temperature rhythms that exists today. It has become routine to record body temperature along with other variables in the study of both human and animal sleep. This paper will review studies supporting a hypothesis that the interaction of temperature and sleep reflects fundamental features of the mechanistic control of sleep by the brain. Specifically we hypothesize that a preoptic hypothalamic and adjacent basal forebrain (POA/BF) neural network that generates sleep is coupled to neural mechanisms that regulate body temperature and metabolism. This mechanism could provide a basis for understanding the interaction of sleep and 24 hour temperature rhythm.

THE PREOPTIC HYPOTHALAMIC AND BASAL FOREBRAIN (POA/BF) HYPNOGENIC SYSTEM

The POA/BF was first suggested as a hypnogenic site on the basis of neuropathological findings in victims of encephalitis with insomnia before death (53). This hypothesis has been confirmed through the use of experimental lesions in several species. While bilateral 1-2 mm diameter lesions of the POA in rats (7) and cats (50) may induce partial sleep loss followed by recovery, larger bilateral 3-5 mm lesions or transections which extend into the adjacent BF induce total or near

total insomnia sometimes leading to death (34, 41, 46). *The size of the lesion seems to determine the magnitude of the sleep deficit.* More lateral BF as well as medial POA lesions may suppress sleep (51). These studies suggest that the POA/BF hypnogenic mechanism is distributed within the POA/BF. The POA/BF lesion literature is reviewed in detail in the chapter by Szymusiak in this volume.

The POA/BF was recognized as a thermoregulatory control site on the basis of effects of local warming and cooling, lesions, and microinjection, and neuronal unit recording studies. For example, POA/BF warming induces heat loss responses such as panting (9), and POA/BF cooling will elicit increased metabolic rate at a discrete temperature threshold (14). Above the threshold, heat production was proportional to the thermal stimulus. Such experiments suggested that heat loss and heat production processes were controlled by a neural "thermostat" having a discrete temperature threshold and that thermoeffector outputs were proportional to the hypothalamic temperature stimulus deviation from the threshold or "set point", namely, $T_{hypo}-T_{set}$. The threshold for heat production was lowered during NREM sleep, and no responses could be elicited in REM sleep.

POA/BF warming was also shown to trigger NREM sleep or EEG slow wave activity in cats (44), rabbits (54) and rats (8). Sakaguchi et al. (45) demonstrated tonically increased NREM with sustained warming in kangaroo rats. In the same experiment they measured the hypothalamic response threshold temperature for increased metabolic rate (T_{set}) at different ambient temperatures, and showed that during sustained POA/BF warming total sleep time was proportional to $T_{hypo}-T_{set}$. Thus, control of sleep could be conceived to be similar to control of thermoregulatory processes, with sustained sleep behaving like a thermoeffector output.

We found that in cats POA/BF warming increased EEG slow wave activity within sustained periods of NREM (32). Enhanced EEG synchrony was not due to changes in sleep architecture, but is like that induced by sleep deprivation. On the other hand, mild POA/BF cooling completely suppressed both NREM and REM sleep for 3 hours at circadian time (CT) 3-6, when rats normally sleep almost continuously. These types of studies show that the expression of sleep can by exquisitely controlled by POA/BF thermal stimuli.

NEURONAL BASIS OF POA/BF SLEEP REGULATION

Responses to localized POA/BF warming or cooling must be mediated by responses of warm-sensitive or cold-sensitive neurons (WSNs or CSNs) that have been found within the region (10). Such neurons are identified by having a brisk discharge rate response to local thermal stimuli and are defined by standard criteria. Most neurons (typically 70-80%) recorded *in vivo* are unresponsive or weakly-responsive to changes in local temperature and are thought to be "temperature-compensated". The minority population of WSNs and CSNs are hypothesized to be specialized to regulate thermoregulatory and sleep-wake processes that are evoked by local thermal stimuli. Our work focused on two questions. 1. Could

POA/BF WSNs and CSNs play a role in spontaneous sleep as well as sleep regulated by local thermal stimuli? 2. Do such neurons exhibit properties that could account for subtle features of sleep-wake regulation including the metabolic response threshold changes that accompany sleep?

We recorded single neuronal discharge in POA/BF adjacent to water perfused thermodes in chronically-prepared cats and rats using the microwire method (2-5). Cells were identified as sleep-active, that is, more active during NREM sleep than waking (NREM/Wake discharge rate ratio ≥ 1.2), wake-active (NREM/Wake ≤ 0.8), or state-indifferent. Thermosensitivity was tested by warming or cooling trials during waking, and, in some cases during both NREM and REM sleep with 60-90 sec. Local temperature was usually measured with a microthermocouple close to the recording site. Approximately equal numbers of WSNs and CSNs were identified in both cats and rats in the restricted POA/BF regions we studied.

Fig. 1A shows a thermosensitivity test response identifies the cell as a WSN. Fig. 1B-C shows the sleep-wake behavior of the same neuron. Neuronal discharge increased prior to and during each episode of EEG synchronization, and decreased during periods of arousal. Such a neuron was identified as sleep-active. We found that the majority of WSNs were sleep-active and most CSNs were wake-active in both rats and cats (Fig. 1D). As suggested by the samples in Fig. 1B-C, a systematic analysis of state transitions (Fig. 1E) showed that WSN discharge increased during the transition from wake to sleep, typically several seconds before the first EEG spindle. CSNs exhibited decreased discharge during the transition.

The changes in WSN discharge occurring during spontaneous sleep correspond to those induced by an approximately 2.0 (cats)-3.0 (rats) °C change in local temperature during waking, a strong stimulus that would reliably facilitate sleep. In addition to the changes in baseline rate during NREM, we also showed that thermosensitivity, the proportional change in discharge rate with temperature, increased during NREM sleep, from 1.6 to 4.3 impulses/ sec/°C (4). Moreover, a group of 9 neurons that were thermo-insensitive during waking became WSNs by our criteria during NREM sleep. CSNs exhibited reduced thermosensitivity during NREM. Under conditions of enhanced thermosensitivity of WSNs and reduced thermosensitivity of CSNs in NREM sleep, any slight increase in temperature would elevate WSN discharge and decrease CSN discharge. These responses would reinforce the NREM state. Thus, changes in thermosensitivity within NREM would tend to stabilize the NREM state. WSNs and CSNs exhibited mirror-image changes in rate and thermosensitivity in NREM compared to waking. This is consistent with the idea of inhibitory interactions between WSNs and CSNs.

Since WSN activation and/or CSN deactivation by local thermal stimuli are sufficient to induce NREM sleep, and these same discharge changes occur prior to and during spontaneous NREM, it is reasonable to conclude that the changes in WSN and/or CSNs play a critical role in spontaneous NREM sleep onset. It should be noted that sleep-active neurons within the POA/BF had been reported in several previous studies (13, 21). Our results provided a basis for the integration of sleep-wake regulation and thermoregulation in this brain region. Changes in discharge
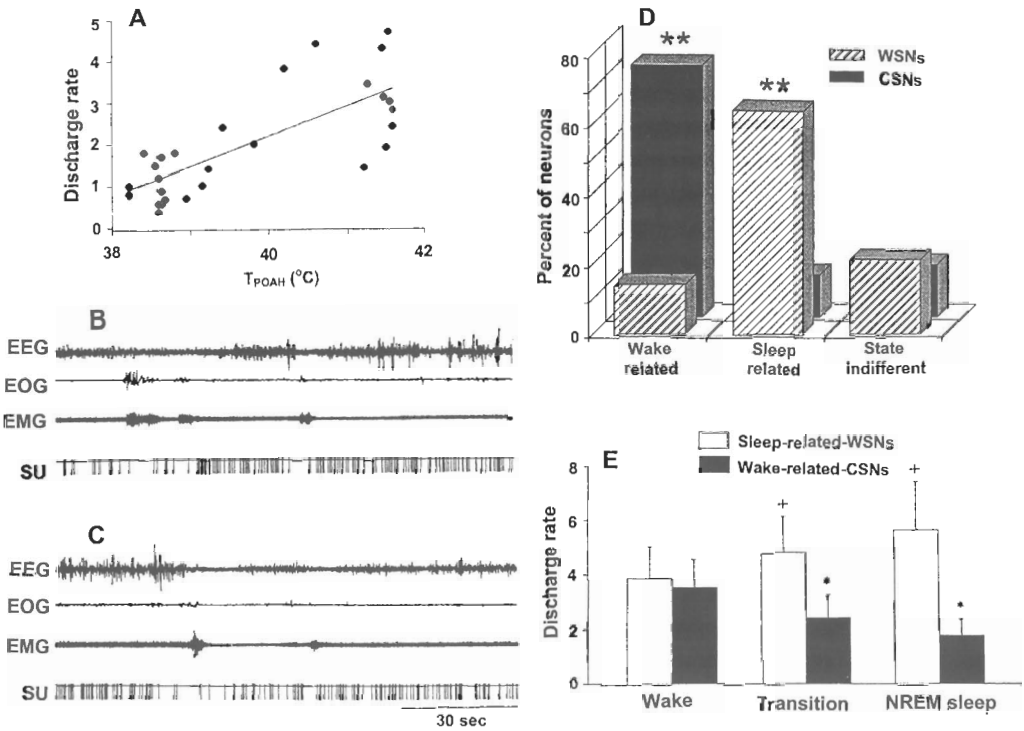
Fig. 1. - *POA/BF temperature-sensitive neurons and the sleep-wake cycle.*

A: A warm-sensitive neuron (WSN) based on the demonstration of increasing discharge rate with increasing local temperature. Cold-sensitive neurons (CSNs) showed decreasing discharge with increasing temperature. B: Time course of unit discharge (SU) of a typical WSN in a transition from waking to NREM sleep. Increased discharge preceded appearance of EEG synchrony (top trace). C. The same WSN exhibiting reduced discharge during transient arousal from sleep, as indicated by increased EMG activity and EEG activation in the example. D: Percentages of WSNs and CSNs showing sleep-related discharge or wake-related discharge. Most WSNs were sleep-related; most CSNs were wake-related. E: Analysis of discharge rate changes at state transitions in samples of WSNs and CSNs. WSNs showed increased discharge during the sleep onset transition; CSNs showed reduced discharge. Thus, these observations are consistent with a hypothesis that POA/BF temperature-sensitive regulate state changes. From Alam *et al.* (2).

in WSNs and CSNs at sleep onset are not responses to local temperature. Indeed, temperature is falling during sleep onset, so WSNs would be expected to exhibit reduced, rather than increased, discharge. The regulation of WSN and CSN discharge during sleep-waking is not understood, but could reflect the effects of sleep factors or synaptic input (see below). Many POA/BF thermosensitive neurons studied *in vitro* have discrete thresholds or inflection points in their temperature response functions (23), and these thresholds may be increased or decreased by synaptic input (17). We hypothesize that behavioral regulation by POA/BF thermosensitive neurons, including the occurrence of NREM and REM sleep, is determined by the synaptic regulation of these thresholds.

HOMEOSTATIC PROCESSES

A critical problem is concerned with the basis of sleep drive, the increased propensity for sleep after sleep deprivation. Szymusiak et al. (49) investigated the effects of sleep deprivation on the behavior of sleep-active neurons localized within the ventrolateral preoptic area (VLPO). This subregion of the POA/BF was investigated because it is a site of high density of neurons that exhibit c-fos protein immunostaining following sleep (47). C-fos labeling marks expression on an
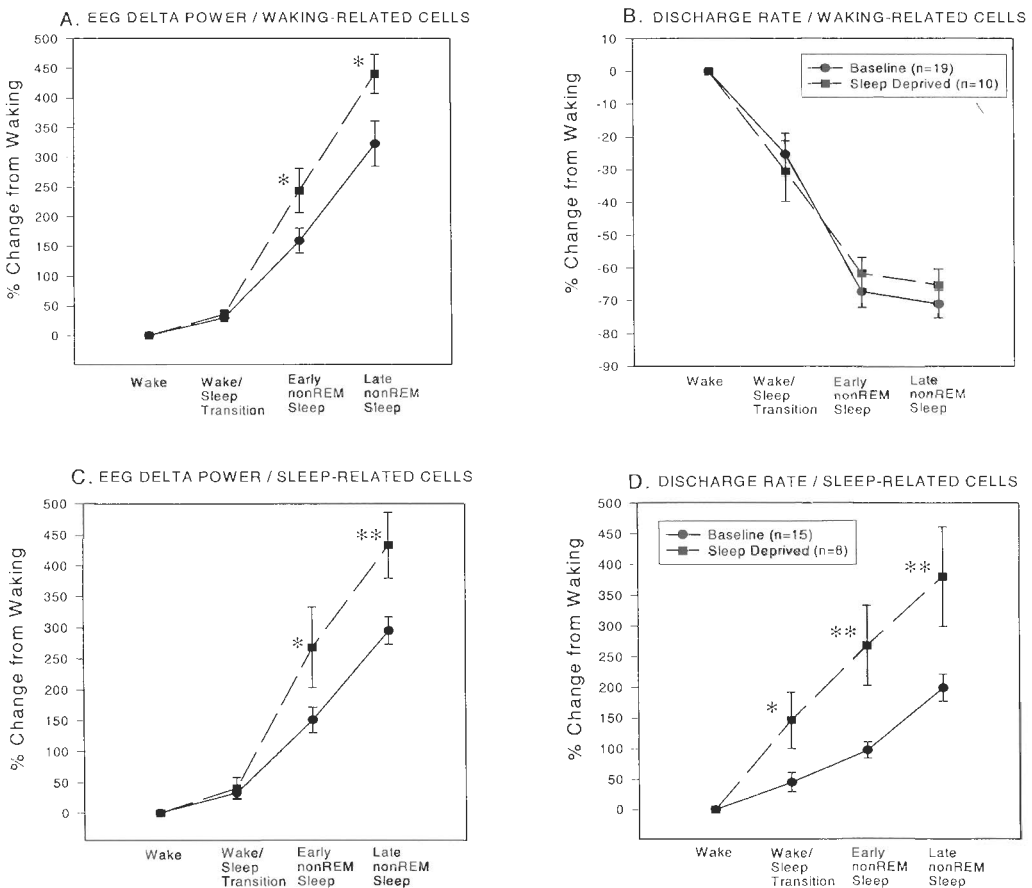

Fig. 2. - *Effects of 12-14 hours sleep deprivation on discharge rate of VLPO sleep-related and wake-related neuronal discharge and EEG delta power.*

Data from baseline and sleep-deprived conditions were obtained at the same circadian times at the sleep onset transition and early and late in a NREM sleep episode. Delta power was increased during sleep following sleep deprivation during studies of both wake-related and sleep-related cells, as expected (Fig. 2 and C). In sleep related cells discharge rate was increased at all stages of the NREM sleep cycle following sleep deprivation (Fig. 2D), but no change occurred in wake-related neurons (Fig. 2B). After sleep deprivation, in late NREM, sleep-related discharge increased almost 400% over awake baseline. From Szymusiak *et al.* (49).

immediate early gene which identifies elevated activity of neurons in most sites (37). Our neuronal unit recording study confirmed the interpretation that elevated c-fos expression during sleep was associated with increased neuronal discharge during sleep in the VLPO. We next compared that activity of VLPO sleep active neurons after 12-14 hours sleep deprivation with neurons recorded after *ad libitum* sleep. Neuronal discharge was related to the amplitude of delta EEG activity derived from power spectral analysis of the same epochs which provided unit discharge rates. Increased delta power is a good index of a response to sleep deprivation. In this study, we did not test all cells evaluated in the sleep-deprivation experiment for thermosensitivity.

Findings are shown in Figure 2. During sleep after sleep deprivation, EEG delta power was increased compared to baseline (Fig. 2A and C). Wake-active neurons recorded in this region were unaffected by sleep deprivation (Fig. 2B). Sleep active neurons showed greatly increased discharge *during sleep* at 3 stages of the sleep cycle, the sleep-onset transitional period, early NREM, and late NREM (Fig. 2D). During late NREM, the rates of sleep-active neurons nearly doubled their baseline sleep rates, from 200% to almost 400% above the awake rate. The increased discharge was associated with increased delta EEG activity that was measured concurrently with unit discharge rate (Fig. 2C). However, neither wake-active or sleep-active neurons exhibited changed discharge during waking after sleep-deprivation. These results show that the effects of sleep-deprivation are expressed in the activity of sleep-active neurons during sleep. However, we could not find evidence for the representation of sleep-deprivation in neuronal discharge during waking.

CIRCADIAN FACTORS

In constant stimulus conditions, sleep is jointly controlled by homeostatic and circadian processes, the latter originating in the SCN. In humans, within the circadian cycle, sleep onset and a decline of body temperature are normally coincident, but this doesn't mean that the two processes are coupled. However, under certain experimental conditions, including short sleep-wake cycles (28), internal desynchronization (11), and forced desynchronization (12), the interactions of the temperature rhythm and sleep propensity can be partially isolated from effects of prior waking and other circadian factors. These studies show that sleep propensity is increased primarily on the late descending phase of the circadian temperature rhythm and is highest when temperature is low. "Morning" awakenings tend to occur as temperature increases, even if sleep time is short. There is an evening "wake-maintenance zone" which is preceded by an afternoon period of increased sleepiness. Under entrained conditions sleep onset occurs at the time of maximum rate of fall of core temperature (38). Sleep evokes a further decrease in temperature, even with continuous bedrest (12). There have been attempts to show that the critical variable is not temperature itself but some correlated variable such

as melatonin secretion. However, melatonin is a weak hypnogen and is not applicable to nocturnal species (26). The most parsimonious hypothesis is that the *circadian control of sleep propensity is directly coupled to the mechanism that reduces body temperature.* Many SCN efferents terminate in the adjacent POA/BF where thermoregulation is controlled (35). There are circadian rhythms in the "set point" or threshold of thermoeffector functions (48).

A THERMOREGULATORY MODEL OF SLEEP

Nakao et al. (40) developed a formal mathematical model of human sleep control based on the interaction of thermoregulatory and circadian processes that predicts subtle features of sleep behavior. Please see the original paper for the mathematical derivation of model properties. In this model sleep is controlled in a manner similar to thermoregulatory processes, namely, through the interaction of hypothalamic temperature and a set point, T_{hypo}-T_{set}. The set point is modulated by a circadian oscillator controlling the temperature rhythm (X). A second oscillator modulates the activity of WSNs to control sleepiness (Y). The two oscillators, which are separated by a fixed phase difference under entrained conditions, were required to generate both late afternoon sleepiness and nocturnal sleep. The assumption of multiple oscillators is consistent with circadian physiology, since it is known that the SCN regulates a variety of hormonal rhythms with differing phase relationships. In the model, the sleep-evoked fall in body temperature provides part of the feedback signal to the hypothalamic controller. The final common path for sleep-wake control is the activity of hypnogenic WSNs. Sleep onset and offset are determined by thresholds in the output of these WSNs.

In the original model the homeostatic drive for sleep was based on the thermal history of the animal. In humans afternoon or evening whole body heating for 60-90 min. in baths or saunas increased stage 3-4 sleep that night, and that increased stage 3-4 sleep after exercise depends on body heating (18, 19). In rats, we showed that warming in a 33-35°C ambient temperature increased *subsequent* sleep with slow wave activity (S2 in the rat) for 3 hours compared to either sleep-matched or sleep-deprived controls (36). The "heat load" increased S2 more than total sleep-deprivation. Brain and body temperature was reduced compared to controls during the recovery period, suggesting that the augmentation of sleep was an element of an energy conserving strategy. A replication of our original result is published (42). In the model, the homeostatic drive for sleep was based on the integration of the awake "heat load", when hypothalamic temperature exceeds the set point. We realize that there could be several additional factors contributing to the homeostatic drive, including the accumulation of sleep factors such as cytokines, prostaglandin D2, or adenosine (16, 27, 43).

Fig. 3 shows the behavior of critical elements of the model under entrained conditions. Sleep onset begins at approximately the middle of the descending phase of the hypothalamic temperature rhythm: morning awakening occurs shortly

after temperature begins to rise. Sleepiness continues to increase after sleep onset. These features conform to known properties of human sleep-wake behavior. Sleep-wake cyclicity and sleepiness are jointly determined by several factors in the model, but the Y oscillator contributes strongly to the evening wake-maintenance by opposing the homeostatic drive. The Y oscillator also maintains sleep at the end of the night as the homeostatic drive (heat memory) and the role of T_{hypo}-T_{set} are diminished. In the model, sleep onset occurs near the time when the difference
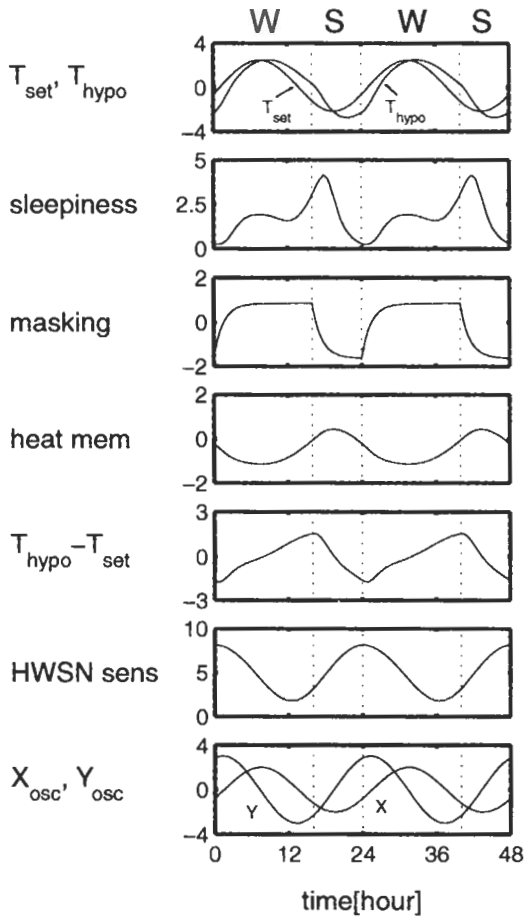

Fig. 3. - *Behavior of a thermoregulatory feedback control model of human sleep, solved by differential equations, in which sleep is controlled by hypnogenic warm-sensitive neurons (HWSN) with discharge controlled by T_{hypo}- T_{set} and modulated by two circadian oscillators, X and Y.*

A: shows the behavior of various elements of the model. Sleep onset begins in the mid descending phase of T_{hypo}, at the peak of the function, T_{hypo}- T_{set}, and ends just after the beginning of the rising phase. The X oscillator drives T_{set}, and is closely related with the temperature rhythm. The Y oscillator, which is phase shifted about 7 hours from X, contributes to the evening wake-maintenance by opposing the effects of homeostatic drive, but enhances sleep at the end of the night. In this model, homeostatic drive is generated by a heat memory which increases when T_{hypo} exceeds T_{set}. From Nakao et al. (39).

between the "set point" and hypothalamic temperature is greatest. The hypothesis that there are two distinct circadian contributions to hypnogenic drive is supported by the recent description of bimodal melatonin secretory activity during the night in some human subjects (56) and bimodal sleep under extended dark conditions or short photoperiod (55).
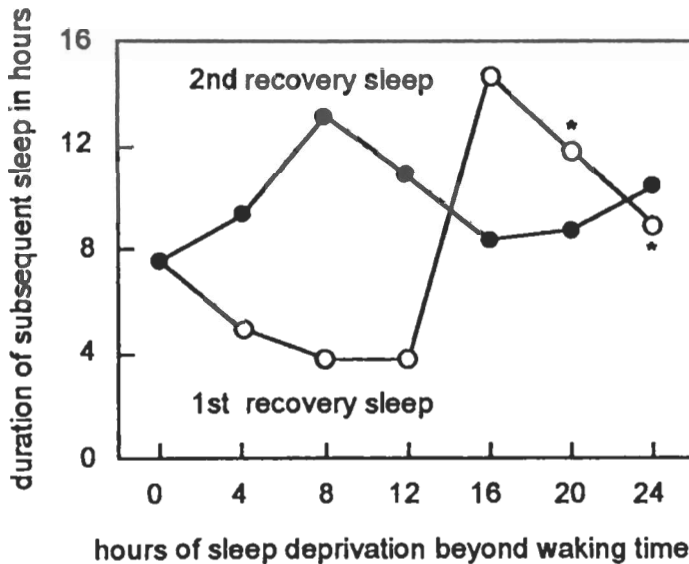

Fig 4. - *Thermoregulatory model behavior, showing the duration of sleep after varying lengths of sleep deprivation from the time of usual sleep onset.*

Four to 12 hours deprivation is followed by short recovery sleep, but at 16 hours, recovery sleep jumps to a long duration. This behavior, which was not considered in the development of the model, closely mimics the findings of Akerstedt and Gillberg. The model predictions concerning sleep duration on the second recovery "night", shown in Fig. 4, have not been assessed.

Fig 4. shows predictions of the model on effects of varying durations of sleep deprivation on the subsequent sleep duration. These predictions were not incorporated into the original design. The predictions concerning the first recovery night, including the sudden increase in sleep duration from 12 to 16 hours deprivation closely match existing data (1). The predictions concerning the second recovery night haven't been tested.

CONCLUSIONS

Our model shows that subtle features of human sleep-wake patterns and the interactions of the temperature rhythm and sleep can be generated by a thermoregulatory control system. The occurrence of sleep onset on the descending

phase of the circadian temperature rhythm is compatible with such a model. It must be emphasized that the evaluation of the thermoregulatory control model of sleep cannot be based on the measurement of body temperature alone. In the model and in human subjects sleep begins at an intermediate body temperature and ends at a relatively low body temperature. These events are closely related to T_{hypo}-T_{set}, but not to absolute temperature. Thus, predictions about the timing of sleep relative to core temperature also depend on knowledge of the set point. Inferences about the set point can be derived from observations of peripheral heat exchange processes such as vasodilation. It is notable that sleep onset has been correlated with maximum vasodilation, as indicated by foot temperature, an indicator of heat loss (24). This would correspond to peak level of T_{hypo}-T_{set} in our model.

How does the POA/BF hypnogenic system bring about sleep? Acute inactivation of the posterior hypothalamic (PH) wake-promoting system can reverse the insomnia resulting from inactivation of the POA/BF hypnogenic system (46). This result is consistent with the hypothesis that the POA/BF induces sleep by suppressing PH and other wake-promoting systems via inhibitory pathways. We have demonstrated that local POA/BF warming suppresses activity of putative arousal-promoting neurons in the PH (25), dorsal raphe nucleus (15), and BF (6). POA/BF stimulation inhibits midbrain arousal-related neurons (52). EEG deactivation and hyperpolarization of thalamic relay neurons was found to result from withdrawal of activating input from brainstem serotonergic, cholinergic, and histaminergic arousal systems, through disinhibition of K^+ channels in thalamus (29, 31). Thalamic hyperpolarization, in turn, activates Ca^{++}-dependent slow depolarization and after-hyperpolarization that contributes to delta waves and spindles (30). Thus, through inhibition of brainstem, PH, and BF arousal systems, POA/BF warming can readily control EEG slow wave activity, as we have demonstrated in the cat. We summarized evidence that POA/BF sleep active neurons show increased activity during sleep after sleep deprivation. Increased sleep-active discharge was correlated with increased delta EEG activity. Thus, we may hypothesize that the activation of POA/BF sleep-active neurons is the substrate of sleep drive. We can further hypothesize that the integration of circadian and homeostatic processes occurs in the POA/BF. The mechanistic details of this integration are not yet worked out.

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