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Role of the preoptic area in sleep regulation

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SUMMARY

Alteration in the amount of sleep with changes in ambient temperature, brain temperature or any part of peripheral and core body temperature, suggests a close relationship between these two regulations. A strong reason for this belief is the fact that the hypothalamus, especially the medial preoptic area (mPOA), participates in the regulation of sleep and body temperature. Thermosensitive neurones of the mPOA have been implicated not only in the regulation of body temperature but also in sleep. Simultaneous changes in sleep and body temperature, produced either on lesion or on stimulation of the mPOA, have given reasons to suggest that these two functions are controlled by the same set of neurones of the mPOA. It is proposed that the function of the mPOA is not restricted to regulation of sleep and body temperature, and their interlinking. But it may be essential for the homeostatic regulation of energy balance of the body, in response to alterations in the environmental and body temperature, on the one hand, and sleep-wakefulness, on the other.

INTRODUCTION

The sleep related changes in body temperature (1, 2, 3), and the effects of environmental temperature on sleep (4, 5) had given rise to the thought that the regulation of sleep and of body temperature are generally intimately related. The 24 hour periodicity of our environment, which can be assumed to have developed to optimise the adjustment to this periodic change, has a marked influence on our physiological functions, including rest, activity, sleep and thermoregulation. Another strong reason for the belief that the regulation of sleep and of body temperature are related is the fact that the preoptic area (POA), especially the medial preoptic area (mPOA) participates in the regulation of sleep and body temperature (6, 7, 8, 9). In experimental animals the temperature of the POA can be selectively changed. Increasing and decreasing the POA temperature can produce an increase and decrease of sleep (10, 11). More over, the neurones of the POA that show increased or decreased activities with temperature

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have been implicated in the regulation of sleep (12). These observations have been proposed to support the hypothesis that sleep is modulated by thermosensitive elements of the brain (2, 4, 13). It was also suggested that the thermoreceptors in the POA might provide an input to the sleep-regulating mechanisms situated in this area (14). Most of the recent findings on this subject have come from the studies on rats. Rat is a good animal for the study of the interrelationship between thermoregulatory and sleep regulatory mechanisms, as it shows several episodes of sleep and wakefulness within 24-hour period. They show polycyclic changes in body temperature with the alteration in vigilance state. In these animals, the normal body temperature that varies with the time of the day, which is under the control of a circadian mechanism, and the alteration in body temperature change with episodes of sleep, can be observed separately. The role of the mPOA in the interrelationship between thermoregulatory and sleep regulatory mechanisms in rats, which has given rise to the formulation of several hypotheses on sleep function, will be given due focus in this review.

Brain regions above the brain stem, namely the mPOA of the hypothalamus, play an important role in the regulation of Slow Wave Sleep (SWS). The most important brain regions in the hierarchy of neural structures regulating the body temperature are anterior hypothalamic-preoptic area, and the posterior hypothalamus. The mPOA, which forms the part of the anterior hypothalamic-preoptic area, plays the most important role in both physiological and behavioural thermoregulatory responses (9, 15, 16). The heat loss or gain measures are initiated by the degree of activity of the temperature receptors in the anterior hypothalamic-preoptic area. However, the temperature signals from the peripheral areas of the body, especially from the skin and certain deep body tissues (the spinal cord and the abdominal viscera), also alter the "set-point" of the hypothalamic temperature control centre. The "set-point" increases as the skin temperature decreases, and when the skin temperature is high, the "set-point" decreases. The posterior hypothalamus, which can be described as the sympathetic centre, controls the vasoconstriction of the skin blood vessels.

Apart from the subconscious mechanisms for body temperature control, the body has yet another temperature-controlling mechanism that is even more potent. This is the behavioural control of temperature. Whenever the internal body temperature becomes too high, signals from the brain temperature controlling areas give the person a psychic sensation of being overheated. Conversely, whenever the body becomes too cold, signals from the skin, and probably also from the deep body receptors, elicit the feeling of cold discomfort. Therefore, the person makes appropriate environmental adjustments to re-establish comfort. Indeed, for man, this is the only really effective mechanism for body heat control in severely cold environs. But to study the neural mechanism involved in these regulations and interrelation we depend a lot on the information obtained from lower animals like rats.

Body temperature changes

Lesion studies in rats had provided information that proved invaluable in understanding the thermoregulatory

function of the POA. The electrolytic lesions of the POA, which destroyed the cells and fibres of passage, produced hyperthermia (or increased body temperature) with impaired heat defence abilities in rats (17). It was suggested that the hyperthermia resulted from impaired heat defence abilities. This lesion effect could be either due to the destruction of the POA neurones, nerve fibres of passage and the afferent terminals. Use of neurotoxins like N-methyl D-aspartic acid (NMDA), which could selectively destroy the neurones, leaving most of the nerve fibres and the afferent terminals intact, provided a very useful tool for further investigations in this field. After selective destruction of the mPOA neurones (using local injection of NMDA) there was increase in body temperature. This increase was more marked during the initial one or two weeks. This was followed by a phase during which the body temperature was reset at a level that was higher than normal but lower than that during the initial week after the lesion. The shift in core temperature could be either due to a failure in thermoregulatory ability, or a change in the "set temperature" for thermoregulation. This hyperthermia produced by the NMDA lesion of the mPOA was without impaired heat defence abilities (9). The thermoregulatory ability was tested by noting the changes in the rectal temperature of the rats when they were kept for two hours inside hot (37°C) and cold (6°C) chambers. The mPOA lesion did not produce any change in the response pattern of rectal temperature on heat exposure (Fig.2). This showed that the ability of the animal to regulate its body temperature, when exposed to a hot environment, was not affected. On the other hand, its ability to maintain a stable rectal temperature, on cold exposure, was affected after the mPOA lesion, as the rectal temperature showed greater reduction in the lesioned animals than in the normal ones. Though the rectal temperature was drastically lowered during the initial half an hour of exposure to cold, it was maintained at this lowered level on continued exposure to a cold environment. So the mPOA neuronal lesion produced an increase in the range of thermostat setting, rather than a failure in thermoregulation per se. In other words, in the mPOA lesioned rats, there was a change in the "set temperature" for thermoregulation, and they were able to defend their temperature within this reset range.

Sleep changes

There was a reduction in the time spent in all the stages of sleep, and an increase in wakefulness after the mPOA lesion. All the stages of sleep were reduced throughout the 22 days of study. There was greater suppression of S2. There was more reduction in daytime sleep, resulting in a change in night-day sleep ratio.

There was a significant decrease in their duration of SWS episodes. The decrease was found in the duration of both S1 and S2 episodes. The number of SWS episodes showed a trend of increase. This was primarily due to an increase in short duration episodes. The number of short duration SWS episodes were increased on all the days after the lesion. There was also an increase in the number of awake episodes.

Reduction in the PS episode duration was significant only on the 2nd day, though its frequency was significantly reduced on the 2nd, 4th and 22nd days after the lesion. The reduction in the frequency and duration of the PS episodes, after the lesion, during the light and dark periods, followed the trend recorded in the 24h data.

Body temperature variation with sleep-wake cycles

Body temperature shows variation with the circadian rhythm and sleep-wake cycles. Both these variations were affected after lesion of the POA. Animals with polycyclic sleep-wakefulness are ideally suited for the study of body temperature variation with sleep-wake cycles. In animals with monocyclic pattern of sleep-wakefulness, the variation in body temperature with sleep-wake cycles do coincide with the circadian changes. On the other hand, in polycyclic animals like rats and hamsters it is possible to see the changes in body temperature with sleep-wake cycles, as it does not coincide with the circadian rhythm.

The amplitude of the circadian rhythm of the body temperature was shown to be much larger than normal in golden hamster with POA lesions (18). The body temperature of the rats shows cyclic variation with sleep-wake cycles (3). The average duration and amplitude of these cycles were 5-7 min and 0.26-0.29°C respectively. The magnitude of body temperature variations was increased after the mPOA lesion. The mPOA could be involved in the fine tuning of the set point for thermoregulation ie, to prevent large deviations from the normal thermal set point, by promptly activating appropriate thermoregulatory responses. Without the mPOA, these responses would not be as effective as in the normal, and the ultradian and circadian deviations would therefore be much larger. Change in ambient temperature could be a greater challenge for rats with mPOA damage, than for the normal. There was higher ultradian variation in body temperature of the lesioned rats when they were exposed to changes in ambient temperature. A delayed compensatory response in the mPOA-damaged rats would have produced the exaggerated temperature fluctuations. The increased amplitude of the body temperature variations after the lesion indicates the possibility that the mPOA thermoregulatory system may oppose rather than defend the ultradian and circadian alterations of body temperature in normal rats (3). This could also suggest the possibility that the larger deviation in the body temperature may also contribute towards the increase in wakefulness.

Temporal sequence of changes in body temperature and sleep during the postlesion period

Hyperthermia during the first week after the mPOA lesion was severe. This was followed by a constant mild hyperthermia during the subsequent weeks (8, 9). On the other hand, there was reduction in sleep after mPOA lesion, and there was no variation in the magnitude of reduction in sleep throughout the post-lesion period. Thus, there was no temporal correlation between sleep and temperature changes after the mPOA lesion. This certainly shows that there are neurones in the mPOA which play a role in the regulation of sleep and body temperature. Though this observation does not support the multimodal neurone theory, it does not totally disprove this possibility. It also suggests that the change induced in one parameter is not totally dependent on the other parameter. At the same time, one cannot rule out the possibility that the compensatory measures might have contributed to the differences in the sleep and temperature changes.

a. The changes in body temperature and sleep on local injection of neurotransmitter agonists and antagonists at the mPOA

If changes in either sleep or body temperature can be elicited (without affecting the other parameter), by selective stimulation of different sets of neurones, it can be put forward as an argument in favour of the assumption that these two functions are controlled by different sets of neurones. Selective stimulation of different sets of neurones could be achieved by chemical stimulation of the mPOA. The changes in sleep and body temperature were studied in free moving animals, after the injection of neurotransmitters and their antagonists at the POA, through chronically implanted cannulae. Injections at the POA usually produced alterations in both sleep and body temperature more easily from the mPOA than the lPOA. Direction of changes in these two parameters indicate the following possibilities.

1. Carbachol (acetylcholine agonist) and noradrenaline (NE) administration at the mPOA produced hypothermia and arousal (19, 20, 21, 22, 23, 24). This may indicate that sleep and body temperature were altered by the same set of neurones of the mPOA. Application of alpha adrenergic antagonists phenoxybenzamine and phentolamine at the mPOA produced opposite changes in sleep and body temperature, ie there was injection bound sleep and hyperthermia (19, 24). These findings after application of adrenergic antagonists supported the possible role of noradrenergic system at the mPOA in the regulation of sleep and body temperature. It could be also taken to indicate that a tonic activity of noradrenergic system is responsible for the maintenance of wakefulness and normal body temperature (20, 21). So it is reasonable to assume that sleep and body temperature were altered by the same set of neurones of the mPOA, and they are under tonic influence of inputs coming to this area, like the inputs through noradrenergic system.
2. Detailed analysis of sleep and body temperature responses elicited by the above mentioned drugs casts doubts on the assumption that these changes are brought about by the same set of neurones of the mPOA. The neurotransmitters and their antagonists, injected at the mPOA, did not always produce simultaneous alterations in sleep and body temperature (22, 24, 25). Arousal induced by Carbachol and NE outlasted the reduction in body temperature (22, 24). Sleep induced by phenoxybenzamine and phentolamine was far shorter than the duration of temperature change (22). Moreover, there were instances when only one of these parameters (sleep or body temperature) was only altered. Administration of serotonin at the mPOA produced hyperthermia without any change in S-W (26). Alpha-2 agonist (clonidine) administration at the mPOA produced arousal (27), but it was not effective in producing any change in temperature (28, 29). The initial short-lasting rise in temperature after the injection could be attributed to the non-specific effect of handling and injection. So, it may be suggested that the mPOA controls sleep and temperature through independent, but overlapping, neuronal circuits. This conclusion, which is primarily based on studies in our laboratory, is also supported by the observations of Krueger and Takahashi (30).

3. Further support for the assumption that there are separate controls of sleep and body temperature came from the studies in which various noradrenergic agents were applied at the mPOA (31, 32). In an area innervated by noradrenergic fibres, locally applied NE could act on both post-synaptic and pre-synaptic receptors (33). A pre-synaptic site of action of hypothalamically-injected NE was suggested (34). Studies using alpha-2 adrenergic agents provided some insight into the mechanism of action of NE. Application of NE at the mPOA in normal rats produced arousal and hypothermia. NE injected at the mPOA can act on alpha-1 or alpha-2 adrenergic receptors, apart from beta-receptors, and many other receptors about which very little is known. Alpha-2 receptors are predominantly present in pre-synaptic terminals. Alpha-2 agonist (clonidine) administration at the mPOA produced arousal (27), but it was not effective in producing any change in temperature (28, 29). Clonidine injection can result in the activation of pre-synaptic alpha-2 receptors, and bring about decreased release of endogenous NE at the synaptic cleft (29). Clonidine injection into the mPOA resulted in the activation of pre-synaptic alpha-2 receptors, on both the groups of noradrenergic afferents, but it brought about a decreased release of endogenous NE in those neurones in which there was a tonic release. This decreased release of endogenous NE produced arousal in sleeping animals (27). Clonidine also acted on the inactive terminals, which synapse on the temperature regulatory neurones. Since these fibres normally secrete very little NE, there was no change in the body temperature when this drug was applied. Yohimbine, an alpha-2 antagonist, blocks the pre-synaptic receptors and facilitates the release of endogenous NE from nerve terminals. Post-synaptic action of the released NE on alpha-1 receptors, induces sleep in normal animals (27). Yohimbine failed to exert facilitated release of NE from those nerve terminals that synapsed on the temperature regulatory neurones, since they are normally inactive. Hence, there was no change in the body temperature on application of this drug.

4. Before it is concluded that there are two different sets of neurones controlling these two functions, the possibility of one of these changes affecting the other has to be considered. It is also well known that sleep (i.e. SWS) is associated with a fall, and arousal with a rise, in body temperature (1, 2, 3). So, any drug that produces sleep (especially SWS) can be expected to produce a fall in body temperature, and that which produce arousal with a rise in body temperature. In the above-mentioned drug induced changes, alpha-adrenergic antagonists phenoxybenzamine and phentolamine produced sleep and rise in body temperature. Carbachol and NE produced arousal and fall in body temperature. Thus the changes in the body temperature (hypothermia with arousal and hyperthermia with sleep) would not have resulted from the changes in sleep-wakefulness (S-W).

This can be put forward as a strong argument in favour of the assumption that different sets of neurones are controlling these two functions.

5. After ruling out the possible influence of S-W changes on body temperature, the changes in S-W, which might have been induced by the alterations in body temperature, need to be considered. Here, one cannot rule out the possibility that the induced change in body temperature may have affected the S-W (35). It is possible that the wakefulness may have resulted from a decrease in body temperature, induced by the central injection of drugs. It has been shown that systemic injection of phentolamine produces reduction in sleep and fall in body temperature. There was no reduction in sleep, when the fall in body temperature was prevented (35). It was suggested that the reductions in sleep, observed after the injection of the drug, could have resulted from a fall in body temperature, rather than from a direct action of the drug on the arousal inducing system. This argument can be extended to state that the changes in S-W, induced by the above-mentioned drugs, were influenced by the changes in body temperature. It could even be asserted that the drugs (neurotransmitter agonists and antagonists) produced change only in body temperature, and not in S-W. This is not likely to be true, as can be seen from the subsequent sections.

6. From the evidences put forward so far, it is reasonable to assume that α_1-adrenergic system at the mPOA is involved in sleep and hypothermia. Changes induced in body temperature and sleep-wakefulness on microinjection of an α_1 agonist, methoxamine (0.5, 1 and 2 µmols), into the mPOA were studied in rats. Methoxamine injection produced hypothermia, but there was no major change in sleep-wakefulness during the 3 hrs after the drug injection, except for a short period (15 min) of sleep after 120 min of injection. Coinciding with the maximum fall in body temperature (at 30 min after the injection), there was a short period of wakefulness when methoxamine was administered at higher doses. There was no change in sleep latency after the drug injection. Hypothermia induced by methoxamine might have masked the hypnogenic action of this drug. The study indicates that the α_1 adrenergic receptors participate in the preoptically mediated thermoregulatory measures which bring down the body temperature. It also suggests that the α_1-adrenergic system at the mPOA is involved in sleep.

b. The roles of noradrenergic terminals in the mPOA in regulating sleep and body temperature.

A clear indication regarding separate control of sleep and body temperature came from the studies in which noradrenergic agents were applied at the mPOA, in animals with and without lesion of the noradrenergic fibres projecting to the mPOA (31, 32). It was suggested that the Clonidine and NE injection at the mPOA could result in the activation of pre-synaptic alpha-2 receptors, and bring about decreased release of endogenous NE at the synaptic cleft. In order to test this proposition further, NE was locally administered at the mPOA in rats, whose

noradrenergic fibre terminals were degenerated.

The noradrenergic terminals in the POA come mainly from the lateral tegmental noradrenergic cell groups in the medulla (36, 37). The fibres of the medullary noradrenergic group ascend through the ventral noradrenergic bundle (VNA) to reach the POA. So, the noradrenergic fibres in the POA can be destroyed by injecting 6-hydroxy dopamine at the VNA (29, 38, 39). NE injection at the mPOA induced sleep in the VNA lesioned animals. As the pre-synaptic adrenergic receptors were not available at the mPOA in these rats (as the noradrenergic terminals had already degenerated), the response elicited must have been due to the action of NE on the post-synaptic receptors (38).

Application of NE at the mPOA in the rats with noradrenergic fibre lesion brought about sleep and decreased body temperature. It could be argued that the decreased body temperature was a result of sleep. It could be also argued that the decreased body temperature and sleep are actively produced by multimodal neurones of the mPOA, and that thermoregulation and sleep regulation are inter-linked at this area of the brain. But, local application of clonidine and yohimbine, in the rats with noradrenergic fibre lesion, further clarified our concept (27, 29). Though arousal was produced in normal rats by the injection of clonidine, at the mPOA, it did not have the same effect on the rats with noradrenergic fibre lesion. Clonidine did not alter the rectal temperature in normal rats but it induced hypothermia in the lesioned rats. Injection of yohimbine, at the mPOA, induced sleep in rats with intact noradrenergic fibres. However, the sleep inducing effect of this drug was very much attenuated in the lesioned animals. There was no significant change in body temperature, in both normal and noradrenergic fibre lesioned animals, after yohimbine administration. On the basis of these findings, it was suggested that there are two separate groups of afferent noradrenergic inputs, ending on the mPOA neurones. One of them, terminating on sleep inducing neurones, is activated during sleep. Those afferents, which synapse on the temperature regulatory neurones, are suggested to be normally inactive and may be activated only when the heat loss mechanism is to be stimulated (29). An intact catecholaminergic pathway within the anterior hypothalamus is required for the rat's physiological control of heat loss in a warm environmental temperature (40). It can be concluded that there are separate sets of noradrenergic terminals for regulation of sleep and body temperature.

Local application of isoproterenol, a beta agonist, into the mPOA, in the VNA lesioned animals, did not produce any significant change in S-W, though it produced arousal in normal rats. Thus, the increase in wakefulness obtained on isoproterenol administration was probably the result of its action on the pre-synaptic noradrenergic terminals (39). The possible involvement of sexual arousal in the isoproterenol-induced increase in wakefulness is discussed in the subsequent section.

Regulation of body temperature at various vigilance states

Body could be divided into two distinct compartments, ie core and shell, for describing the process of thermoregulation. But, when we consider changes in body

temperature, the brain temperature needs to be considered separately from rest of the core. The brain shows temperature changes, which are different from the rest of the body. SWS is associated with a decrease in brain temperature, and REM sleep with an increase, in many mammalian species like rabbit, rat, cat and sheep (3, 41, 42). In this description we will be considering the changes in core, brain and skin temperatures separately. There are several external and internal factors, which either alter, or tend to alter, the body temperature from the "set-point". In these situations, appropriate physiological and behavioural responses are initiated by the brain to bring the temperature back to the "set-point" (10, 11, 43). Changes in brain, core and skin temperatures, associated with transitions in the arousal states, occur in rats throughout the 24-hour diurnal cycle. In the case of body temperature control, we have seen that it is important for the internal core temperature to change as little as possible despite marked changes in the environmental temperature. The skin temperature, in contrast, rises and falls with the temperature of the surroundings, in an awake individual or animal.

Slow wave sleep:- Attempts were made to study the changes in tail skin temperatures during SWS, at different atmospheric temperatures (44). Skin temperature is regulated by sympathetic nerves, which are under hypothalamic control. At 10°C and 21°C, during awake state, the skin is cold as there is partial vasoconstriction of skin blood vessels brought about by the tonic activity of the sympathetic nerves. Falling asleep was accompanied by an increase in skin temperature and vasodilation at these lower temperatures of 10°C and 21°C. At 29°C, the skin is warm during awake state, as the skin blood vessels became intensely dilated. This happens as the sympathetic centres that cause vasoconstriction are inhibited. At this warm temperature, there is no further dilation and increase in skin temperature with sleep onset as the skin vessels are already dilated.

There was a decrease in core temperatures (including brain temperature) during SWS at all the above mentioned temperatures of 10°C, 21°C and 29°C (44). The brain temperature alterations followed the changes in S-W (3). This indicates the strong possibility that these temperature changes result from the alterations in S-W. This leads to the question whether these changes are brought about by a failure in thermoregulation during sleep or is there an active regulatory process which brings about these changes.

Involvement of an active regulatory process has been suggested as there is an alteration in the hypothalamic thermostat during sleep, rather than a failure in thermoregulation. According to this concept, the brain temperature is actively down regulated during SWS. It has been shown that the hypothalamic set points for heat production and heat loss are at a lower level during SWS in the kangaroo rat and the pigeon (43, 45). This has been described as a down regulation of brain temperature. It was proposed that the function of SWS is to cool the brain (13). According to this proposition the heat load accumulated during prior wakefulness determines the SWS intensity by appropriately down regulating the brain temperature (46). It was suggested that there was a lowering of the set point and an increase in heat dissipation with transitions from waking to SWS (10, 45). It was thus suggested that SWS is a part

of the thermoregulatory process that controlled the body and brain temperature.

Taking clues from the active down regulation of body / brain temperature during SWS, it was hypothesised that the SWS-induced brain and body cooling would lower the energy utilisation and reduce cerebral metabolism. In other words, SWS acts as a protection of the brain against the sustained high temperatures of wakefulness. As the mPOA is the most important region of the brain for maintenance of SWS, it is reasonable to assume that this area plays an important role in bringing down the body / brain temperature during SWS. But, the brain temperature variations with sleep-wake changes were not only present, but were even higher in the mPOA lesioned rats (3). So, it was concluded that the mPOA was not involved in the down regulation of brain temperature at various vigilance states.

As there was a reduction in the sympathetic tone and heat production during SWS, it may be assumed that the efficiency of the thermoregulatory mechanism is decreased during this phase of sleep. In man, the largest fall in body temperature, associated with SWS, occurs at the beginning of sleep. This is associated with the change in body posture from an upright position to a recumbent position, and not with the depth of SWS, or stages 3 and 4 of sleep (47). In rats also, the increase of slow wave activity (mean power density in the 0.75-4.0 Hz range) and the decrease of cortical temperature in SWS episodes, were not correlated (48). So, the decrease in body temperature, at least during the initial part of sleep, was independent of SWS (49).

The vigilance dependent changes in the hypothalamic (and brain) temperature of homeotherms are brought about by adjustments in arterial blood flow that could cool the brain. However, there are different mechanisms for brain cooling, i.e. systemic and selective brain cooling. They are affected by the changes in body posture and vasoconstrictor sympathetic outflow related to wake-sleep states (50).

REM sleep:- Core and skin temperature show variations during REM sleep. But, there has been a lot of speculation and debate about the changes in brain temperature. REM sleep was associated with a rise in brain temperature, and the rise was the largest in the cold environment and was attenuated at the warm environment in rats (3, 44). There was no change in brain temperature, when the rats were maintained at 30°C, though there was increase in the brain temperature with a shift from deep SWS to REM sleep at 18°C and 24°C environmental temperature (3). Increase in brain temperature with REM sleep occurs in most mammalian species that have been investigated. But, still there is some doubt about the changes in brain temperature in primates. It has been reported that there was no change in brain temperature in monkeys during REM sleep (51). In human subjects, the tympanic temperature (which could be taken to represent the brain temperature), and even the forehead skin temperature, increase during the REM sleep (52).

Even if it is assumed that the brain temperature alteration during REM sleep is an active process (45), it is likely that the mPOA may not be responsible for this change (3). On the other hand, the posterior hypothalamic lesions produced either a suppression of the increase (or even a decrease) of brain temperature during REM sleep, while skin temperature variations

were not modified. The decrease in cerebral blood flow, which was also always associated with increase in brain temperature, was suppressed after the posterior hypothalamic lesion. So, it was hypothesised that the decrease in brain blood flow depends upon an active vasoconstriction process originating in the posterior hypothalamus (53).

Increase in brain temperature with REM sleep was attributed to an increase in local metabolic rate, and changes in cerebral blood flow (53). During REM sleep, common carotid artery blood flow is spontaneously decreased (54). Simultaneously there is an increase in the amount of vertebral artery blood flowing into the brain (through the circle of Willis). In other words, an increase in brain temperature during REM sleep is characterised by a shift from the carotid artery to the vertebral artery, and probably also to other arterial sources (55). The increase in vertebral artery blood flow appears primarily as an autoregulatory response to the drop in carotid artery blood flow during REM sleep, in response to brain activation in REM sleep (56).

Core temperature decreased and skin temperature increased in the cold, whereas core temperature tended to increase, and skin temperature to decrease, in the heat. This paradoxical peripheral vasomotion during REM sleep supports the previous suggestions on severe thermoregulatory impairment during REM sleep in rats and other species (44). In the cold ambient temperature, deep interscapular (just below the brown fat lobes) temperature decreases during desynchronized sleep. This change in temperature probably results from a depression in sympathetic vasoconstrictor influences, producing blood and brown fat cooling during this stage of sleep (57, 58). But the increase in hypothalamic temperature during this stage of sleep occurs independently of a transfer of heat from interscapular brown fat (57, 58).

It was generally believed that during REM sleep, thermoregulatory responses are virtually absent and that body temperature becomes temporarily dependent on ambient temperature. Therefore, REM sleep has been referred to as a poikilothermic state (59). On the other hand, during REM sleep, sweat gland activity persists though at a lower level than during SWS (60). The observation that REM sleep propensity is highest when core body temperature reaches its lowest physiological level, led to the suggestion that REM sleep represents a regulated mechanism for warming the central nervous system (61). It is difficult to accept that the functions of SWS and REM sleep are to cool and heat the brain respectively, as both the sleep stages were increased with higher ambient temperature (3).

There are some basic differences in REM sleep in animals and humans. REM sleep is the deepest stage of sleep in animals. But, human subjects could be more easily woken up from REM sleep than from SWS. There was an increase in oxygen consumption in human subjects during REM sleep (52). The temperature of the skin of the limb extremities declined at 21°C during REM sleep. Thermoregulation is not likely to be suppressed during REM sleep in humans, unlike in other mammals, as there is peripheral vasoconstriction, increased tympanic temperature and oxygen consumption, and no reduction in REM sleep, when they are exposed to cold (52). Skin temperature showed a small, but significant, increase during REM sleep at

29, 34, and 37°C, but the rectal temperature did not change during REM sleep at any atmospheric temperature. Shivering, which was present during wakefulness at 21°C and 24°C, occurred only occasionally during stages 1 and 2 sleep at 21°C. The increases in oxygen consumption and the absence of marked changes in vasomotor tone during REM sleep in the cold were unexpected (as compared to other mammals), and possibly indicate that this phase of sleep is not as thermally disruptive in humans as in other mammals (62). These differences in thermoregulation should be also viewed along with the differences in REM sleep itself, in man and in other animals.

Effect Of Ambient and Body Temperature on Sleep

Further evidence of a close relationship between sleep regulation and temperature regulation has been derived from experiments in which sleep was analysed after experimental manipulations of ambient temperature, body temperature or brain temperature.

a. Effect of Ambient Temperature on Sleep

Acute exposure to an ambient temperature outside the thermoneutral range has a prominent effect on both temperature regulation and sleep regulation. Though it is possible to define the thermoneutral zone as the comfortable ambient temperature range for human beings, it is difficult to define the same for experimental animals. If the thermoneutral range is defined as the range of ambient temperature in which metabolic heat production is minimal, for the inactive rat, this range is approximately 26-33°C (17, 63). If the absence of behavioural thermoregulation of the rat is taken as a criterion, the range is 18-28°C (63). The maximum REM sleep time is also used to define the thermoneutral temperature. At approximately 30°C, maximum values of REM sleep are obtained (5, 64). REM sleep seems to be more sensitive to changes in ambient temperature than SWS. In the rat a general linear decrease in the percentage of REM sleep from 23°C to 10°C has been reported (44, 65). Thus the REM sleep is reduced during that period in which the regulation of body temperature is suspended. The amount of SWS is also decreased by low ambient temperature (5, 44, 65).

The changes in S-W were studied in rats when they were exposed to different ambient temperatures of 18°C, 24°C and 30°C (5). There was an increase in REM sleep and SWS, and a decrease in wakefulness at higher ambient temperatures. The increase in sleep was primarily due an increase in the duration of sleep episodes.

The increase in the amount of sleep with enhanced ambient temperature may be considered as an adaptation to thermal load aimed at energy conservation (4). REM sleep has been shown to be very sensitive to slight variations in the thermal environment and it varies significantly even within 25°C and 30°C, which have been defined as the thermoneutral zone for rats on the basis of the minimal metabolic rate (66).

It was suggested that when the ambient temperature is low, the central nervous system has to call for an increase in the relative amount of arousal, at the expense of the sleep stages, especially desynchronised sleep, in order to maintain

the body temperature (67). An increase in arousal in cold is necessary for the production of more heat by increasing motor activity. REM sleep, in which the regulation of body temperature is said to be suspended, is incompatible with low ambient temperature, during which appropriate thermoregulatory responses are needed to protect the animals from hypothermia (68). In other words, the functional state of wakefulness enables the organism to optimise thermoregulation.

The changes in S-W were also studied during their exposure to different ambient temperatures after the destruction of the mPOA neurones by NMDA. The mPOA neuronal destruction produced a decrease in sleep at all the three different ambient temperatures. There was a decrease in sleep, particularly the deeper stages of sleep (deep SWS and REM sleep) after the mPOA lesion (8, 69). But, there was a linear increase in sleep with higher temperatures (5). The sleep induced by higher temperatures in the lesioned rats was qualitatively different from that in the normal animals. In normal animals, there was an increase in long duration SWS episodes with higher ambient temperature. But on the other hand, after the mPOA lesion, 30°C ambient temperature produced an increase in the number of short duration SWS episodes. It has been reported that the mPOA is thus important for the maintenance of sleep, as it was the sleep duration, which was primarily affected by the mPOA lesion (8). The warm environment could increase the amount of sleep, even after the mPOA lesion, but the higher ambient temperature was more efficient in initiating sleep rather than in maintaining it. In other words the ability to maintain SWS was affected after the mPOA lesion, and this ability could not be restored by exposure to a warm environment. The findings indicate that the mPOA is essential for sleep maintenance and improving the quality of sleep with higher ambient temperatures.

The decrease in REM sleep frequency might have resulted from a decrease in SWS. REM sleep normally appears after the animal has spent some time in SWS. So, it is possible that the decrease in the duration and frequency of deep SWS, after the mPOA lesion, had resulted in the decreased frequency of REM sleep (8). Though the REM sleep was reduced after the mPOA lesion, the warm environment could prolong the duration of REM sleep episodes, once they were initiated. Thus, the warm environment could influence the REM sleep even in the absence of an intact mPOA. This is understandable, as the major REM sleep generating structures are outside the mPOA.

From the results of this study, it can be concluded that the mPOA is essential to increase sufficiently the duration of sleep episodes (especially SWS) by thermal stimulus, though sleep could be induced through structures other than this area. In other words, the mPOA is essential for organising the sleep architecture (especially SWS), as per the thermoregulatory requirement. It may be mentioned here that one suggested function of the mPOA is to provide a fine-tuning of the energy balance, which will be discussed later (8, 70, 71).

b. Effect Of Body and Brain Temperature on Sleep

Despite thermoregulatory responses, body temperature and brain temperature in the rat increase by more than 1°C over a 24-hour period if the ambient temperature is increased from 21°C to 29°C (44). This

increase in brain temperature and body temperature can evoke an increase in SWS in animals and in human subjects (13, 46, 72, 73, , 74). Even radio frequency diathermic warming of the POA in cats and opossum could induce sleep. Cooling the POA produces huddled posture. Roberts and Robinson (14) have suggested that the POA thermoreceptors may provide an input to the sleep-regulating mechanisms in this area itself. Stimulation of central receptors by changing blood temperature is likely to be an important source of impulses driving the sleep inducing structures of the basal forebrain (75). It was hypothesised that the SWS in mammals and birds is controlled by thermoregulatory mechanisms (13).

Studies have shown that SWS is facilitated when brain temperature exceeds a threshold level (13). This threshold is hypothesised to be determined by responses of preoptic-anterior hypothalamic thermosensitive neurones and to be regulated by both circadian and homeostatic processes. Local warming of the POA produces sleep (14, 76, 77). Preoptic-anterior hypothalamic warming increases EEG delta frequency activity during SWS (78). So, it was suggested that the preoptic-anterior hypothalamic thermoregulatory mechanisms participate in the regulation of the depth of SWS. According to Nakao et al. (79) the SWS is controlled by thermoregulatory mechanisms of the preoptic-anterior hypothalamus. Circadian and homeostatic thermoregulatory processes may be integrated in this brain area.

c. *Effect Of Chronic Exposure to Cold Environment on Sleep*

Changes in S-W induced by acute cold stress may not persist during long-term exposure, as homeostatic regulatory mechanisms may reset the various components of sleep, during the period of thermoregulatory acclimatisation. It was hypothesised that circadian and homeostatic processes regulate the activities of the thermosensitive neurones that control the amount of SWS (13). Continuous recording of S-W for 24hrs, during chronic exposure to cold, along with brain temperature, showed that there was a decrease in sleep, especially paradoxical sleep (PS), during the initial days of exposure to a mild environment of 18°C. Though the sleep parameters came back to the control level by two to three weeks of exposure, the brain temperature remained high, even on continued exposure to cold for four weeks. It is proposed that the elevated brain temperature also played a role in homeostatic restoration of sleep, especially S2 and PS. It was during S2 and PS that the brain temperature was maintained at a higher level, compared to pre-exposure values. This increased brain temperature could be interpreted as a resetting of thermoregulation (or thermostat) to ensure adequate sleep, especially S2 and PS. It has been shown that increasing the body temperature, especially the brain temperature around the preoptic area does induce sleep (4, 11, 13, 80). The adaptive resetting of brain temperature may provide continued stimulus to the sleep generator.

Homeostatic mechanisms would have ensured that the changes in S-W on acute exposure to a low ambient temperature did not persist during long-term exposure. In this study it was observed that the circadian variations in sleep, as well as brain temperature, were disrupted during the acute exposure to a low ambient

temperature During the acclimatisation to low ambient temperature, several factors might have come into operation and reset the various components of sleep and brain temperature. It was observed that there was restoration in circadian variations in S-W and brain temperature by the fourth week of cold exposure. It was suggested that the functional state of wakefulness enable the organism to optimise thermoregulation (44, 68, 80). Though it could be true to some extent during acute cold stress, thermoregulation may be readjusted to ensure homeostatic regulation of sleep during chronic cold exposure.

Preoptic Neuronal Activity as the Basis for Sleep Temperature Interlink

The modulation of the thermo-regulatory responses by the vigilance state could be observed even at the level of neuronal activity. It has been demonstrated that there are neurones in the mPOA involved in the regulation of sleep and body temperature (81, 82, 83). The number of neurones in the preoptic-anterior hypothalamus that were thermosensitive, as well as the thermosensitivity of individual neurones, were reduced in SWS as compared to the wakeful state (84). Most neurones became thermo-insensitive in REM sleep. Thermosensitive neurones of the preoptic-anterior hypothalamic area have been implicated in the regulation of both body temperature and SWS (85). The activation of sleep-related warm-sensitive neurones and the deactivation of wake-related cold-sensitive neurones may play a key role in the onset and regulation of SWS (86). During SWS, a majority of preoptic-anterior hypothalamus warm-sensitive neurones exhibit increased discharge as compared to the wakeful stage. Cold-sensitive neurones exhibit less discharge in SWS, than in wakefulness. Warm-sensitive neurones with increased discharge in SWS exhibited increased thermosensitivity during SWS than in wakefulness. Cold-sensitive neurones with decreased discharge during SWS exhibited decreased thermosensitivity in SWS. In addition, a few neurones that were thermo-insensitive during wakefulness became warm-sensitive during SWS (12).

Warm-sensitive neurones did not exhibit a significant change in thermo-sensitivity during REM sleep as compared to wakefulness and SWS (85). In contrast, cold-sensitive neurones exhibited decreased mean thermosensitivity during REM sleep than in wakefulness. Cold-sensitive neurones as a group did not retain significant thermosensitivity in REM sleep. These findings are consistent with evidence that thermoeffector responses to cooling are lost in REM sleep, whereas some responses to warming are preserved (85).

Osaka & Matsumura (83) examined the effects of NE on the activity of sleep-related neurones in the POA and the neighbouring basal forebrain in the rat. NE and the alpha 2-agonist clonidine generally inhibited sleep-active neurones, whereas the alpha 1-agonist methoxamine and the beta-agonist isoproterenol had no effect on them. Thus, alpha 2-receptors mediated the NE-induced inhibition. NE and methoxamine excited the waking-active neurones, whereas isoproterenol and clonidine did not produce any effect. Accordingly, alpha 1-receptors probably mediated the NE-induced excitation. State-indifferent neurones and REM sleep-active neurones were mostly insensitive to NE. According to Osaka & Matsumura (83), these results suggest that NE promotes wakefulness by inhibiting sleep-active neurones and by exciting waking-active neurones.

Food intake, energy conservation and sleep regulation

It has been hypothesised that hibernation, which is a state showing extreme adaptations for energy conservation, is an evolutionary extension of SWS (87). Phylogenetic and ontogenetic associations between sleep and endothermy are consistent with the hypothesis that sleep evolved in conjunction with endothermy to offset the high energetic cost of endothermy (88). According to them the electrophysiological and thermoregulatory continuum of SWS, circadian torpor and hibernation substantiates a primordial link between sleep and energy conservation. When energy stores decline, energy is conserved by lowering Tb proportionally during sleep or by increasing the daily duration of sleep. Furthermore, these states of hibernation and torpor are entered via SWS (87). These observations prompted some scientists to hypothesise that SWS is an adaptive behaviour for energy conservation in homeotherms (42, 87). But, hibernation is regularly interrupted by short periods during which body and brain temperatures are up regulated to euthermic levels. Though the function of these energetically very expensive episodes is unknown, animals spent most of this time in SWS (89, 90, 91). Sleep, daily torpor and hibernation are no longer considered homologous processes. Animals emerging from these states spend most of their time in sleep, indicating that they were deprived of sleep during torpor. After termination of the torpor-associated hypothermia, there is a compensatory increase in SWS, as it happens subsequent to sleep deprivation.

Earlier reports have shown that the alteration in food intake can disrupt sleep (92). There are reports in the literature that indicate that REM sleep deprivation or total sleep deprivation increases the food intake (93, 94, 95). But the decrease in SWS and REM sleep, resulting from the mPOA lesion, did not produce any increase in food intake and water intake (8). Food deprivation in birds and squirrels resulted in a lowering of the thermoregulatory set point during sleep along with increased SWS (88).

Though there was no significant persistent change in food intake, there was a reduction in the body weight of the rats after the mPOA lesion with NMDA, and electrolytic lesion of the POA (8, 64). Higher locomotor activity and increased body temperature, after the mPOA lesion, produced increased energy expenditure. This might have resulted in a decrease in the body weight because there was no concomitant compensatory addition in energy intake (food intake), in spite of the increase in locomotor activity, rectal temperature and awake period. Therefore, after the lesion, the animal did not recognise low energy reserves, and so it did not bother to conserve energy. Thus, it can be hypothesised that the mPOA lesioned animals had lost the mechanism for the fine-tuning of food intake, in response to the alteration in body homeostasis. The functional integrity of the mPOA may be essential for the regulation of food intake, in response to alterations in the temperature, locomotor activity and S-W. It can also be argued that the mPOA would normally facilitate sleep, an energy-conserving state, when energy reserves are at a critical level (8).

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