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Interrelation between Thermoregulation and Sleep Regulation

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Simultaneous changes in sleep-wakefulness (S-W) and body temperature with 24-hour periodicity were attributed to the evolutionary influence of our environment. The normal body temperature that varies with the time of the day is under the control of a circadian mechanism. The other factor, which has been suggested to bring about this change in body temperature, is the vigilance state itself. This is apparent in many animals, which have several episodes of sleep and wakefulness within 24-hour period. They show polycyclic changes in body temperature with the alteration in vigilance state. Alteration in the amount of sleep with changes in body temperature, suggests a close relationship between these two regulations.

The interrelation between thermoregulation and the vigilance state could be observed even at the neuronal level. A strong reason for this belief is the fact that the preoptic area, 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. Recent studies have shown that the change induced in one parameter (either in sleep or body temperature), by lesion of the mPOA, is not dependent on the change in the other parameter. Chemical stimulation studies showed that the mPOA controls sleep and body temperature through independent neuronal circuits. There are separate sets of noradrenergic terminals in the mPOA for regulation of sleep and body temperature. 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.

Key Words: Sleep, Wakefulness, Thermoregulation, Body temperature, Medial preoptic area, REM sleep, Slow wave sleep, EEG, Interrelation, Lesion, Stimulation

Introduction

The objective of this review is to explain the interrelation between thermoregulation and sleep regulation, and throw some light on the physiological basis of this interrelation. The sleep related changes in body temperature (Kawamura & Sawyer 1965, Parmeggiani et al. 1975, Thomas & Kumar 2002), and the effects of environmental temperature on sleep (Obal et al. 1983, Thomas & Kumar 2000) had given rise to the thought that the regulation of sleep and of body temperature are generally intimately related. Another strong reason for this belief is the fact that the preoptic area (POA), especially the medial preoptic area (mPOA) participates in the regulation of sleep and body temperature (Nauta 1946, John et al. 1998, John & Kumar 1998, Kumar & Khan 1998). In experiments on animals the temperature of the POA can be selectively changed. Increasing and decreasing the POA temperature produce an increase and decrease of sleep (Hammel et al. 1963, Satinoff 1983). Moreover, the neurones of the POA that show increased or decreased activities have been implicated in the regulation of both slow wave sleep (SWS) and body temperature (Alam et al. 1996). These observations can be taken to support the hypothesis that sleep is modulated by thermosensitive elements of the brain (Parmeggiani et al. 1975, Obal et al.1983, McGinty &

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Szymusiak 1990). It was also suggested that the thermoreceptors in the POA might provide an input to the sleep-regulating mechanisms situated in this area (Roberts & Robinson 1969). Most of the recent findings on this subject have come from the studies on rats. 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.

Sleep and its Regulation

It is reasonable to assume that the 24-hour periodicity of our environment has a marked evolutionary influence on our physiological functions, including rest, activity, sleep and thermoregulation. The circadian clocks virtually modulate every aspect of mammalian physiology (Chandrashekaran et al. 1997, Schibler & Sassone-Corsi 2002). Though we can wake up and do things at anytime of the night (or day), the need to sleep has a powerful influence over our behaviour. If we go without sleep or drastically reduce it, the desire or need to sleep is so powerful that we cannot stay awake even to avoid death. This strongly suggests that sleep is not only necessary for our health, but it is also vital for our survival. In addition, human beings spend about one third of their lives in sleep. They organise their time for recreation and other social activities to meet the demands for sleep.

Half a century ago, Aserinsky and Kleitman described a phase of sleep during which binocularly synchronous rapid eye movements (REM) are seen. Muscle atonia, and irregular (and at times accelerated) activity of the autonomic nervous system are characteristic features of this phase. Recordings of electrical signals from central nervous system strongly suggest that the brain (or at least the cortex) is at a higher level of activity during REM sleep, than during the other phase of sleep called SWS (which is predominated by slow electrical waves in the EEG). This term "slow wave sleep" may be inappropriate, as all phases of SWS are not predominated by slow electrical waves. But, still this term is extensively used to describe this phase of sleep in animals. In this review, the term SWS will be used to describe all non-REM sleep. There are no visible eye movements and twitches during the SWS.

Traditionally, three primary measures have been used to define physiological sleep, the different sleep stages and wakefulness (Kumar 1998, 2000). These are electroencephalogram, electrooculogram and electromyogram. Electroencephalogram, conventionally abbreviated as "EEG", and popularly known as "brain waves", are small voltages recorded from the scalp. The electrooculogram (conventionally abbreviated as EOG), that indicates eye movements, is recorded when electrodes are placed on the skin near the eye. The electromyogram (EMG), is a record of the electrical activity of muscles, conveniently recorded from electrodes placed on the skin overlying a muscle. In humans, the EMG is typically recorded from under the chin, since the muscles in this area show very dramatic changes associated with the sleep stages. Though the sleep pattern (and EEG waves) in non-human mammals are not identical to that of humans, there are essential similarities in the EEG, EOG and EMG of all mammals.

In practice, the EEG, EOG and EMG are simultaneously recorded, so that relationships among the three can be seen immediately. During wakefulness the EEG alternates between two major patterns. One is low voltage "activation" or desynchronised pattern, when subjects are alert, and the other is "alpha" activity, which is most abundant when the subject is relaxed with the eyes closed. The sleep pattern of human subjects can be divided into five different physiological stages, namely stages 1,2,3 and 4 non-REM sleep, and REM sleep. REM sleep is also called paradoxical sleep, as the EEG shows a low voltage desynchronised pattern, which is common during wakefulness. Though, both the terms are commonly used, this phase of sleep will be referred to as REM sleep in this article.

In mammals, wakefulness is usually classified as quiet wakefulness and active wakefulness, whereas sleep is classified into three stages, namely light SWS, deep SWS and REM sleep (Kumar et al. 1993, John & Kumar 1998, Ramesh & Kumar 2000). The term "depth of sleep", frequently used to qualify sleep, has been defined as resistance to being awakened by an external stimulus, such as a sound. In humans, Stages 3 and 4 are "deep" sleep in the specific sense that it takes a louder sound to awaken a subject from these stages than from Stages 1, 2 or

REM. However, a louder sound is required to awaken cats and rats from REM than from other stages. So the generality of even this specific "depth of sleep" measure is limited.

Neural Structures Involved in the Regulation of Various Vigilance States

There are specific brain regions that promote SWS and others that are responsible for REM sleep (Kumar 1991, 1998, 2000). This may be an oversimplified statement, as the brain region that promotes SWS may also be playing some role in REM sleep, or even wakefulness. But, still it is possible to describe some areas as playing a role either in SWS, REM sleep or wakefulness (Moruzzi 1972). Neurones in the midbrain reticular formation, primarily making up the ascending reticular activating system (ARAS), are important for production of low-voltage, fast-frequency, EEG pattern, commonly associated with wakefulness. The old notion that sleep is a passive phenomenon resulting from the inactivation of the ARAS is not true. Brain regions above the brain stem, namely the mPOA of the hypothalamus, play an important role in the regulation of SWS. The importance that was previously given to the thalamus, for the regulation of SWS, is now seriously questioned, although it is still considered important for the genesis of the EEG spindles of normal sleep. There is growing evidence in favour of the theory that the hypothalamus is the major centre regulating SWS, sleep-wake cycle, and even wakefulness, while recent findings confirm the importance of the brain stem in the genesis of REM sleep (Datta 1995, 1997).

Thermoregulation

The body temperature can be defined as a balance between heat production and heat loss from the body (Crawshaw 1980). The body temperature is regulated within a certain range in homeotherms. Whenever, the body temperature deviates from this "set-point", appropriate physiological and behavioural responses are initiated by the brain (Hammel et al. 1963, Satinoff 1983). The mechanism for the control of body temperature is a very effective system with a high feedback gain. The gain of the temperature control system can be defined as the ratio of the change in environmental temperature to the consequent change in body temperature.

For the purpose of describing thermoregulation, the body can be divided into two compartments, i.e. the core and the shell. The skin, subcutaneous tissue and the adjoining body mass lying in the periphery constitute the shell. The rest of the internal tissue forms the core. In the case of body temperature control, it is important for the internal core temperature to change as little as possible despite marked changes in the environmental temperature. In man, if the internal body temperature goes above 37°C, the physiological measures are geared to increase the heat loss. As a result, the body temperature falls and re-approaches the 37°C level. If the body temperature goes below this level, the rate of heat production becomes greater than heat loss, so that the body temperature rises and approaches the 37°C level. Therefore, this critical temperature level is called the "set-point" of the temperature control mechanism. That is, all the temperature control mechanisms continually attempt to bring the body temperature back to this "set-point" level.

The temperature control system employs vasodilation, sweating and decrease in heat production to reduce body heat when the body temperature goes high. When the body temperature goes down, the control system institutes skin vasoconstriction, piloerection and increase in heat production. Most of the heat is generated in the deep organs of the body, especially the liver, brain, heart, and skeletal muscles. This heat is transferred from the deeper organs to the skin, where it is lost to the air, and other objects in contact with it. The rate of heat loss from the body is determined by the speed of conduction of heat from the core to the skin and then from the skin to the surroundings. Heat is conducted from the core to the skin by the blood, and the flow of blood to the skin is controlled by the degree of vasoconstriction of the arterioles. This vasoconstriction, in turn, is controlled by the sympathetic nervous system.

In human subjects, sweating causes a sharp increase in the rate of evaporative heat loss from the body when the core temperature rises above the critical temperature level of 37°C (98.6°F). Piloerection is not important in the human being, but in lower animals upright projection of the hairs allows them to entrap a thick layer of "insulator air"

next to the skin so that the transfer of heat to the surroundings is greatly depressed. Heat production by the metabolic systems is increased by promoting shivering, excitation of sympatho-adrenal system, and thyroxin secretion.

Role of the mPOA in Thermoregulation

The most important brain regions in the hierarchy of neural structures regulating the body temperature are the 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 (Kumar & Khan 1998, Ray et al. 2001, Pal et al. 2002). The heat loss or gain measures are initiated by the degree of activity of the heat 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.

Lesion studies on rats had provided information that proved invaluable in understanding the thermoregulatory function of the mPOA. The electrolytic lesions of the mPOA, which destroyed the cells and fibres of passage, produced hyperthermia (or increased body temperature) with impaired heat defence abilities in rats (Szymusiak & Satinoff 1982). 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 or nerve fibres, including the afferent terminals. The discovery that neurotoxins, like N-methyl D-aspartic acid (NMDA) could selectively destroy the neurones, leaving 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 hyperthermia without impaired heat defence abilities (Kumar & Khan 1998). The shift in core temperature could be either due to a failure in thermoregulatory ability, or a change in the "set temperature" for thermoregulation. The thermoregulatory ability of the rats could be tested by noting the changes in their rectal temperature when they were kept for two hours inside hot (37°C) and cold (6°C) environments. The mPOA lesion did not produce any change in the response pattern of rectal temperature on heat exposure. 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.

The body temperature of the rats shows cyclic variation with S-W alterations (Thomas & Kumar 2002). 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. It is reported that the amplitude of the circadian rhythm of the body temperature was much larger in rats with POA lesions (Osborne & Refinetti 1995). 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 (Thomas & Kumar 2002). This could also suggest the possibility that the larger deviation in the body temperature may also contribute towards the increase in wakefulness.

Changes in Sleep and Thermoregulation after Preoptic Lesion and Stimulation

Simultaneous changes in sleep and body temperature, produced either on lesion or on stimulation of the mPOA, have given reasons to think that those two functions may be interrelated.

Possible reasons for simultaneous changes in sleep and body temperature, produced on lesion and stimulation of the mPOA

The reasons for simultaneous changes in these parameters could be the following:

1. There are probably some neurones in the mPOA, which can bring about changes in both sleep and body temperature. They could be termed as multimodal neurones.
2. There may be separate sets of neurones that modify these two functions, independently. Though they exist in the same location, they are not interlinked or interconnected. Both the responses were simultaneously occurring only because the experimental manipulations (like stimulation and destruction) affect both the sets of neurones. Selective stimulation or lesion of neurones in the mPOA could explore this possibility.
3. The neurones involved in the two functions may be different, as mentioned above, but may have some short loop interconnection. Selective stimulation and lesion, as suggested above may not be sufficient to explore this possibility.
4. There exists a distinct probability that one of the elicited functions affects the other function, through the long loop system, which may involve many areas of the brain, including many physiological systems of the body. For example, if there are some changes in the body temperature, induced by mPOA manipulation it can affect sleep. Similarly, if there are some changes in sleep induced by the mPOA manipulation, it can also produce a change in the body temperature, as body and brain temperature do show alterations with sleep.
5. In addition to neurones, and non-neural cells, the mPOA has several afferent terminals. Afferent terminals involved in sleep regulation and thermoregulation may be common. Lesion and stimulation of these afferents, would affect both these functions simultaneously, even if there are two separate sets of target neurones for these afferents.
6. Corollary of the above mentioned possibility is also worth considering. There may be different sets of afferent fibres, which can bring about changes in sleep and body temperature. They may be having their input on the same multimodal neurones in the mPOA. Even if they are ending on two different sets of neurones, they may be having the same type of neurotransmitters and receptors. In such situations also the two functions will be affected simultaneously in most of the experimental manipulations.
7. If the neurotransmitters or the receptors are different, in the above-mentioned possibility, they could be elicited separately by using modern lesion and stimulation techniques.

A combination of one or more of the above mentioned possibilities also needs to be considered. Techniques are now available which can produce selective stimulation or destruction of either neurones or afferents. Results of studies using these techniques have improved our understanding, which will be discussed in the following sections.

The changes in body temperature and sleep on destruction of the mPOA neurones

The changes in body temperature and sleep on lesion of the mPOA could have been brought about by the destruction of either the neurones, afferent fibres, fibres of passage, or all of them. This possibility could be tested by local injection of neurotoxins as mentioned earlier. There was an alteration in both body temperature and sleep, in the rats in which the neurones of the mPOA had been selectively destroyed. This shows that the manipulation of the neurones of the mPOA can alter both these functions. The time course and magnitude of changes in temperature and sleep can give some idea about the interrelationship of induced changes in these two parameters (Kumar et al. 1996).

Hyperthermia during the first week after the mPOA lesion was severe. This was followed by a constant mild hyperthermia during the subsequent weeks (John & Kumar 1998, Kumar & Khan 1998). 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.

The changes in body temperature and sleep on local injection of neurotransmitters 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 mPOA, through chronically implanted cannulae. These injections usually produced alterations in both sleep and body temperature. Carbachol (acetylcholine agonist) and noradrenaline (NE) administration at the mPOA produced hypothermia and arousal (Kumar et al. 1984, Datta et al. 1985, Kumar et al. 1986, Datta et al. 1988, Mallick et al. 1988, Talwar & Kumar 1994). Alpha-adrenergic antagonists produced sleep and hypothermia. 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 SWS is associated with a fall, and arousal with a rise, in body temperature (Kawamura & Sawyer 1965, Parmeggiani et al. 1975, Thomas & Kumar 2002). So, the changes in the body temperature (hypothermia with arousal and hyperthermia with sleep) would not have resulted from the changes in 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.

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 (Kent & Satinoff 1990). It is possible that the induced wakefulness may be dependent on a decrease in body temperature, resulting from 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 (Kent & Satinoff 1990). It was suggested that the reduction in sleep induced by 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.

Another argument in favour of the assumption that different sets of neurones are controlling these two functions, is the observation that the changes in these two physiological parameters did not have a temporal correlation. The neurotransmitters and their antagonists, injected at the mPOA, did not always produce simultaneous alterations in sleep and body temperature (Datta et al. 1988, Osborne et al. 1994, Talwar & Kumar 1994). The induced arousal response outlasted the reduction in body temperature. Whenever sleep was induced with increased body temperature, the sleep period was far shorter than the duration of temperature change (Datta et al. 1988, Osborne et al. 1994, Talwar & Kumar 1994). Moreover, there were instances when only one of these parameters was only altered. Administration of serotonin at the mPOA produced hyperthermia without any change in S-W (Datta et al. 1987). Clonidine produced arousal without producing any change in temperature (This is discussed in detail in the next section). So, it is possible that the changes in S-W resulting from chemical stimulation of the mPOA are not always dependent on the body temperature changes. Thus, 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 (1997).

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 (Kumar 1993, 2003). Application of NE at the mPOA in normal rats produced arousal and hypothermia. In an area innervated by noradrenergic fibres, locally applied NE could act on both post-synaptic and pre-synaptic receptors (Starke 1987). A pre-synaptic site of action of hypothalamically-injected NE was suggested (Booth 1968). Studies using alpha-2 adrenergic agents provided some insight into the mechanism of action of NE. 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 (Ramesh et al. 1995), but it was not effective in producing any change in temperature (Tsoucaris-Kupfer & Schmitt 1972, Ramesh & Kumar 1998). 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, if there is a tonic release of this transmitter. It has been postulated that there are two separate groups of afferent noradrenergic inputs, ending on the mPOA neurones. One of them, terminating on sleep inducing neurones, is tonically active during sleep (Ramesh & Kumar 1998). Clonidine injection into the mPOA, in normal rats, 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 (Ramesh et al. 1995). 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. Post-synaptic action of the released NE on alpha-1 receptors induces sleep in normal animals (Ramesh et al. 1995). Yohimbine failed to exert facilitated release of NE from those fibres 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.

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 (Moore & Bloom 1979, Day et al. 1980). 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 (Kumar et al. 1993, Sood et al. 1997, Ramesh & Kumar 1998). 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 (Kumar et al. 1993). Application of NE at the mPOA in the rats with noradrenergic fibre lesion brought about sleep and decreased body temperature (Kumar et al. 1993). 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 (Ramesh et al. 1995, Ramesh & Kumar 1998). 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 (Ramesh & Kumar 1998). An intact catecholaminergic pathway within the anterior hypothalamus is required for the rat's physiological control of heat loss in a warm environmental temperature (Myers & Ruwe 1978). 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 (Sood et al. 1997). 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

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" (Hammel et al. 1963, Satinoff 1983, Heller et al. 1983). The normal body temperature varies with the time of the day and is apparently under circadian control (Heller et al. 1983, Stephenson et al. 1984). The other factor, which has been suggested to reset the body temperature, is that which occurs with alteration in vigilance states. In man and in most mammals, the body temperature is altered during the various vigilance states. In a young man, cyclic alterations in the vigilance and body temperature occur at 24-hour periodicity. So, it is rather difficult to separate the circadian variation in body temperature from that brought about by the alterations in the vigilance state. But, in many animals (and also in very young and very old human subjects) the S-W rhythm is polycyclic, unlike young adult human rhythm, which is monocyclic. In other words, the polycyclic animals go through several cycles of S-W during the 24 hours. It is possible to see separately the polycyclic changes in

body temperature brought about by the vigilance state, and the monocyclic change brought about by the circadian rhythm, in these animals. In the rat, the major part of the variation of brain (cortical) temperature is accounted for by the vigilance state, whereas only a minor part can be attributed to a direct effect of the circadian pacemaker (Franken et al. 1992).

It has been described earlier that the core and shell can be taken as two distinct compartments 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 those in the rest of the body. In this description we will be considering the changes in core, brain and skin temperatures separately.

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 (Hayward & Baker 1969, Valtex et al. 1973, Obal Jr et al. 1985, Thomas & Kumar 2002). The close correlation between thermoregulation and sleep is formed in mammals even at an early stage of postnatal life (Aristakesian & Vataev 1993). The increase in the brain temperature together with the decrease in muscle temperature during REM sleep, as well as the decrease of both temperatures during SWS sleep were observed even in 4-day old rat puppies. The brain temperature invariably increases during REM sleep 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 (Reite & Pegram 1968). 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 (Palca et al. 1986).

Slow wave sleep:- 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 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. Attempts were made to study the changes in tail skin temperatures during sleep, at different atmospheric temperatures (Alfoldi et al. 1990). During awake state, at 10°C and 21°C there was partial vasoconstriction of skin blood vessels, because of the tonic activity of the sympathetic nerves. At 29°C, the skin blood vessels became intensely dilated by the inhibition of the sympathetic centres that cause vasoconstriction. Falling asleep was accompanied by an increase in skin temperature and vasodilation at lower temperatures (10°C and 21°C). At 29°C, as skin vessels were already dilated, further dilation and increase in skin temperature were not found on sleep onset.

There was a decrease in both brain and core temperatures at all the above mentioned temperatures (Alfoldi et al. 1990). The brain temperature showed a gradual decrease, as the animal passed from active wakefulness to deep SWS (Thomas & Kumar 2002). The brain temperature alterations followed the changes in S-W. This indicates the strong possibility that the body temperature changes result from the alterations in S-W.

It has been suggested that 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. The hypothalamic set points for heat production and heat loss are at a lower level in SWS in the kangaroo rat and the pigeon (Glotzbach & Heller 1976, Heller et al. 1983). Down regulation of brain temperature during SWS gave rise to the hypothesis that the SWS intensity is a function of the heat load accumulated during the period of wakefulness (Horne & Shackell 1987). It was proposed that the function of SWS is to cool the brain (McGinty & Szymusiak 1990). It was suggested that there was a lowering of the set point and an increase in heat dissipation with transitions from waking to SWS (Hammel et al. 1963, Glotzbach & Heller 1976). 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. So, it could be suggested that the mPOA, which is the most important region of the brain for maintenance of SWS, brings down the body/brain temperature during SWS. But, the brain temperature variations were present, and were even higher in the mPOA lesioned rats (Thomas & Kumar 2002). 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 also probably a reduction in heat production, during SWS, it may be assumed that there was decreased efficiency of the thermoregulatory mechanism, during SWS. 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 (Kleitman & Doktorsky 1933). So, the decrease in body temperature in the initial part of a sleep period was independent of SWS (Beersma & Dijk 1992).

In rats also, the increase of slow wave activity (mean power density in the 0.75-4.0 Hz range) of rats, and the decrease of cortical temperature in SWS episodes, were not correlated. The lack of a relationship between changes in cortical temperature and slow wave activity indicates that separate mechanisms underlie the regulation of brain temperature and sleep intensity (Franken et al. 1992). 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 (Parmeggiani 1995).

REM sleep:- Core and skin temperatures 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 sharp rise in brain temperature (Thomas & Kumar 2000). The change in brain temperature occurred after the shift in vigilance state from SWS to REM sleep. So, the ultradian brain temperature change in rats is the result of an alteration in vigilance state. Moreover, this interrelationship was observed even after the mPOA lesion. So, even if it is assumed that the brain temperature alteration during S-W change is an active process (Glotzbach & Heller 1976), it is likely that the mPOA may not be responsible for the brain temperature changes occurring with S-W. 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 brain temperature increase, 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 (Denoyer et al. 1991). The rise in brain temperature was the largest in the cold environment and was attenuated at the warm environment in rats (Alfoldi et al. 1990, Thomas & Kumar 2002). A shift from deep SWS to REM sleep produced a slight increase in the brain temperature at 18°C and 24°C. But, there was no change in brain temperature, with a shift from deep SWS to REM sleep, when the rats were maintained at 30°C (Thomas & Kumar 2002).

Increase in brain temperature with REM sleep was attributed to an increase in local metabolic rate, and changes in cerebral blood flow (Denoyer et al. 1991). During REM sleep, common carotid artery blood flow is spontaneously decreased (Azzaroni & Parmeggiani 1993). 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 (Edvinson et al. 1993). 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 (Parmeggiani et al. 2002).

Core temperature decreased and skin temperature increased in the cold, whereas core temperature tended to increase, and skin temperature to decrease, in the heat during REM sleep. This paradoxical peripheral vasomotion during REM sleep supports the previous suggestions on severe thermoregulatory impairment in rats during REM sleep as in other species (Alfoldi et al. 1990). 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 (Calasso et al. 1989a,b). But the increase in hypothalamic temperature during this stage of sleep occurs independently of a transfer of heat from interscapular brown fat (Calasso et al. 1989a,b).

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 (Parmeggiani 1988). On the other hand, during REM sleep, sweat gland activity persists though at a lower level than during SWS (Libert et al. 1982). 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 (Wehr 1992). 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 (Thomas & Kumar 2000).

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 (Palca et al. 1986). 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 (Palca et al. 1986). 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 (Haskell et al. 1981). 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 Temperatures 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 (Bach et al. 2002, Liao 2002).

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 (Bach et al. 2002). 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 (Poole & Stephenson 1977, Szymusiak & Satinoff 1981). The range of thermoneutral ambient temperature is 18-28°C if the absence of behavioural thermoregulation of the rat is taken as a criterion (Poole & Stephenson 1977). The maximum REM sleep time is also used to define the thermoneutral temperature. At approximately 30°C, maximum values of REM sleep are obtained

(Szymusiak & Satinoff 1984, Thomas & Kumar 2000). 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 (Valatx et al 1973, Alfoldi et al. 1990). 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 (Valatx et al. 1973, Alfoldi et al. 1990, Thomas & Kumar 2000).

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 (Thomas & Kumar 2000). 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 to 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 (Obal et al. 1983). 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 (Roussel et al. 1976).

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 (Parmeggiani & Raini 1970). 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 (Schmidek et al. 1972). 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 (John et al. 1994, John & Kumar 1998). But, there was a linear increase in sleep with higher temperatures (Thomas & Kumar 2000). The sleep induced by higher temperatures in the lesioned rats was qualitatively different from that in the normal animals. In the latter, 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 (John & Kumar 1998). 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 for 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 (John & Kumar 1998). 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 (John & Kumar 1998, Kumar 1999a, Kumar 1999b).

Effect of Body and Brain Temperatures 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 (Alfoldi et al. 1990). This increase in brain temperature and body temperature can evoke an increase in SWS in animals and in human subjects (Horne & Staff 1983, Horne & Shackell 1987, Shapiro et al. 1989, McGinty & Szymusiak 1990, Morairty et al. 1993). Even radio frequency diathermic warming of the POA in cats and opossum could induce sleep. Cooling the POA produces huddled posture. Roberts and Robinson (1969) have suggested that the POA thermo-receptors 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 (Morruzi 1972). It was hypothesised that the SWS in mammals and birds is controlled by thermoregulatory mechanisms (McGinty & Szymusiak 1990).

Studies have shown that SWS is facilitated when brain temperature exceeds a threshold level (McGinty & Szymusiak 1990). 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 (Roberts & Robinson 1969, Parmeggiani et al. 1974, Benedek et al. 1976). Preoptic-anterior hypothalamic warming increases EEG delta frequency activity during SWS (McGinty et al. 1994). 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. (1995) SWS is controlled by thermo-regulatory mechanisms of the preoptic-anterior hypothalamus. Circadian and homeostatic thermoregulatory processes may be integrated in this brain area.

Preoptic Neuronal Activity as the Basis for Sleep Temperature Interlink

The modulation of the thermoregulatory 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 (Schmid & Pierau 1993, Osaka & Matsumura 1994, 1995, McGinty & Szymusiak 2001). The number of neurones in the preoptic-anterior hypothalamus that were thermosensitive, as well as the thermosensitivity of individual neurones, were reduced during SWS as compared to the wakeful state (Parmeggiani et al. 1987). 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 (Alam et al. 1996). 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 (Alam et al. 1995b). 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 during SWS, than during wakefulness. Warm-sensitive neurones with increased discharge during SWS exhibited increased thermosensitivity during SWS than during 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 (Alam et al. 1996).

Warm-sensitive neurones did not exhibit a significant change in thermosensitivity during REM sleep as compared with wakefulness and SWS (Alam et al. 1995a). In contrast, cold-sensitive neurones exhibited decreased mean thermo-sensitivity during REM sleep than during wakefulness. Cold-sensitive neurones as a group did not retain significant thermo-sensitivity during REM sleep. These findings are consistent with the evidence that thermoeffector responses to cooling are lost in REM sleep, whereas some responses to warming are preserved (Alam et al. 1995a).

Osaka and Matsumura (1995) 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 and Matsumura (1995), 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 (Berger 1984). 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 (Berger & Phillips 1995). 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 (Berger 1984). These observations prompted some scientists to hypothesise that SWS is an adaptive behaviour for energy conservation in homeotherms (Berger 1984, Obal et al. 1985). 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 (Allison & Van Twyver 1972, Dann et al. 1991, Trachsel et al. 1991). Sleep, daily torpor and hibernation are no longer considered as homologous processes. Animals emerging from these states spent most of their time in sleep, indicating that they were deprived of sleep during torpor (Palchykova et al. 2002). After termination of the torpor-associated hypothermia, there is a compensatory increase in SWS, as it happens subsequent to sleep deprivation.

There are reports in the literature that indicate that REM sleep deprivation or total sleep deprivation increases the food intake (Dement et al. 1967, Siegel 1975, Bhanot et al. 1989). But the decrease in SWS and REM sleep, resulting from the mPOA lesion, did not produce any increase in food intake and water intake (John & Kumar 1998). Earlier reports have shown that the alteration in food intake can disrupt sleep (Danguir & Nicolaidis 1979). Food deprivation in birds and squirrels resulted in a lowering of the thermoregulatory set point during sleep along with increased SWS (Berger & Phillips 1988).

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 (Szymusiak & Satinoff 1984, John & Kumar 1998). Higher locomotor activity and increased body temperature, after the mPOA lesion, do produce an increase in 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 homeostatic regulatory mechanism of the animal did not recognise low energy reserves, and so it did not bother to increase energy intake (or 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 (John & Kumar 1998).

Future Direction of Research

It is very evident from the review that there is an overlap of thermoregulation and sleep regulation in the mPOA. It has to be emphasised that the brain areas involved in the regulation of these two functions are not restricted to the mPOA. Several studies are required to find out the extent of the overlap of brain areas regulating these two functions. There is also a need to record the sleep-wakefulness of an animal in an ambient temperature, which is selected by the animal itself. There are no studies available in which thermal preference, the sleep-wakefulness and locomotor activity were assessed at the same time. This requires a specialised environmental chamber where the animal can select its own preferred temperature. Moreover, the animal should be able to move about freely without connecting wires for recording of EEG, EMG and EOG. The combination of telemetric recording in a specialised environmental chamber can provide an accurate method to determine sleep-wakefulness and thermoregulatory behaviour at preferred ambient temperatures. Future research should also give special emphasis on the role of thermal afferents in regulating sleep.

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