Neuroscience and Biobehavioral Reviews, Vol. 16, pp. 379-397, 1992
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0149-7634/92 $5.00 + .00

A Brain-Warming Function for REM Sleep

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Received 30 November 1989

WEHR, T. A. *A brain-warming function for REM sleep.* NEUROSCI BIOBEHAV REV **16**(3) 379-397, 1992.—During REM sleep, arterial blood flow, neuronal firing rates, metabolism, and temperature increase in many parts of the CNS. Eye muscle tone also increases, and the eyes exhibit bursts of rapid movements. If one of the functions of sleep is to conserve energy, then it is curious that energy is so conspicuously expended in the vicinity of the CNS during REM sleep. The author hypothesizes that homeotherms use REM sleep to produce heat in order to maintain a high, stable temperature in a restricted CNS core during sleep. The fact that several of the active features of REM sleep heat the CNS, and the fact that REM sleep propensity increases when core temperature physiologically decreases, seem consistent with the hypothesis that REM sleep is a regulated mechanism for warming the CNS.

REM sleep Thermogenesis Thermoregulation Homeothermy Metabolism Circadian rhythm
Slow-wave sleep Hypothalamus Rhombencephalon

"Such prosaic events as the diurnal fall in body temperature . . . may be the direct cause of CNS changes which manifest themselves as dreaming."

—Aserinsky & Kleitman, 1955 (9)

IN the 40 years since the discovery of REM sleep, many hypotheses about its function have been proposed, yet it remains an enigma. In their original description of REM sleep, Aserinsky and Kleitman speculated that the daily decline in body temperature might trigger REM sleep, but it is not clear whether they had any particular thermoregulatory function in mind (9). In this paper, the author hypothesizes that REM sleep is programmed to occur when CNS temperature is low and that it has a thermoregulatory function—that homeotherms use REM sleep to produce heat in order to maintain or increase temperature in the CNS during sleep.

THE PHASES OF SLEEP AND THEIR FUNCTIONS

Sleep is characterized by two very different states that alternate with one another cyclically, REM sleep and non-REM sleep (40) (Figs. 1a and 4).

NREM sleep is a state of behavioral and physiological quiescence (75). Body temperature, heart rate, respiratory rate, metabolic rate (1,24,51), resting muscle tone (56,70), and spontaneous motor activity decrease compared with the waking state (56) (Figs. 1, 2, and 12). These changes are accompanied by diffuse slowing and synchronization of the electroencephalogram (EEG) (75). (In human beings, the portions of NREM sleep in which slow waves are most prominent (sleep stages III and IV) are called slow wave sleep (SWS) or delta sleep. Some investigators have considered SWS to be an expression of the intensity of NREM sleep (20). In animals, the entire NREM sleep phase is often referred to as SWS. In this paper, SWS mainly refers to the intensity dimension of NREM sleep.)

REM sleep is a seemingly paradoxical state in which behavioral and physiological activities increase in some parts of the body and decrease in others (75). Central nervous system activity increases dramatically in many regions. CNS neuronal firing rates (48,75,135), blood flow (83,84,90,110), metabolism (1,24,51,136), and temperature (46,62,79,80,104,152) increase, and the EEG exhibits low voltage, fast activity similar to that which occurs during wakefulness (1,75,110) (Figs. 1, 2, and 5). Activity in structures adjacent to the CNS also increases. Resting tone in the rectus muscles of the eyes increases (92), and phasic bursts of rapid eye movements occur (75). In newborn animals, muscles of mastication also become active (112). Non-shivering thermogenesis appears to switch on in brown adipose tissue (BAT) adjacent to the spinal cord (52). In addition, respiratory movements become rapid and irregular (75,112).

At the same time, activity in many peripheral structures decreases during REM sleep. Although skeletal muscles exhibit twitches in conjunction with the phasic events of REM sleep, they are paralyzed most of the time, and spinal reflexes are abolished (57,75). Skeletal muscle tone, which decreases at the onset of sleep, remains low during REM sleep (70). In addition, tone in head and neck muscles decreases further and is lost during REM sleep (70). The activities of peripheral thermoregulatory effector mechanisms, such as shivering, panting, and sweating, are largely suspended during REM sleep (103).

If, as some think, one of the basic functions of sleep is to conserve energy, then it is curious that energy is so conspicu-

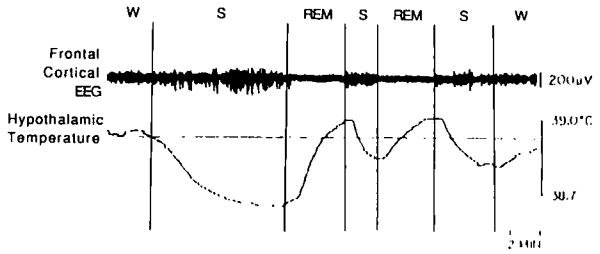

FIG. 1A. Changes in the electroencephalogram of the frontal cortex (top) and in pre-optic hypothalamic temperature (bottom) during wakefulness (W), slow wave (NREM) sleep (S) and REM sleep (REM) in a rabbit. Hypothalamic temperature declines during slow-wave sleep and rises sharply during REM sleep as the two states alternate [adapted with permission from Kawamura, H.; Sawyer, C. H. Elevation in brain temperature during paradoxical sleep. Science 150; 1965 (79)].

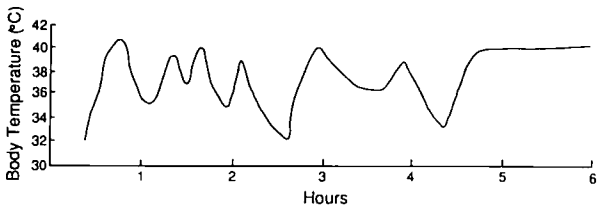

FIG. 1B. Diurnal course of body temperature in a desert iguana studied in a concentric thermal gradient. Body temperature is controlled by an on-off mechanism that causes the animal to move to cooler positions in the gradient when its body temperature becomes warm and causes it to move to warmer positions in the gradient when its body temperature becomes cool. The example shows that this type of body temperature regulation can be rather imprecise, and that there is no "critical" lower threshold for triggering movements into the warm part of the gradient [data of Dewitt (43)]. Compare temperature recording in this figure with temperature recording in Figure 1A.

ously expended during REM sleep. It suggests that REM sleep has an essential function. Although various functions have been proposed for REM sleep since its discovery forty years ago, no consensus has emerged. In fact, some investigators have even suggested that the physiological changes that accompany REM sleep are a form of autonomic dysregulation and have no useful function (106).

Although the function of REM sleep remains obscure, a series of observations and experiments suggest a possible function for SWS. It has been argued that SWS is part of a thermolytic process whose function is to down-regulate core temperature after sleep onset (88,146). The evidence for this is as follows: First, there is an association between the occurrence of SWS and down-regulation of core temperature:

- SWS is most abundant at the beginning of sleep when core temperature declines most rapidly (Fig. 3);
- animals enter the low temperature states of torpor and hibernation during SWS (146);
- ontogenetically, SWS appears at the same time that animals become capable of maintaining high temperatures during wakefulness (145).

Second, SWS responds in a counterregulatory manner to thermal stress:

- external heating prior to sleep augments SWS (25,67).

SWS AND REM SLEEP AS OPPOSITE STATES WITH OPPOSITE FUNCTIONS

A clue to the function of REM sleep may lie in the fact that SWS and REM sleep are opposite in several respects:

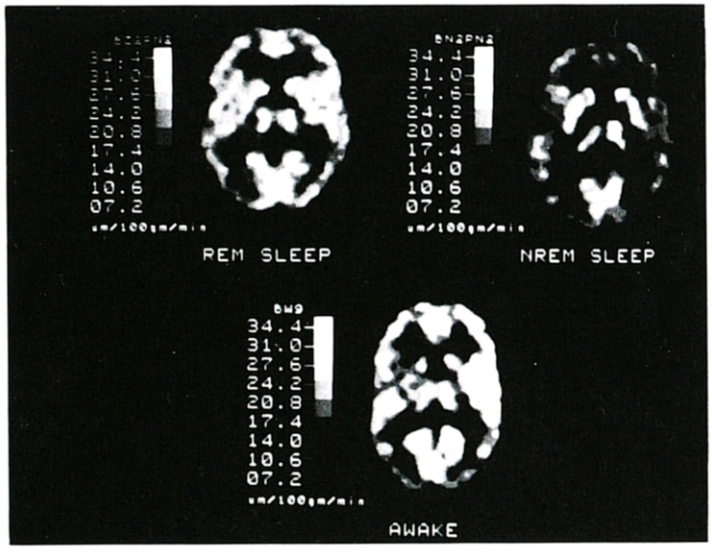

FIG. 2A. Positron Emission Tomography (PET) scans at the midventricular level in human beings show that glucose metabolic rate is low during NREM sleep but high during REM sleep. Metabolic rates during REM sleep are not different from those during wakefulness [reprinted with permission from Buchsbaum et al. Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. Life Sci. 45; 1988. (24)].

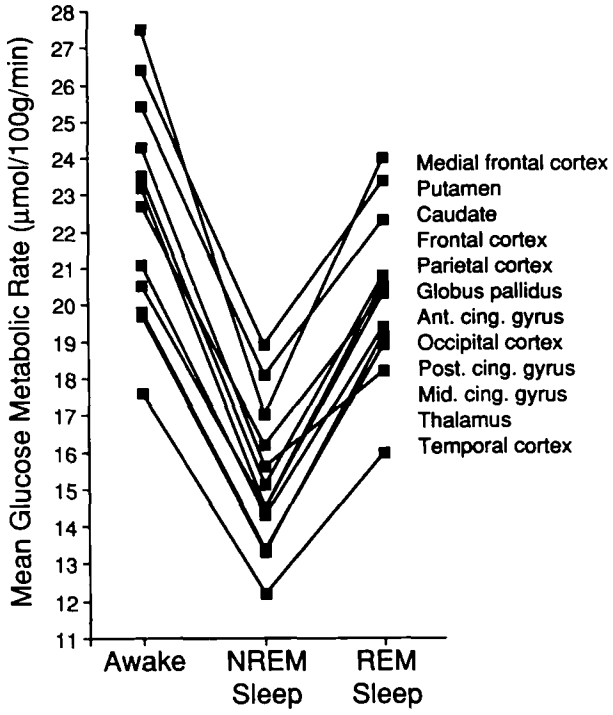

FIG. 2B. Glucose metabolic rates at various sites in the human brain are consistently low during NREM sleep and high during REM sleep and wakefulness [data Buchsbaum et al. (24)].

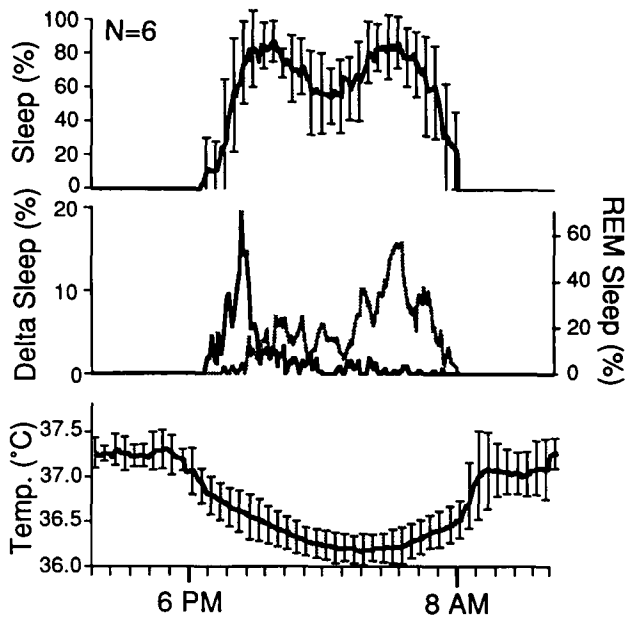

FIG. 3. Average daily profiles of sleep (top), delta sleep (middle: black line), REM sleep (middle: gray line) and rectal temperature (bottom) in six young men who slept during a 14-hour dark period each night for 4 weeks (149). Data are taken from the last 2 weeks of the experiment. Sleep became bimodal. Delta sleep (SWS) reached peak levels shortly after sleep onset, when levels of rectal temperature were declining. REM sleep reached peak levels not long before the onset of wakefulness, when levels of rectal temperature reached a minimum and were beginning to rise (previously unpublished data of the author).

- They occupy opposite phases of an ultradian cycle that oscillates throughout the sleep period.
- They have opposite temporal distributions during sleep (see Fig. 3). Slow wave sleep reaches peak levels near the beginning of the sleep phase, when body temperature is high but rapidly declining, and it decreases exponentially during the course of the sleep phase. REM sleep increases during the course of the sleep phase, reaching peak levels near the end when body temperature is low but rapidly rising. SWS follows transitions from wakefulness to sleep; REM sleep precedes transitions from sleep to wakefulness (see Fig. 4).
- Behavioral and physiological changes during SWS and REM sleep are also opposite in many respects. As described above, SWS is a quiescent state, while REM sleep (in the CNS) is an active state.

If SWS and REM sleep have opposite and symmetrical features, then I suggest that they may also have opposite and symmetrical functions. Specifically, assuming that slow wave sleep is part of a thermolytic process that lowers core temperature, I propose that REM sleep is part of a process that produces and conserves heat and raises core temperature. This possibility has been raised before in publications by Snyder (134) and Palca, Walker, and Berger (98). In making this proposal, I consider body warming in REM sleep to differ from waking modes of body heating by being confined to a cooler and smaller core, limited mainly to the CNS and vital organs such as the heart (see discussion below).

Several features of REM sleep appear to be consistent with a CNS-heating function:

- CNS temperature usually rises during REM sleep.
- The propensity for REM sleep is greatest when core temperature reaches its lowest physiologic levels.
- Several of the most characteristic features of REM sleep are inherently thermogenic.

CNS TEMPERATURE USUALLY RISES DURING REM SLEEP

CNS temperature usually rises dramatically during REM sleep, (Figs. 1a and 5) (3,79,80,104,152), and the highest levels of REM sleep, near the end of the daily sleep phase, are associated with a rapid rise in core temperature toward levels that are maintained during wakefulness (Fig. 3). Species in which CNS temperature is reported to increase during REM sleep include rat (3,123), cat (64,104), sheep (64), and rabbit (64, 79,80).

In squirrel monkeys, brain temperature is also reported to increase in REM sleep (46). However, in rhesus monkeys results are conflicting. The same investigators reported that deep brain temperature increased during REM sleep in one experiment, and decreased in another experiment (63,64). Indirect evidence (tympanic temperature) suggests that brain temperature rises during REM sleep in human beings (98).

During REM sleep, peripheral sympathetic vasomotor tone is lost. Consequently, heat exchange between the skin and the environment increases, and arterial blood temperature is more strongly influenced by the ambient temperature to which the animal is exposed (3,64,104). For this reason, peritoneal temperature rises during REM sleep if ambient temperature is high, and falls during REM sleep if ambient temperature is low. In spite of this fact, CNS temperature in certain animals rises during REM sleep regardless of whether ambient temperature is high or low (3,104). Furthermore, during REM sleep

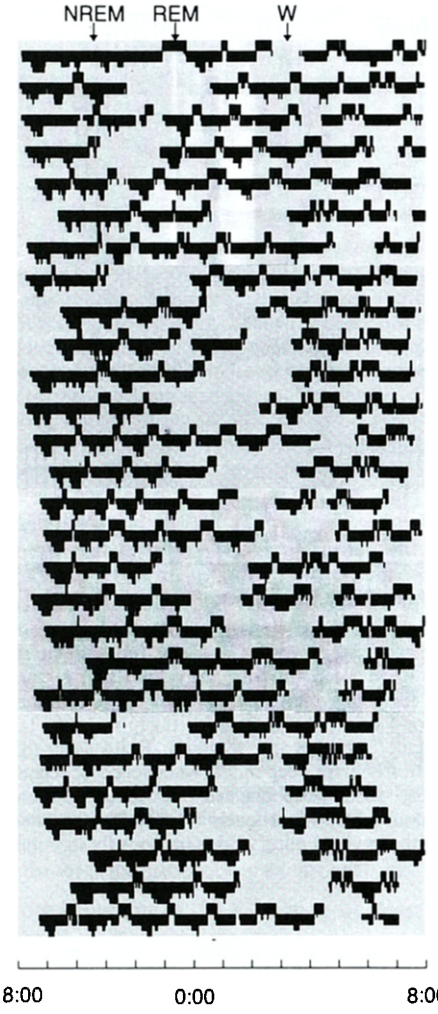

FIG. 4. Nightly patterns of sleep in one individual who participated in the experiment described in the legend of Fig. 3. Shaded area indicates the nightly period of darkness. In each line of data, upper dark bar represents REM sleep, and lower dark bar indicates NREM sleep, with gradations for stages I-IV. Note that spontaneous awakenings during the night almost always follow REM sleep phases (previously unpublished data of the author).

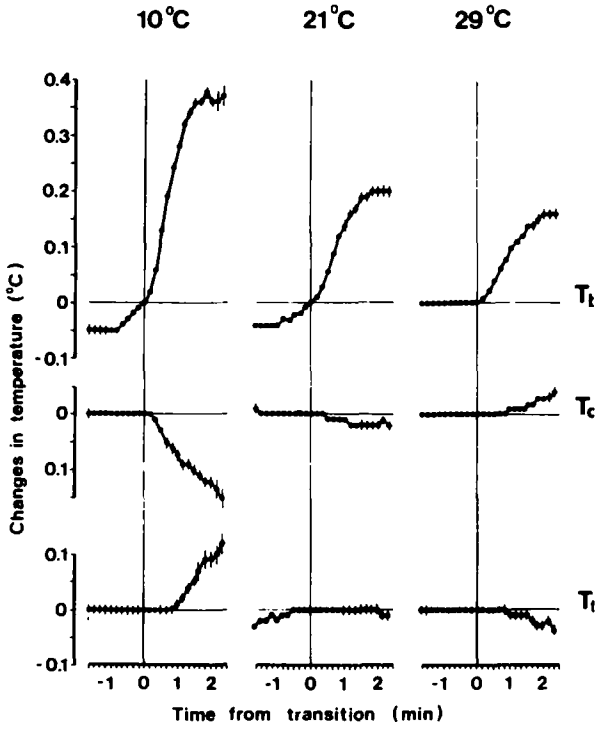

FIG. 5. Variations in brain temperature (T_{br}) (row 1), core temperature (T_c) (row 2) and tail temperature (T_t) (row 3) in the course of transitions from NREM sleep to REM sleep at various ambient temperatures in the rat. Although T_c rises during REM sleep at higher ambient temperatures and falls at lower ambient temperatures, T_{br} rises at both higher and lower ambient temperatures, and it rises more at lower ambient temperatures [data of Alföldi, Rubicsek, Cserni, and Obál (3)].

in rats (3) and possibly in human beings (98), CNS temperature rises more when ambient temperature is low than when it is high. However, in the pocket mouse (147), harvest mouse (141), hamster (141), and possibly the rhesus monkey (see above), brain temperature during REM sleep rises in high ambient temperatures but falls in low ambient temperatures. The fact that in low ambient temperatures these latter animals' brain temperatures decline during REM sleep would appear to pose a problem for the theory that a function of REM sleep is to warm the brain.

In considering investigations of brain temperature during REM sleep, and investigations of the effects of thermal challenges on REM sleep (which will be discussed later), there is a fundamental problem of interpretation when animals are studied at low temperatures in non-physiologic, laboratory situations. For example, the rhesus monkeys referred to above were studied while they were restrained in chairs in air-conditioned chambers. In nature, animals usually sleep in insulated refuges, and they often make heat-conserving postural adjustments. Moreover, small animals often sleep huddled together. These adaptations greatly diminish the rate at which heat is lost from the body during sleep. Furthermore, animals are usually acclimated gradually to the thermal stresses to which they are exposed during the course of the year. Given the importance of ecological and behavioral factors that modify heat loss during sleep in natural settings, it is debatable how much can be inferred about the function of REM sleep from behavior in laboratory settings where animals may not have access to a refuge, where they may not be able to make heat-conserving postural adjustments, where they may not be able to huddle together with other animals, where heat-conducting materials are attached to their skulls, where they are exposed to circulating air, and where they may not have become acclimated to the thermal stresses to which they are exposed. Behavior in natural settings is likely to be relevant to function because it was selected during the course of evolution. We cannot be certain that the same is true of behavior in non-physiologic laboratory settings.

It is also debatable whether the responses to low ambient temperatures of heterothermic (hibernating) animals, such as hamsters and certain other rodents, should be decisive in accepting or rejecting the theory. Heterothermic animals sometimes respond to cold exposure by suspending thermogenesis and allowing CNS temperature to fall. For these reasons, the

decline in brain temperature that is observed in some of these animals in low ambient temperature cannot be accepted uncritically as evidence against the theory.

REM SLEEP PROPENSITY IS HIGH AT LOW PHYSIOLOGIC BODY TEMPERATURES

Consistent with the theory, there are three situations in which physiological lowering of CNS temperature is associated with an increased propensity for REM sleep:

- In intact, adult animals NREM sleep usually precedes REM sleep. As mentioned above, the transition from wakefulness to NREM sleep is associated with a regulated lowering of core temperature (58,103,146). In this situation, changes in REM sleep propensity are inverse to changes in body temperature. When ambient temperature is low, REM sleep is most likely to occur when hypothalamic temperature becomes low during NREM sleep and is least likely to occur when it remains high (102,103) (Fig. 6). NREM episodes that fail to terminate in REM sleep terminate in wakefulness. This type of arousal tends to occur when ambient temperature is too cold, and it has been interpreted as a behavioral thermoregulatory response that originates in the hypothalamus and overrides rhombencephalic REM sleep mechanisms (103). According to this interpretation, REM sleep can only occur if hypothalamic controls permit the homeothermic core to reach a sufficiently low temperature.
- CNS temperature is raised and lowered each day by the oscillations of a circadian pacemaker. Within the range of this physiological variation, REM sleep is least likely to occur when core temperature is high, and most likely to occur when it is low (Fig. 7). In fact, REM sleep often occurs immediately after sleep onset when sleep begins near the daily temperature minimum (32,35,151,154).

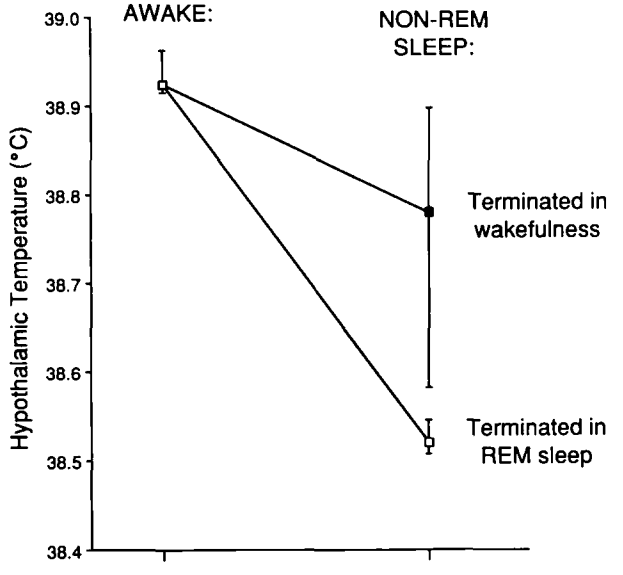

FIG. 6. In cats exposed to an ambient temperature of 0° C, REM sleep is most likely to occur when hypothalamic temperatures reach low levels during NREM sleep and is least likely to occur when they remain high. Median hypothalamic temperatures and 99% confidence intervals are shown during wakefulness (left) and during NREM sleep (right) for episodes of NREM sleep that terminated in wakefulness (upper right) and for those that terminated in REM sleep (lower right) [data of Parmeggiani, Agnati, Zamboni, and Cianci (102)].

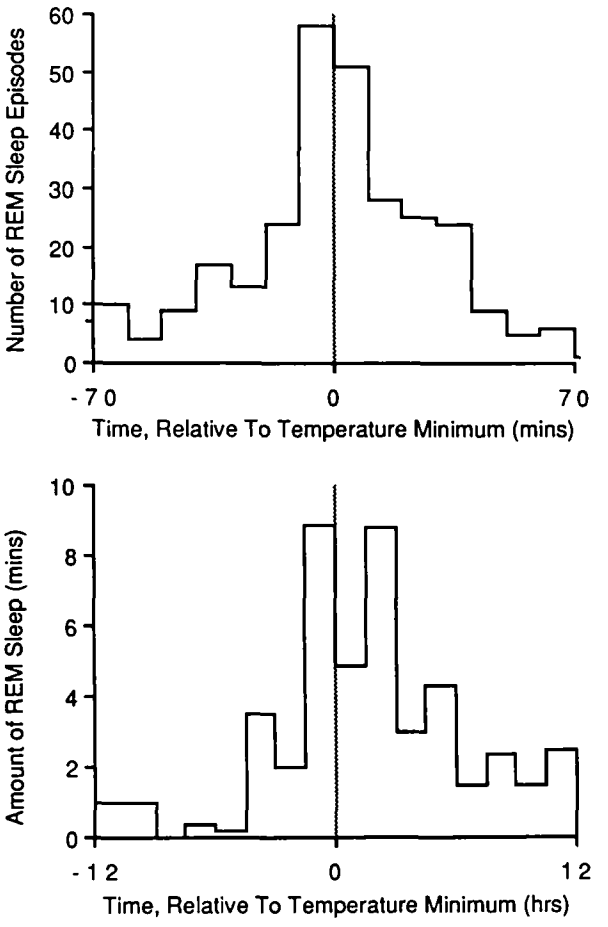

FIG. 7. The fact that the probability of occurrence of REM sleep in several situations is highest when core temperature is lowest is consistent with the hypothesis that REM sleep is a regulated CNS warming-mechanism that is triggered by a cold-sensitive rhombencephalic thermostat. Two examples of such situations are shown in this figure. Top: In cats from which much of the CNS above the level of the rhombencephalon has been removed, REM sleep occurs most frequently near the time of the minimum of a cycle of core temperature generated by an incubator thermostat. The number of REM sleep episodes is shown as a function of their time of occurrence relative to the time of the temperature minimum of the temperature cycle [data of Jouvet et al. (76)]. Bottom: In human beings living on a 90 minute sleep-wake schedule, the amount of REM sleep is greatest near the time of the minimum of the circadian rhythm of temperature. Minutes of REM sleep are shown as a function of the time sleep began relative to the time of the minimum of the temperature rhythm [data of Carskadon and Dement (32)].

- Core temperature is low at birth and increases gradually with maturation of thermoregulatory mechanisms (23,118, 145). At the beginning of life, when body temperature is low, REM sleep is most abundant, and it often occurs immediately after sleep onset (77,144). Later, as temperature rises, REM sleep declines, and its appearance after sleep onset is delayed (77) (Fig. 8).

A SMALLER AND COOLER CORE DURING REM SLEEP

Homeothermic temperature regulation is characterized by the maintenance of a high, stable temperature in a core region

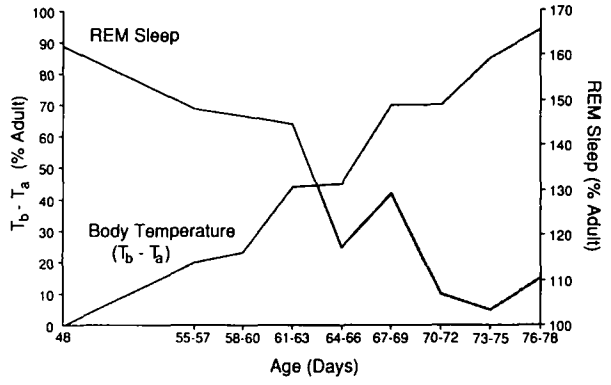

FIG. 8. During growth and development the probability of occurrence of REM sleep is highest when core temperature is lowest. For example, as young opposums grow, their capacity to maintain body temperature at a level above ambient temperature increases, while the amount of their REM sleep declines. The number of degrees above an ambient temperature of 30° C that these animals can maintain body temperature ($T_b - T_a$) at different ages is shown expressed as a percent of adult values. The REM sleep fraction of recording periods at different ages is shown expressed as a percent of adult values [data of Walker and Berger (145)].

of the body (34,60,120,131). The portion of the body that surrounds the core, the shell, is less critically regulated, and it serves as insulation for the core. The size and the temperature of the core can change over time to adapt to different conditions. During wakefulness, the homeothermic core extends into the extremities, and it depends to a large extent on muscles of the limbs and trunk for the production of its heat.

During sleep the homeothermic core is maintained at a lower temperature than during wakefulness (58,146). Lowering of temperature is a direct effect of sleep (146) and of the temperature circadian rhythm, which normally reaches its minimum during the sleep period (35,55).

In sleep, resting tone and thermogenesis in skeletal muscles decline significantly. As a result, skeletal muscles become less a part of the organism's homeothermic core and more a part of its insulating shell (103,123). As the shell expands, the core contracts. As envisioned here, the core becomes confined mainly to the CNS and its vicinity and vital organs, such as the heart. Instead of skeletal muscles, which now lie outside the core, structures lying within the anatomical boundaries of this smaller core are recruited to produce heat for it. According to this interpretation, the recruitment of structures in the CNS and its vicinity for thermogenesis is responsible for some of the active features of REM sleep, such as increased CNS metabolism and rapid eye movements. Moreover, because their function is thermogenesis, the active features of REM sleep are not confined to a few areas, but are widely distributed in the CNS (Fig. 2).

MECHANISMS FOR CNS WARMING DURING REM SLEEP

At least two of the active features of REM sleep, increased intracranial bloodflow and increased neuronal activity and metabolism, have been implicated as causes of the warming of the CNS that occurs during REM sleep (see Fig. 4):

1. *Increased intracranial arterial bloodflow.* Intracranial arterial blood flow increases dramatically during REM sleep, and the influx of warm arterial blood appears to be a significant cause of the elevation of brain temperature during REM sleep (18,45,62,64,78,105,110,126,127,139).

Increased intracranial bloodflow could also be expected to promote conservation of heat in the CNS. Cool blood from superficial veins of the face and scalp can return to the heart through venous drainage of the central nervous system via emissary veins, including the angular vein, or it can bypass the CNS and drain externally through tributaries to the external jugular vein (27,71) (Fig. 9). During exercise or other forms of thermal stress the shunting of cool venous blood from the face and scalp into the intracranial venous system is thought to play a role in selective cooling of the central nervous system (22,27,97). When intracranial arterial blood flow increases during REM sleep, the resulting increase in flow of venous blood from intracranial sources, in the absence of any corresponding increase in flow of venous blood from extracranial sources, could be expected to impede the shunting of cool venous blood from the face and scalp into the CNS and thereby reduce cooling of the CNS by this mechanism.

Countercurrent heat exchange between parallel vessels within the CNS maintains an intracerebral thermal gradient that would tend to retain heat produced in the CNS during REM sleep (64,124).

2. *Increased neuronal activity and metabolism in the CNS.* During REM sleep, neuronal firing rates, blood flow, glucose consumption and oxygen consumption increase in most parts of the brain and spinal cord (1,24,48,51, 75,83,84,90,110,135,136) (Fig. 2). Chemical processes associated with this activity produce heat (37,39,62,79,80, 104,121,139,152) (Fig. 1). Parmeggiani and coworkers have shown, on the basis of a detailed analysis of relationships between hypothamamic, skin, and ambient tempera-

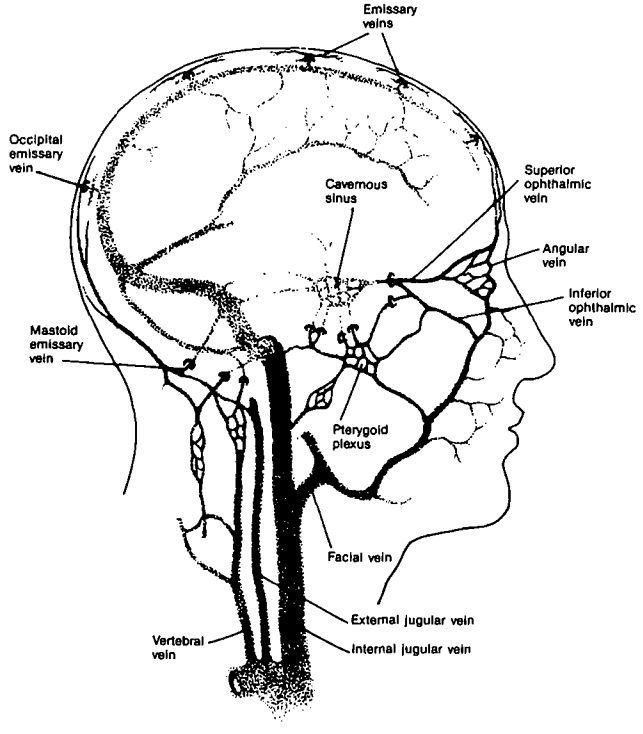

FIG. 9. Intracranial and extracranial routes of venous drainage of the head. Emissary veins connect the internal and external systems at sites shown (redrawn with permission from Gray's Anatomy. Philadelphia: Lea and Febiger; 1965:741).

ture in the cat, that increased local CNS metabolism also plays a significant role in raising CNS temperature during REM sleep (104). In connection with the present theory, I interpret activation of neural tissue during REM sleep to be a form of non-shivering thermogenesis. To the extent that cerebral activity in REM sleep is not engaged in the performance of work in the external world, this activity could be compared to "futile" metabolic cycles used to produce heat in other tissues (115). The widely distributed nature of the neural activation that occurs in REM sleep (1) (see Fig. 2) has sometimes been viewed as an impediment to understanding the function of REM sleep. However, this distribution could be regarded as a clue to function, if REM sleep has a function like thermogenesis, that would be best served by widespread activation of heat-producing tissue.

In addition to these two known causes of CNS warming during REM sleep, I would like to suggest several other possible mechanisms. By comparison, the evidence for these additional mechanisms is at present incomplete and, sometimes, speculative or contradictory.

3. *Increased resting tone of the rectus muscles of the eyes and rapid eye movements.* Heat generated by resting tone in skeletal muscles is a major source of heat in the body. The tone of the rectus muscles increases during REM sleep (92). The heat produced by this increased tone, provided it is sufficient, might act locally to warm the eyes, and in particular the retina, which is an extension of the CNS (Fig. 10). A thermogenic function of eye-related muscles has been demonstrated in other vertebrate species. For example, some fish are equipped with orbital muscles that use chemical and vascular mechanisms to heat the eyes and the brain (31).

   In biology, there are many examples of muscles that have specific mechanical functions but can also be recruited to generate heat, often with repetitive, seemingly purposeless movements. Shivering is a familiar example. Wing-vibration in insects is another (13). During REM sleep vigorous phasic bursts of rapid eye movements occur. The mechanical heat produced by these movements and the convected heat from increased arterial bloodflow to the eye muscles might also warm the eyes, including the retina. Since the veins of the eye muscle can drain into the cavernous sinus, this heat might also contribute to the warming of blood in the venous plexuses and lakes of the CNS (Fig. 3). The effect of this warming would probably be greatest for the pituitary, whose small arteries pass through the cavernous sinus (111), and possibly for portions of the hypothalamus, which can receive blood from the pituitary circulation (15,107). However, the magnitude and biological significance of the warming effect of increased tone and rapid movements of eye muscles has not been precisely determined. (In human beings, eyelid temperature increases about 0.5° C during REM sleep and during 5 minutes of voluntary rapid eye movements during wakefulness, unpublished data of the author.)

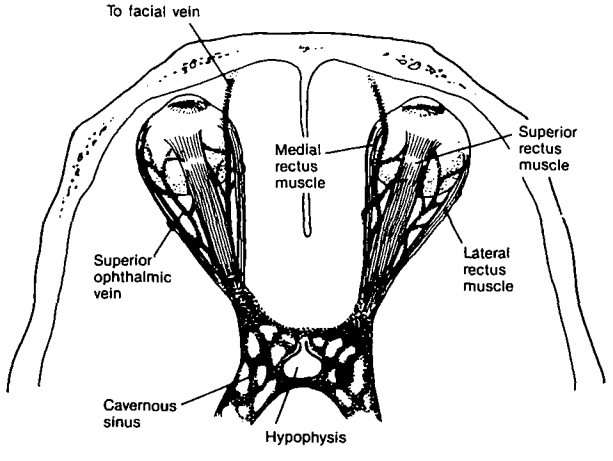

FIG. 10. Extraocular muscles and their veins. Heat produced by the increased tone and rapid movements of these muscles during REM sleep might warm the eyes and retinas (see text).

4. *Sucking movements.* In infants, vigorous sucking movements are prominent at the beginning of REM sleep, and they produce mechanical heat (112). The muscles of mastication are surrounded by a rich plexus of veins, the pterygoid plexus, that could collect heat from the muscles and convey it into the cavernous sinus (12,30) (Fig. 9). By this route sucking movements might also contribute to warming of blood in the venous plexuses and lakes of the CNS. Again, it remains to be determined whether such warming would be biologically significant.
5. *Activation of brown adipose tissue (BAT).* BAT lies in deposits along the cervical, thoracic, and lumbar spine. It is especially well-developed in neonatal and in cold-adapted animals, and its function is to generate heat in a restricted core region of the body (2,108,132,133). A portion of this heat passes convectively to the spinal cord by shunting of warmed blood to the vertebral venous plexus (133) (Fig. 11). In several species, BAT also surrounds the carotid arteries, which convey heat from BAT directly to the brain (2,108). The ontogeny of BAT parallels that of REM sleep. It is abundant at the beginning of life and declines with the development of more mature forms of homeothermic regulation (133). However, significant amounts of BAT may be present in adult animals, including human beings, when they live in cold environments (69). The possibility that BAT switches on and helps to warm the CNS during REM sleep is suggested by recent evidence that BAT temperature rises during REM sleep in young rabbits exposed to low ambient temperatures (52). However, this evidence is indirect and open to other interpretations. The temperature increase might simply reflect a warming effect of increased arterial blood flow in BAT during REM sleep. However, in other situations BAT blood flow and BAT activity are strongly coupled (52). In human infants, who have well-developed BAT, metabolic rate increases 25% during exposure to cold in REM sleep, as compared to 8% in NREM sleep (49). In rats, heat production during REM sleep increases significantly when ambient temperature is reduced to low levels (123). As Horne points out (68), these observations are consistent with the interpretation that BAT becomes activated during REM sleep if ambient temperature is low, and they are inconsistent with the interpretation that thermoregulation is suspended during REM sleep. However, temperature in BAT actually decreases during REM sleep in small cold-exposed animals, such as rats and hamsters (28,52). A possible explanation is that an influx of cool arterial blood into BAT in these animals may mask an increase in BAT thermogenesis during REM sleep [see discussion in (52)].

   If BAT switches on during REM sleep, then the capacity of REM sleep to produce heat and focus it in a restricted core would be greatly enhanced by acclimation to cold, because long-term exposure to cold stimulates growth and

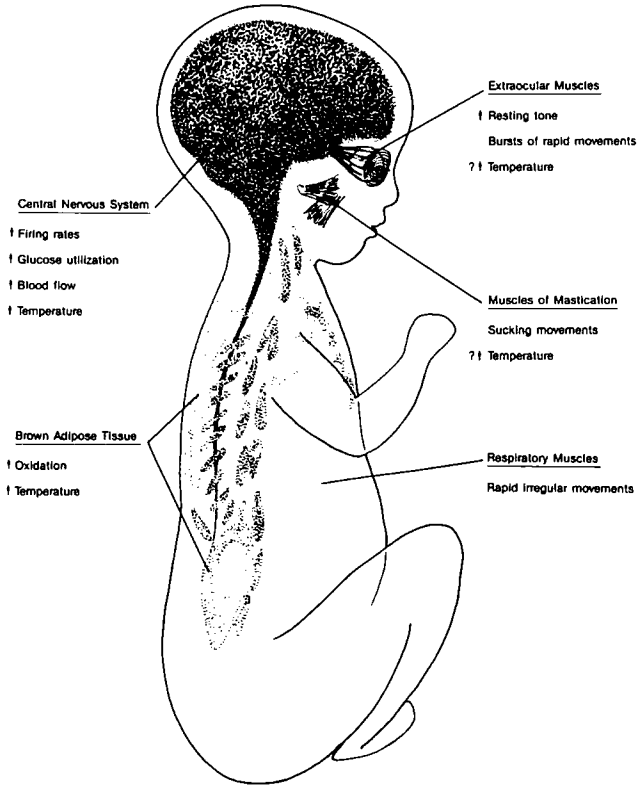

FIG. 11. Features of REM sleep in a human infant with a possible thermogenic function. Rapid, irregular respiratory movements that occur during REM sleep may help to heat the spinal cord by shunting venous blood that has been warmed by brown adipose tissue (BAT) during REM sleep to the vertebral venous plexus that surrounds the cord (see text). Between the muscles of mastication lies the pterygoid plexus, which communicates with the intracranial venous system (see Fig. 9). By this route heat produced by sucking movements during REM sleep could be conveyed to the CNS. Veins of the extraocular muscles also can drain into the intracranial venous system. Thus, a small portion of the heat produced by rapid eye movements during REM sleep might be conveyed to the CNS by this route. The figure is adapted with permission from Hull, D. In: Whittow, G. C., ed. Comparative Physiology of Thermoregulation, Vol. III. New York: Academic Press; 1973.

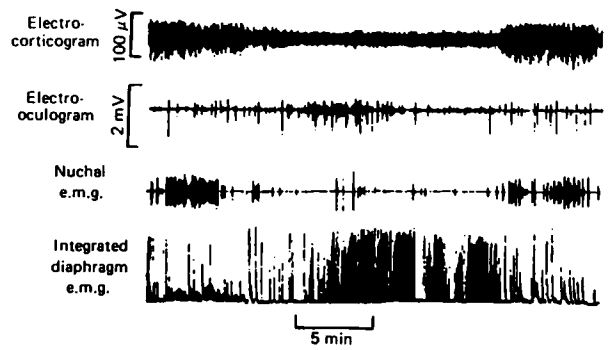

FIG. 12A. 40-minute recording of biparietal EEG, EOG, nuchal muscle EMG and integrated diaphragm EMG activity in a fetal lamb at 127 days gestational age. Rapid, irregular respiratory movements occur during an episode of REM sleep that begins in the middle of tracing. The transition to REM sleep is marked by reduced EEG voltage, rapid eye movements, and loss of tone in neck muscles (reprinted with permission from Clewlow et al., J. Physiol. 341:463–476; 1983).

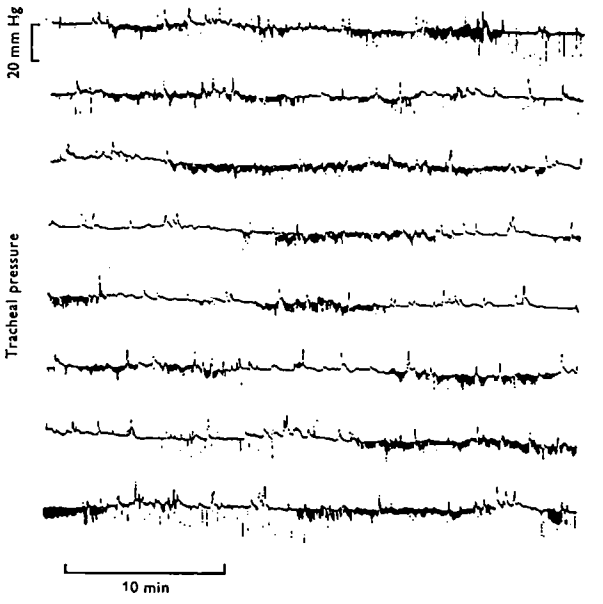

FIG. 12B. This continuous 4 $\frac{1}{2}$ hour recording of tracheal pressure in a fetal lamb in utero at 122 days gestation shows cyclic recurrences of rapid, irregular breathing associated with episodes of REM sleep [reprinted with permission from Dawes et al. (37)]. This type of respiratory activity might help to heat the spinal cord during REM sleep by shunting warm venous blood from BAT, which appears to switch on during REM sleep, into the vertebral venous plexus (see text).

function of BAT. Increased efficiency of thermogenesis due to hypertrophy of BAT may explain why REM sleep readily occurs when cold-adapted animals are exposed to cold but is replaced by wakefulness when non-adapted animals are exposed to cold (see "Reactive Thermoregulatory Control of REM Sleep").

6. *Rapid, irregular respiratory movements.* The pumping action of respiratory movements is believed to play an important role in shunting warm blood from BAT into the vertebral venous plexus, where it heats the spinal cord (21,133) (Fig. 11). This proposed hemodynamic function provides a possible explanation for the rapid and irregular respiratory movements that occur in REM sleep, especially in the fetus, in which they cannot have a respiratory function (37,112) (Fig. 12). The fact that respiratory movements are relatively insensitive to input from chemoreceptors during REM sleep (37) has been interpreted as dysregulation (105), but it is consistent with the non-respiratory function proposed here. The fact that heat can completely suppress fetal respiratory movements is also consistent with that idea (14). However, the impact of respiratory movements on the circulation of blood from BAT to the vertebral venous plexus has not specifically been investigated in REM sleep.
7. *Atonia in muscles of the head and neck.* Resting tone in muscles of the head and neck might help to determine the route of venous drainage from the head. During REM sleep

only the muscles of the head and neck become atonic (70). The specificity of this change suggests that it might have a particular function in REM sleep. One possibility is that loss of resting tone in these muscles might decrease resistance to flow in the external jugular system—by reducing extracranial arterial inflow and by mechanically decompressing the veins—and promote drainage by this route (Fig. 9). Like increased intracranial arterial blood flow, this change could be expected to impede the shunting of cool blood from the face and scalp into the CNS and to thereby reduce cooling of the CNS.

In comparison with other striated muscles, the branchiomeric muscles of the head and neck have an unusual evolutionary history. They are derived from smooth muscles that were controlled by the autonomic nervous system in ancestral vertebrates (114). The vasomotor action proposed here for their function in REM sleep might reflect this heritage.

Since the muscles of the head and neck lie close to the CNS, it must be acknowledged that their decreased tone, by decreasing thermogenesis, could also be seen as tending to reduce brain-warming, contrary to the theory.

In the absence of direct measurements of venous blood flow, the idea that atonia of the muscles of the head and neck conserves CNS heat by promoting external venous drainage of the head is speculative. Whether the net effect of head and neck muscle atonia is to facilitate or antagonize brain-warming remains to be investigated.

ENLARGEMENT OF THE INSULATIVE SHELL IN REM SLEEP

Other changes associated with REM sleep could be construed as mechanisms for modifying the state of peripheral structures to make them more shell-like (106). These include:

1. maintenance of low resting tone and reduced thermogenesis in skeletal muscles (56,70,116,123), and
2. suspension of various peripheral thermoregulatory effector mechanisms, such as sweating, panting, and shivering (103).

The shell-like portion of the organism not only enlarges during sleep, but it also becomes more insulative (i.e., the thermal conductance of the organism decreases) (8). Suspension of sweating and panting, and decreased blood flow to muscles may be partly responsible for the decreased conductance (8). During its sleep phase, the organism further reduces thermal conductance by resorting to an insulated refuge, by modifying its posture and sometimes by huddling with other organisms, as mentioned previously.

FUNCTION OF HOMEOTHERMIC CORE CHANGES DURING REM SLEEP

The most likely function of this reduction of the size and temperature of the homeothermic core during sleep is to conserve energy by reducing the amount of energy expended on thermogenesis [energy-savings obtained in this way would probably be more significant for small animals than for large ones—see discussions of this controversial issue by Berger and Walker (16,146), Berger and Phillips (17), Allison and Van Twyver (4), and Horne (68). The strongest evidence that sleep has an energy-conserving function is the observation that core temperature progressively declines during successive nights of sleep when feeding is restricted (17); the strongest evidence that sleep has functions other than, or in addition to, energy-conservation is the observation that hibernating animals expend large amounts of energy to emerge briefly from hibernation in order to sleep (36)]. At the same time, by continuing to maintain a homeothermic core in the CNS, the organism can continue to enjoy some of the advantages of homeothermy, especially the capacity to be easily aroused and to respond to external stimuli in a flexible manner. In this way, meaningful external stimuli could arouse animals from any stage of sleep, and animals could awaken spontaneously at the end of REM sleep episodes to sample the environment, as previously suggested by Snyder in his "sentinel hypothesis" of REM sleep (134) (Fig. 4). The efficiency of REM sleep as a mode of homeothermic temperature regulation may explain why it is so abundant at the beginning of life, when energy conservation is critical, as noted by Horne (68,77,112) (Fig. 8). Other ideas about the function of REM sleep as an alternate mode of homeothermic thermoregulation are discussed in greater detail in a later section entitled "The Function of CNS Homeothermy During Sleep."

CNS-heating associated with REM sleep may have a special additional function when it occurs near the end of the daily sleep phase. At this time, when core temperature has reached its daily minimum and begins to rise, REM sleep increases in intensity and duration (35) (see Fig. 3). To whatever extent this increase in REM sleep contributes to the rise in CNS temperature at this time, it may serve to anticipate and facilitate the organism's daily emergence from the hypothermia of sleep into wakefulness and activity (just as the increase in SWS at the beginning of the sleep phase facilitates the organism's daily entry into the hypothermia of sleep). The fact that spontaneous arousals from sleep very often follow REM sleep (Fig. 4) (81,82,113,134), is highly consistent with the idea that a function of CNS heating during REM sleep is to anticipate and prepare for arousal from sleep, as noted by Snyder (134) and Palca et al. (98).

THERMOREGULATORY CONTROL OF REM SLEEP

If REM sleep has a brain-warming function, then how is this brain-warming regulated? I will approach this question by considering two possible types of homeostatic regulation: reactive and predictive. The terms were introduced by Moore-Ede to distinguish between homeostatic mechanisms that take corrective actions in response to a challenge that has already occurred and homeostatic mechanisms that take corrective actions in anticipation of a predictably-timed challenge (93). An example of reactive thermogenesis is the increase in heat production that occurs after exposure to cold; an example of predictive thermogenesis is the circadian rise in heat production that occurs near the end of the sleep phase in anticipation of the need for higher body temperature during wakefulness. The reactive mechanism is flexible and responds in a counter-regulatory fashion to thermal challenges; the predictive mechanism is pre-programmed and does not necessarily respond to such challenges.

REACTIVE THERMOREGULATORY CONTROL OF REM SLEEP

If REM sleep is a mechanism for brain-heating, and if it is controlled by a reactive mechanism, then REM sleep should be facilitated by lowering CNS temperature, and it should be inhibited by raising CNS temperature. In fact, there are several situations in which REM sleep responds to temperature changes in this way. I have already mentioned three circumstances in which physiological changes in temperature are associated with reciprocal changes in REM sleep propensity. REM sleep propensity is highest when temperatures become low during NREM sleep; when the temperature circadian

rhythm reaches its daily minimum; and when temperatures are low early in development. A problem with the latter two examples is that the temperature changes are highly predictable. This means that the associated changes in REM sleep could be triggered by a predictive type of mechanism. Thus, correlations between REM sleep and temperature in these situations are consistent with a brain-heating function for REM sleep, but they do not help to establish whether REM sleep is regulated by a reactive mechanism, i.e., a thermostat.

Responses of REM sleep to thermal challenges might help to clarify this issue. In a subsequent section, I suggest that if there is a thermostat that controls REM sleep, it could be located in the same structure that is thought to generate REM sleep, the rhombencephalon (66,73,74,87). If REM sleep is regulated by such a thermostat, then cooling the thermostat ought to trigger REM sleep and heating ought to suppress it. It should be possible to test this hypothesis experimentally by manipulating rhombencephalic temperature and monitoring effects on REM sleep. Brain temperature could be manipulated directly by thermal probes, or indirectly by modifying environmental temperature.

Unfortunately, this simple scheme fails to take into account the complex way in which thermoregulatory control mechanisms are organized in the CNS. Probably because of the way in which they evolved, these mechanisms are present at multiple levels of the neuraxis (120). They appear to be organized in a hierarchical fashion, with the highest level of integration in the hypothalamus. If there are thermostats in the rhombencephalon that control REM sleep, evidence suggests that they are probably subordinate to hypothalamic thermoregulatory control mechanisms that can interfere with their responses to changes in temperature (Fig. 13). As discussed above, REM sleep only occurs when core temperature drops to a lower level during NREM sleep (103). In this situation, according to Parmeggiani's interpretation, the hypothalamus functions during NREM sleep as a "temperature gate" for REM sleep. When ambient temperatures are too cold, hypothalamic thermoregulatory control mechanisms prevent body temperature from dropping during NREM sleep, abort REM sleep, awaken the animal, and activate behavioral thermoeffector mechanisms. Parmeggiani's concept of a hypothalamic temperature gate for REM sleep could be integrated with the concept of a rhombencephalic thermostat for REM sleep. REM sleep could be triggered by cooling of a rhombencephalic thermostat, but this thermostat might be overridden by a hypothalamic thermostat if ambient temperature were too low to permit this cooling to take place safely. According to this interpretation, the rhombencephalic REM sleep thermostat is permitted to operate only within a restricted range of temperatures defined by hypothalamic thermoregulatory control mechanisms.

If this model is correct, then it would be necessary to free the rhombencephalic thermostat from hypothalamic controls in order to investigate its responses to temperature manipulations. One experimental approach might be to study effects of temperature manipulations on REM sleep in newborn animals in which hypothalamic thermoregulatory control mechanisms are immature, or in adult animals from which the hypothalamus has been removed. With regard to the first possibility, certain procedures that are known to lower core temperature in immature animals, such as handling or isolation from the litter, do increase REM sleep (41,42,85). Similarly, exposure to cold (18–21° C) appears to trigger and to prolong REM sleep episodes in newborn human infants (49). Also, during

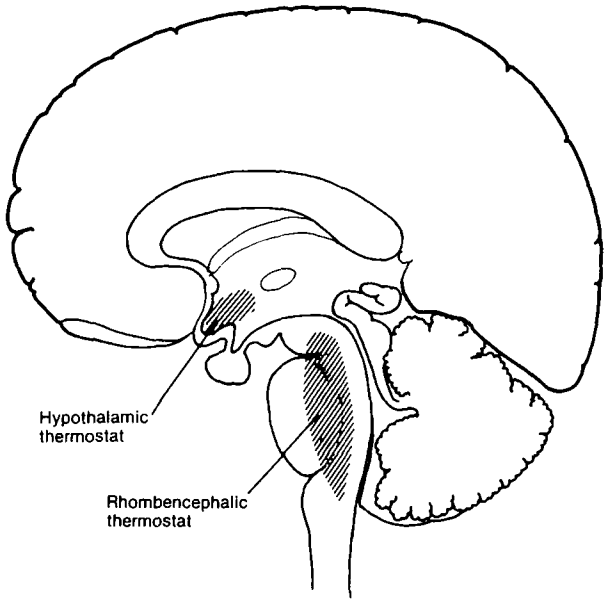

FIG. 13. The figure shows the sites of two thermoregulatory control systems that are hypothesized to control REM sleep. According to the model, REM sleep occurs when a hierarchically dominant hypothalamic thermostat permits a rhombencephalic thermostat to be cooled to lower temperatures, which cause it to trigger REM sleep. During REM sleep the hypothalamic thermostat is inactivated, and the locus of thermoregulatory control shifts to the rhombencephalon. During NREM sleep the rhombencephalic thermostat is subordinate to the hypothalamic thermostat, which controls a temperature gate for cold-induced triggering of REM sleep by the rhombencephalic thermostat (redrawn with permission from Gray's Anatomy. Philadelphia: Lea & Febiger; 1965:878).

REM sleep metabolic rate increases 25% when infants are exposed to cold, whereas in NREM sleep it only increases 8%, as was mentioned previously. All of these observations appear to be consistent with the hypothesis that brain-heating occurs in REM sleep, and that this brain-heating is a regulated, adaptive response to heat loss.

With regard to the second possibility, there is evidence that cooling triggers REM sleep in animals from which all of the brain, except the rhombencephalon, has been removed. Thus, when cats are surgically deprived of the cerebrum, cerebellum, hypophysis, and portions of the midbrain, but retain the pons and medulla, they continue to exhibit REM sleep. Jouvet and his colleagues recently showed that lowering core temperature in this type of preparation (the "pontine cat") triggered REM sleep, and that raising it suppressed it (temperatures were controlled by an incubator) (76). When average temperatures were maintained above 35.4° C, REM sleep was inhibited. When they were maintained below this level, REM sleep was facilitated. Furthermore, the probability of occurrence of REM sleep episodes was greatest at the time of the minimum of a cycle of core temperature that was imposed by an external thermostat (Fig. 7). Finally, the duration of REM sleep episodes increased as temperatures were lowered. Average durations were more than twice as long at 33° as at 35.5°.

A number of investigators have exposed intact, adult animals to different ambient temperatures and evaluated effects on sleep (3,100,106,117,122,130,137,138,144). Several generalizations can be made about the results of these studies.

- At very high temperatures, the percentage of REM sleep declines markedly because animals spend more time awake (106,122,130). This result could be considered consistent with the hypothesis that REM sleep is controlled by a thermostat that switches it off when core temperature is high. However, this interpretation fails to take account of the fact that wakefulness is even more thermogenic than REM sleep. It then becomes necessary to explain why an animal exposed to heat would switch from a lesser to a greater mode of thermogenesis. Presumably, this occurs because waking allows the animal to employ effective forms of behavioral thermoregulation, such as grooming or physical escape, to deal with the danger of overheating.
- At very low temperatures, the percentage of REM sleep can remain high in animals and human beings that have become acclimated to cold (99,130). This result could be viewed as being consistent with the hypothesis that REM sleep is a regulated mechanism for heating the CNS. However, unacclimated animals spend less time in REM sleep and more time awake at very low temperatures (3,117,122,130). When animals in this situation substitute wakefulness for REM sleep, they use the periods of wakefulness to make postural and other behavioral adjustments that help them defend against cold (122). Thus, in place of REM sleep heating mechanisms, they substitute a waking mode of heat-production and conservation which is energetically more expensive, but also more effective (in this situation, waking might even be efficient if it were brief and led to a heat-conserving postural adjustment). If this interpretation is valid, shifting from REM sleep to the waking mode of thermogenesis in response to cold would not necessarily contradict the hypothesis that REM sleep is a regulated brain-heating mechanism.
- In the middle range of temperatures within or near the thermoneutral zone, from about 20° to 30° C, the percentage of REM sleep increases almost linearly as a function of ambient temperature (106,130,137,138,144). These results could also be cited as evidence against the hypothesis. However, this interpretation would fail to take into account the fact that, as temperature increases, REM sleep increases at the expense of wakefulness (Fig. 14). Following the same reasoning as before, the animals, in switching from wakefulness to REM sleep in response to increasing heat load, are switching from a more robust to a less robust form of heating. If this interpretation is valid, the results would not necessarily contradict the hypothesis that REM sleep is a regulated thermogenic process.

The hypothesis might be tested more directly by using thermal probes to manipulate rhombencephalic temperature to determine whether cooling promotes and heating inhibits REM sleep. I am not aware of any studies of this type, with the possible exception of an experiment with pigeons by Graf, Heller, Sakaguchi, and Krishna (61). They found that warming the upper spinal cord inhibited REM sleep. If one assumes that the area warmed included the brainstem, then the results might be consistent with the hypothesis.

Sakaguchi, Glotzbach, and Heller investigated the effects on sleep of local heating and cooling of the hypothalamus in kangaroo rats exposed to ambient temperatures of 20° C and 30° C (119). Local heating of the anterior hypothalamus tends to suppress metabolic heat production and, therefore, to lower body temperature; cooling the anterior hypothalamus stimulates metabolic heat production and raises body temperature. Thus, heating the hypothalmus might be expected to cool the

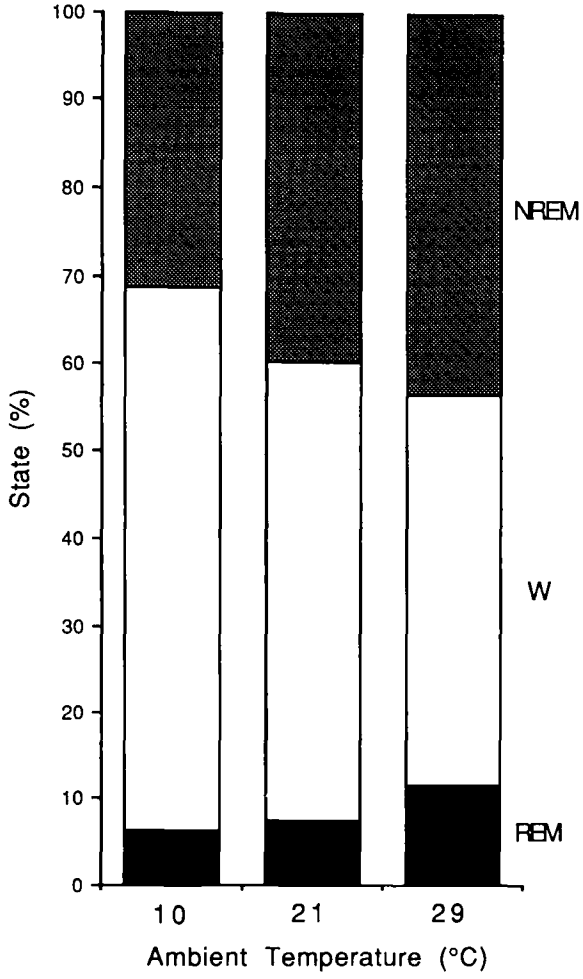

FIG. 14. Percent time in wakefulness (W), NREM sleep and REM sleep at various ambient temperatures in the rat. REM sleep displaces wakefulness at higher temperatures, and wakefulness displaces REM sleep at lower temperatures [data of Alföldi et al. (3)].

putative rhombencephalic thermostat and thereby facilitate REM sleep. Conversely, cooling the hypothalamus might heat the rhombencephalic thermostat and thereby inhibit REM sleep. Consistent with these predictions, Sakaguchi et al. found that mild heating of the hypothalamus increased, and mild cooling decreased, the percentage of REM sleep within sleep at an ambient temperature of 30° C (at 20° C no cooling was performed and mild heating was performed in too few animals to evaluate statistically). With strong heating in the two ambient temperatures, the percentage of REM sleep returned to baseline, possibly owing to the fact that slow wave sleep markedly increased and may have preempted REM sleep. It is remarkable that at an ambient temperature of 20° C, hypothalamic heating reduced body temperature to levels as low as 28.8° C, but did not decrease REM sleep. This experiment could be compared with Jouvet's experiment in the pontine cat. In both experiments body temperature was dramatically lowered in animals in which the hypothalamic temperature gate for REM sleep had been neutralized by local heating or by surgical removal, respectively. In each case REM sleep persisted or even increased at very low body tempera-

tures. These results might be consistent with the hypothesis that a rhombencephalic thermostat facilitates REM sleep at low temperatures, and that when REM sleep fails to occur at these temperatures, it is due to the overriding influence of the hypothalamus.

Somewhat more problematic are the results of Parmeggiani, Zamboni, Cianci, Agnati, and Ricci, who found that heating the anterior hypothalamus at the beginning of REM sleep episodes prolonged them (101). It seems unlikely that this heating would lower rhombencephalic temperature by reducing metabolic heat production, because hypothalamic thermoregulatory controls are relatively insensitive to heating during REM sleep.

The implications of the foregoing observations about the relationship between amounts of REM sleep and changes in body temperature can be summarized as follows:

- Changes in amounts of REM sleep that occur in association with physiological changes in core temperature are consistent with a CNS-heating function for REM sleep, but they are not informative about any possible causal relationship between temperature and REM sleep, and they do not distinguish between reactive and predictive forms of control.
- Changes in amounts of REM sleep that occur in immature mammals and in the "pontine cat" in response to external heating or cooling are consistent with a CNS-heating function for REM sleep, a causal relationship between temperature and REM sleep, and a reactive form of control.
- Changes in amounts of REM sleep that occur in intact, adult animals in response to external heating or cooling can be interpreted as being either consistent or inconsistent with a CNS-heating function for REM sleep. It depends on how one interprets the fact that REM sleep and wakefulness are substituted for one another when ambient temperature is changed. If REM sleep is viewed as a lesser form of heat production and conservation that maintains a smaller and cooler core than obtained in the waking state, then a preference for REM sleep over wakefulness at moderately high ambient temperatures is not necessarily inconsistent with a CNS-heating function for REM sleep. Because the results are open to different interpretations, they do not appear to be decisive either way.

In the future, the hypothesis that REM sleep is regulated by a hierarchy of thermostats that can respond differently to changes in temperature could be evaluated in intact, adult animals by monitoring effects on REM sleep of local manipulations of rhombencephalic temperature while hypothalamic temperature is clamped.

A THERMOSTAT AS AN OSCILLATOR DRIVING THE REM-NREM CYCLE

If REM sleep is controlled by a thermostat, what kind of thermostat is it? Three reactive types of thermoregulatory control mechanisms—proportional, rate-sensitive, and on-off—have been described (34,60,131). With proportional control, the magnitude of effector activity, such as evaporative heat loss and metabolic heat production, is proportional to deviations in the regulated body temperature from its set point. With rate control, rapid shifts in regulated temperatures trigger counterregulatory responses that anticipate thermal stress and may override proportional controls (both reactive and predictive elements are present in this mechanism). With on-off control, effector activity, such as shivering or panting, responds in an all-or-none manner when deviations in the regulated temperature are sufficiently large to trigger a response. Since REM sleep occurs in discrete episodes with clear onsets and offsets, it seems to be an all-or-none phenomenon. Therefore, as a putative effector of CNS-heating, it might be regulated by an on-off type of thermoregulatory control.

An on-off thermoregulatory control mechanism can behave like an oscillator; therefore, it could also be responsible for the cyclicity of REM sleep. On-off control of thermoeffectors can generate cyclic behavior characterized by the alternation of two states. For example, lizards shuttle back and forth between sun and shade to maintain body temperatures within a certain range (142) (Fig. 1b). In a similar manner the REM-NREM cycle might be generated by all-or-none responses of a homeostatic mechanism that switches REM sleep on when CNS temperature falls to lower levels and switches it off when rises to higher levels (Fig. 1a). The duration of the REM-NREM cycle would then be a function of the thermal inertia of the homeothermic core, which is roughly proportional to the mass of the brain: the larger the brain, the greater its thermal inertia, and the longer the REM-NREM cycle. In fact, both for adult animals of different species and during development, the period of the REM-NREM cycle is highly correlated with brain weight (153).

This scheme is reminiscent of a homeostatic REM sleep mechanism proposed by Ephron and Carrington in 1966, except in their model the regulated variable was not core temperature, but "cerebral tone" (47).

Figure 1a shows simultaneous records of sleep and hypothalamic temperature. Note that while the onsets of REM sleep episodes do occur at local low points along the temperature curve, the levels of temperature at these low points vary considerably among the different REM sleep episodes. The low points do not seem to reflect a single critical threshold. It seems more accurate to say that REM sleep episodes begin after a period when hypothalamic temperature has been declining.

The variability of low temperatures at which REM sleep begins is consistent with the known behavior of on-off temperature control mechanisms, which sometimes regulate temperature rather imprecisely. For example, although it is clear that some reptiles can regulate core temperature rather precisely with shuttling-behavior in special laboratory conditions, this is not always the case (43). In the field, the animals tolerate much wider variations of core temperature, and the temperature levels at which switches between sun and shade take place are also quite variable (see Fig. 1b, and compare with Fig. 1a).

NEUROANATOMY OF A PUTATIVE REM SLEEP THERMOSTAT

The results of Jouvet's experiments with the pontine cat suggest that the elements necessary to integrate thermal inputs and provide thermostatic control for REM sleep may be present in the rhombencephalon, where REM sleep is generated. From studies of thermoregulation there is now considerable independent evidence that thermoregulatory control mechanisms may be present in the rhombencephalon. Moreover, some of the specific rhombencephalic structures that have been implicated in the generation and control of REM sleep have also been implicated in the generation and control of thermoregulatory responses.

Rhombencephalic Control of REM Sleep

Although it seems unlikely that there is a discrete REM sleep "center" in the rhombencephalon (66,87), current re-

search continues to implicate populations of cells in the pons and portions of the midbrain and medulla in REM sleep physiology. The fact that cholinergic agonists induce REM sleep suggests that cholinergic neurons might have a REM sleep executive function, and the medial pontine reticular formation (MPRF) has emerged as the principal candidate for a site where terminals of cholinergic neurons might act to trigger REM sleep (5,11,73,74,129). The fact that cholinergic agonists applied to this area induce REM sleep, and can be antagonized by atropine, suggests that muscarinic cholinoceptive neurons there might play an important role in the elaboration of REM sleep. Apparently no cholinergic cell bodies lie within the MPRF; however, two major cholinergic cell groups have been identified that lie near the MPRF and might project to it (129). They are the pedunculopontine nuclei and the dorsal lateral tegmental nucleus. The former appear to play a role in the generation of PGO waves (11), a characteristic feature of REM sleep, and lesions in this area can eliminate REM sleep (148).

The search for cells whose function might be to inhibit REM sleep has focused primarily on noradrenergic neurons whose cell bodies lie in the locus coeruleus and on serotonergic neurons whose cell bodies lie in the raphé nuclei of the brainstem (29,66,86). These nuclei are close to the MPRF and to the cholinergic cells of the pons, and some investigators suggest that they may inhibit REM sleep because, in contrast to most other neurons in the CNS, they cease firing during REM sleep. Although most investigators have refined or abandoned the simple models that were developed a number of years ago to describe the role of the MPRF and the cholinergic and aminergic cell groups in REM sleep, these populations of cells continue to be a major focus of interest in the search for neural mechanisms (66).

Rhombencephalic Control of Thermoregulation

As hypothesized in this paper, REM sleep is controlled by a thermostat. A thermostat mechanism usually consists of thermosensitive elements and thermoeffector control elements linked together in a feedback loop. Independent investigations of the neurophysiology of thermoregulation suggest that both elements are present in the pons and portions of the midbrain and medulla, including the MPRF and the cholinergic and aminergic cell groups.

The rhombencephalon appears to contain several thermoeffector control elements. For example, peripheral thermoeffectors, which are inactivated during REM sleep, may be tonically inhibited by cells in the MPRF (6,7). Lesions in this area of the pons, which abolish muscle atonia during REM sleep, lower thresholds for thermoeffector responses such as panting and shivering, regardless of behavioral state (6,7).

As discussed previously, BAT thermogenesis may be activated during REM sleep. The results of recent research suggest that cells in the pons, possibly in the MPRF, tonically inhibit BAT thermogenesis. Marked increases in BAT thermogenesis occur when a local anesthetic is injected or knife cuts are made in this area (7,128).

The rhombencephalon also appears to contain thermosensitive elements. There is considerable evidence that the locus coeruleus and the raphé nuclei contain large numbers of neurons that respond to afferent thermal stimuli and are themselves thermosensitive (44,60,94,131,140,150). These cells are primarily warm sensitive. However, much of this evidence has been criticized because experiments were performed on anesthetized animals. Recently, investigators showed that locus coeruleus cell firing rates in unanesthetized, awake, freely moving animals increased proportionally when brain temperature was raised with pyrogens (until animals fell asleep) (94). There was no such proportional response when animals were exposed to high external temperatures. These results could be interpreted as evidence that locus coeruleus cells respond to local, but not to peripheral thermal inputs. This interpretation would be consistent with the current view that the locus coeruleus does not directly receive ascending afferent stimuli and is unlikely to play a primary role in the integration of information arising from sensory elements outside of the CNS (10). It would also be consistent with the concept of a rhombencephalic thermostat that uses heat production and conservation in REM sleep to regulate a homeothermic core confined to the CNS and that is indifferent to temperatures outside of the CNS.

These features make the locus coeruleus attractive as a candidate for one of the thermosensitive components of the thermostat that is hypothesized to control REM sleep, particularly since locus coeruleus firing, which has been hypothesized to inhibit REM sleep, has been reported to increase as brain temperature increases (94). If, as some have hypothesized, the REM-NREM cycle arises from an oscillating reciprocal interaction between the activity of locus coeruleus neurons and the activity of REM sleep executive neurons (66), and if cessation of activity of locus coeruleus neurons triggers activity of REM sleep executive neurons, then brain-heating during REM sleep might eventually terminate REM sleep by stimulating firing of locus coeruleus neurons. By the same token, passive cooling of the CNS during REM sleep might eventually lead to a cessation of firing of locus coeruleus neurons, which in turn might disinhibit activity of REM sleep executive neurons and lead to a repetition of the cycle. In this model, the medium of feedback from REM executive neurons to locus coeruleus neurons is thermal rather than neural. Observations that inactivation of the locus coeruleus by cooling beyond the physiological range triggers REM sleep are consistent with the model (29,33); however, the effect of cooling within a physiological range needs to be investigated.

The locus coeruleus may also help to regulate the change in balance of intracranial and extracranial blood flow that occurs in REM sleep. Electrical stimulation of locus coeruleus cells reduces intracranial, and increases extracranial, arterial blood flow (59). Therefore, the cessation of firing of locus coeruleus cells that occurs during REM sleep might be partly responsible for the increase in intracranial, and the decrease in extracranial, arterial blood flow that occurs during REM sleep. As discussed previously, this change in the balance of intracranial and extracranial blood flow could be expected to enhance CNS heat conservation by reducing the selective CNS cooling that is believed to occur when blood from the face and scalp passes through emissary veins and drains through the intracranial venous system.

According to recently published data, cells in the dorsal raphé nucleus are not thermosensitive in awake, freely moving, unanesthetized animals (50). However, they have not been investigated during REM sleep. Also, the magnus raphé nucleus, which in anesthetized animals contains many more thermosensitive cells than the dorsal raphé nucleus, has not been investigated in unanesthetized animals (44,131).

Axons from noradrenergic neurons of the locus coeruleus and serotonergic neurons of the raphé nuclei pass through the median forebrain bundle (MFB) to the anterior hypothalamus. Furthermore, local injections of norepinephrine and serotonin in the anterior hypothalamus elicit powerful responses

from hypothalamic thermoregulatory control mechanisms. These observations suggest that locus coeruleus and/or raphé neurons may play a role in the control of thermoregulation at the level of the hypothalamus, as well as at the level of the rhombencephalon, and that the MFB may serve as a bridge or switch mechanism between thermoregulatory control systems at these two sites (Fig. 13).

PREDICTIVE THERMOREGULATORY CONTROL OF REM SLEEP

In considering ways in which REM sleep might be governed by thermoregulatory control mechanisms, I have thus far focused exclusively on a reactive type of mechanism, on-off thermoregulatory control. As I mentioned previously, reactive mechanisms respond to actual perturbations or deviations in the systems they regulate. Another class of mechanisms is predictive in nature. They modify the systems they regulate in anticipation of conditions that will occur in the future. An important example is circadian rhythms, which alter regulated systems in ways that anticipate conditions that recur on a daily basis.

There is a circadian rhythm of REM sleep propensity, and it reaches its highest level near the time of the minimum of the circadian rhythm of core temperature. This fact was cited previously as possible support for the hypothesis that REM sleep is triggered by an on-off thermoregulatory control mechanism when temperature declines to lower levels during sleep. From this argument one might infer that REM sleep's daily rhythm is imposed upon it by the daily rhythm of core temperature. However, the fact that REM sleep continues to occur at high levels after core temperature begins to rise near the end of the sleep period suggests that this is not entirely so (32,35,151,154) (see Fig. 3). Apparently, the daily rhythm in REM sleep is at least partly independent of the rhythm of core temperature. The rise in REM sleep near the end of the sleep period might be triggered by the rise in glucocorticoid secretion that occurs at this time. This possibility is suggested by the fact that glucocorticoid secretion and REM sleep increases in parallel, and adrenalectomy has been reported to abolish the daily peak in REM sleep (72,91). Regulation of REM sleep by glucocorticoid levels would be consistent with a CNS-warming function for REM sleep because glucocorticoids exert a strong permissive effect on cold-defense responses (38).

The peak of REM sleep near the end of the sleep period may have a special function. If CNS warming is a basic function of REM sleep, then the higher levels of REM sleep at this time may serve to anticipate and facilitate the organism's daily emergence from the hypothermia of sleep into wakefulness. Earlier, I suggested a possible symmetry in the timing and in the functions of SWS and REM sleep (Fig. 3). According to this interpretation, SWS is concentrated at the beginning of sleep, is thermolytic, and facilitates entrance into the hypothermia of sleep; REM sleep is concentrated at the end of sleep, produces and conserves heat in the CNS and facilitates emergence from the hypothermia of sleep. However, there is an important difference in the way the timing of SWS and the timing of REM sleep are controlled. The timing of the peak in SWS is largely determined by the timing of sleep onset, which it follows after a short interval. In contrast, the timing of the peak in REM sleep is largely determined by its circadian rhythm and is relatively independent of the timing of sleep onset. This difference might be explained by the requirement that peak SWS occurs in response to the daily transition from wakefulness to sleep, but that peak REM sleep occurs in anticipation of the daily transition to wakefulness. In this case, the timing of peak REM sleep could not be keyed to the time of sleep onset because in a natural environment the time of sleep onset cannot be used to predict the time of sleep offset, owing to the fact that the interval between sleep onset and sleep offset varies with seasonal changes in the photoperiod. However, a circadian rhythm entrained to the appropriate boundary of the photoperiod (dawn in diurnal animals and dusk in nocturnal animals) could be used to predict the time of this event. Perhaps this is why the timing of the peak of SWS is controlled by sleep onset, while timing of the peak of REM sleep is controlled by a circadian rhythm.

REBOUND AFTER REM SLEEP DEPRIVATION

When animals return to sleep after sleep deprivation, deficits in REM sleep and SWS are partially recovered by a rebound increase in these sleep stages. This rebound seems to indicate that REM sleep and SWS are homeostatically conserved and there are drives for these sleep states (95). According to the theory, REM sleep and SWS play important roles in the organism's management of its energy economy, mainly by conserving energy (SWS down-regulates core temperature and inhibits energy-costly behavior, and REM sleep substitutes a more efficient mode of body-heating for that which occurs during wakefulness). If SWS and REM sleep are viewed as regulated elements of the organism's energy economy, it is not surprising that they exhibit drive-like behavior and are homeostatically controlled. Two other regulated elements of the organism's energy economy, appetite, and weight, are controlled in the same way.

Recent research on the physiological and behavioral effects of chronic sleep deprivation in rats could be construed as being highly consistent with the thermoregulatory function proposed here for REM sleep. For reasons that are not yet clear, animals respond to sleep deprivation as though they were being exposed to extreme cold (109,125). They expend large amounts of energy on heat production, and to compensate, they mobilize energy stores and consume enormous amounts of food. Nevertheless, they lose weight because the demand for energy is so great. Brown adipose tissue, which is a heat-producing organ, increases enormously in size and metabolic activity during chronic sleep deprivation, as occurs in cold-exposure. If allowed to choose their ambient temperature, sleep-deprived animals will select very warm temperatures, suggesting that central thermoregulatory control mechanisms are responsible for the activation of cold-defense responses. In this physiological context, the high amounts of REM sleep that occur when sleep-deprived animals return to sleep are consistent with a CNS-warming function for REM sleep. Augmentation of REM sleep can be interpreted as a continuation into sleep of the vigorous cold-defense response that was in force when sleep began. The behavior of SWS provides a precedent that is opposite, but parallel: heating during the waking phase causes SWS to increase during subsequent sleep (25,67).

THE CONCEPT OF BRAIN-BODY HETEROTHERMY IN REM SLEEP

Is it reasonable to suggest that the homeothermic core could be confined and maintained in the CNS and its vicinity during sleep? There is considerable evidence that the anatomy and physiology of vertebrate thermoregulatory systems are organized and adapted for this purpose. Many vertebrates can maintain stable temperatures in the central nervous system in the face of thermal stresses that markedly alter temperature in the rest of the body.

Selective CNS thermoregulation has been described in fish, reptiles, birds and mammals (12,13,22,26,27,54,55,65,97,142, 143). For example, warm-blooded fish, such as mackerel, tuna, and laminid sharks, can selectively warm the CNS with heat generated by vascular and chemical mechanisms in muscles and adipose tissue which lie near the eyes and brain and are adapted for this purpose (19,31). The function of these structures is analogous to the one proposed here for eye muscles and BAT.

Some animals have specialized vascular structures, such as carotid or ophthalmic rete, which selectively regulate heat loss from blood destined for the central nervous system (12). Even animals lacking these structures can selectively regulate brain temperature. For example, when squirrel monkeys are thermally stressed, they regulate brain temperature much more precisely than rectal temperature (54,55), and indirect evidence suggests that the same is true of human beings (22, 27,89,97,99).

Counter-current heat exchange may play an important role in selective CNS thermoregulation. Counter-current heat exchange could take place between the major arteries and veins of the brain and spinal cord, which lie adjacent to one another, and between these arteries and rich venous plexuses which surround them, and which receive warm blood from venous lakes of the cranium or from BAT along the spine (21,133). These vascular arrangements, which buffer CNS temperature against thermal stresses during wakefulness, could help to define and defend a homeothermic core in the vicinity of the CNS during sleep.

THE FUNCTION OF CNS HOMEOTHERMY DURING SLEEP

One of the principle advantages of endothermy is that it makes available to the organism, time and behavior that would have otherwise been devoted to behavioral thermoregulation. It also permits animals to occupy niches in locations and climates in which poikilotherms could not survive. According to the hypothesis presented here, REM sleep enables endothermic animals to maintain a high, stable temperature in the CNS during sleep. But how does the animal benefit from this?

The maintenance of CNS homeothermy during sleep permits animals to be aroused quickly without depending on external sources of heat. There are several types of advantages of this capacity:

- Animals can sleep in situations that routinely require them to wake up and become active in cold places or at cold times of day or year. As a consequence, they can inhabit geographical and temporal niches that would otherwise be inaccessible. The possibility that brain-heating in REM sleep facilitates this type of awakening is suggested by the fact that the daily peak in REM sleep propensity precedes the daily transition from sleep to wakefulness.
- Animals can wake up periodically during sleep to sample the environment for relevant stimuli, as Snyder proposed in his "sentinel hypothesis" of REM sleep (134). Some investigators have interpreted his hypothesis to mean that animals ought to be more easily aroused by external stimuli in REM sleep than in NREM sleep, and they have rejected the hypothesis because the opposite is true in some animals. This is not what Snyder meant. He proposed that changes during REM sleep led to the brief spontaneous arousals that typically occur at the end of REM sleep episodes (81,82, 113,134), and that animals use these spontaneous arousals to sample the environment (see Fig. 4).
- Animals can interrupt their spontaneous sleep, whether NREM sleep or REM sleep, to respond to meaningful external stimuli. Waking to escape predators or natural disasters is an obvious advantage, but there are other advantages that are less obvious but are probably more important to the day-to-day functioning of organisms and are relevant to many different kinds of animals. For example, many homeotherms are social animals, and bonds between animals—breeding pairs, parents and offspring, and individuals and the group—can be essential for survival. The persistence of CNS homeothermy during sleep may help to maintain the integrity of these bonds by preserving a capacity to respond to social stimuli during sleep. In this way, for example, a parent can respond to the distress of an infant, or an individual can remain attuned to the group's activities and participate in them. In this case, I am not arguing that animals are more easily aroused in REM sleep than in NREM sleep. I am arguing that periodic warming of the CNS during REM sleep ensures that animals are more easily aroused by external stimuli in both NREM and REM sleep than would otherwise be the case.

There is at least one mammal that lacks REM sleep—the dolphin (96). How can this fact be reconciled with an arousal function for REM sleep? The answer appears to be that at least one side of the dolphin's brain is always awake (it sleeps alternatively on one side then on the other). The fact that an animal that needs no arousal mechanism (because it is always partly awake) has dispensed with REM sleep appears to be consistent with the arousal function proposed here.

CONCLUSION

One of the potential advantages of the hypothesis that REM sleep is a regulated mechanism for warming the CNS is that it is concrete. It focuses on dependent variables, such as temperature, that can readily be measured and manipulated. Also, in relating REM sleep to homeothermic temperature regulation, it places the problem of the function of REM sleep in a physiological context about which much is already known. Furthermore, it relates REM sleep to a basic function—endothermy—that is characteristic of organisms that have REM sleep and that may have co-evolved with REM sleep.

Although the hypothesis has many antecedents, it also differs from some previous interpretations of REM sleep. For example, Parmeggiani investigated many aspects of thermoregulation during sleep and concluded that homeothermic temperature regulation is suspended during REM sleep (103). As argued here, REM sleep is not the absence of homeothermy but rather is an alternate mode of homeothermy. However, the inactivation of various thermoeffector mechanisms during REM sleep, which Parmeggiani has emphasized in his work, is consistent with the notion of an enlarged insulative shell and a more restricted core in REM sleep, as envisioned by the hypothesis.

A weakness of the hypothesis is that while some of its arguments are based on established facts, some are based on insufficient or conflicting data or frank speculation. This mixture partly reflects an inadequacy of the theory and partly the limitations of our present knowledge. I have used concepts like hypothalamic override of rhombencephalic control of REM sleep, and the interchangeability of REM sleep and wakefulness as alternate modes of body-heating, to explain certain situations in which REM sleep decreases at low ambient temperatures and increases at high ambient temperatures.

These concepts protect the theory, but they make it complex, and, some might say, too accommodating.

For now, the descriptive evidence that best supports the hypothesis that REM sleep is a regulated mechanism for warming the CNS consists of observations that CNS temperature usually rises during REM sleep and observations of inverse correlations between REM sleep and normal physiological variations in body temperature associated with circadian rhythmicity, NREM sleep progression, and maturational processes. The weakness of this evidence is that it is correlational in nature. Its strength is that it is physiological. The experimental evidence that best supports the hypothesis is the finding that exposure to cold triggers and prolongs REM sleep in human infants (49), increases the rate at which tympanic temperature rises during REM sleep in human adults (98) and increases heat production during REM sleep in human infants (49) and in adult rats (123). The strength of this evidence is that it is based on the responses of intact organisms to thermal stress.

ACKNOWLEDGMENTS

I would like to thank Ralph Berger, Alexander Borbély, Carol Everson, Michel Jouvet, Adrian Morrison, and Steven Wise for their suggestions and advice. I would also like to thank Holly Giesen and Susan Brundage for their technical assistance and Howard Bartner for the anatomical drawings.

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