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Neural Regulation of Sleep as Understood During Pre-Baldev Singh and Baldev Singh Eras

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SUMMARY

Neurons 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 inactivation of the ARAS, is not true. There are specific brain regions that promote slow wave sleep (SWS) and others that are responsible for rapid eye movement (REM) sleep. Brain regions above the brain stem, namely the preoptic area (POA) of the hypothalamus, play an important role in the regulation of sleep. In spite of growing evidence in favour of the theory that the hypothalamus is the major centre regulating SWS, sleep-wake cycle, and even wakefulness, the recent findings confirm the important role of the brain stem in genesis of REM sleep. The importance which 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.

Chemical stimulation and neurotoxic lesion studies showed that the major function of the POA is sleep maintenance, rather than sleep initiation. Though there is interaction between thermoregulation and sleep regulation, there are different sets of neurons in the POA, endowed with the ability to regulate these two functions independently. At the same time, the POA could play an important role not only in integrating these two functions, but also in fine tuning the entire energy balance of the organism.

Key words: Sleep, Wakefulness, Preoptic area, Hypothalamus, REM sleep, Slow wave sleep, Brain stem, Thalamus, Ascending reticular activating system, EEG .

INTRODUCTION

This article is dedicated to the memory of Prof. Baldev Singh who had a deep interest in the field of sleep and consciousness. He had with him several books on sleep which were not available even in our libraries. Buying books was some kind of hobby for him. He used to lend those books to me, and discuss with me the theories of sleep prevalent during

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that period. Neurophysiology of sleep was a pet topic for him, and he used to select this subject, whenever he was invited to deliver lectures. The passion with which he spoke about this topic created such an interest in me that I took up this field of research and I have never deviated from it since then.

The understanding of neural regulation of sleep had undergone a drastic change in the last few decades. According to the classical concept of sleep which was prevalent till the sixties, which could be termed here as Pre-Baldev Singh Era, the neurons of the brain stem reticular formation played a major role in waking, consciousness and sleep. The later section of this article deals with the hypothalamic regulation of sleep, which dominated the scientific thinking during the Baldev Singh Era. The concept of sleep regulation by the brain stem, along with the latest modifications to the classical concepts, are also described here.

Brain stem regulation of wakefulness and passive deafferentation theory of sleep

Till around 1970, the sleep theory which dominated the text books were based on the findings of Moruzzi and Magoun (1). According to their findings, interruption of ascending flow of reticular impulses from from the brain stem (as it happens in the case of acute cerveau isole preparation), would result in a state of EEG recording which is similar to that of slow wave sleep (1). So, they concluded that the ascending influence, exerted by the brain stem on waking structures of the cerebrum, maintains the wakefulness. The sudden withdrawal of the influence of the ascending reticular activating system (ARAS) would be the cause of slow wave EEG pattern obtained during sleep. It was then shown that the EEG pattern observed in acute cerveau isole (isolated brain) preparation is irreversible, similar to that found in a state of coma; rather than that of slow wave sleep (SWS). On the other hand, the EEG pattern observed in SWS is reversible. So, the original theory of withdrawal of ARAS influence was modified.

According to a new version of the old theory of passive deafferentation, a tonic ascending flow of reticular impulses would be responsible for the state of wakefulness, its complete interruption would lead to a state of coma. But, a temporary slackening of the tonic ARAS discharge might be responsible for the onset and the maintenance of natural sleep (2,3,4). These doctrines postulated that sleep is basically an inability to remain awake. When the tonic barrage falls below a critical level, the animal would fall asleep, simply because it is unable to stay awake.

Several years after being first proposed (1), the concept of a tonic reticular control of wakefulness and sleep still maintains some validity. Any level of cerebral activity is probably related to, and actually maintained by, a given level of reticular activation. ARAS projects to the thalamus and excite cells, which in turn send fibres to widespread areas of the cerebral cortex to produce the cerebral

cortical activation that occurs during wakefulness. In addition, brain stem reticular neurons project to the hypothalamus and other regions of the basal forebrain. The neurons which project from there to the cerebral cortex also participate in the maintenance of an "alert" state of the brain. In addition, there are also fibres projecting to the cortex, directly from the brain stem reticular formation. Changes in single unit and integrated discharge of the reticular system undoubtedly occur during the sleep-waking cycle (5,6,7). Whenever an arousal phenomenon interrupts the state of SWS, or when a fit of rage occurs against a background of relaxed wakefulness, there is phasic increase in the ARAS barrage. The level of reticular activity is assumed to be higher during wakefulness than during sleep (8,9,10). Both the mild tonic activation required for the maintenance of wakefulness, and the strong phasic discharge responsible for rage outbursts, require the support of the ARAS. The sudden withdrawal of the activating reticular influence would produce a striking imbalance, which might be responsible for the coma of the acute cerveau isole. The statement does not imply that the ARAS exerts a nonspecific facilitatory control upon the cerebrum (11).

Sleep generating mechanisms in the brain stem

Structures functionally antagonistic to the ARAS have been discovered in the lower brain stem and in the cerebrum itself. At least two of these regions are tonically active, as shown by the fact that their inactivation produces striking hyposomnia. They are localized in the lower brain stem and in the forebrain area (preoptic area). Several experiments suggest that deactivation is an active process, probably related to inhibition of the ascending reticular barrage. There is some electrophysiological evidence to show that the hypnogenic structures inhibit the ARAS (12,13). There are interrelations between activating and deactivating structures, and they have functional significance in sleep inducing mechanisms. Sleep could be broadly divided into two categories, i.e. slow wave sleep and rapid eye movement sleep.

Slow wave sleep (SWS): Several lines of evidence indicate that the nucleus of the solitary tract (NTS) is involved in sleep generation. Distention of the carotid sinus, a powerful stimulus for the NTS region, induced behavioural sleep. Low frequency stimulation of the vago-aortic nerve (which carry impulses from aortic sinus) produced slow waves in the EEG. Electrical stimulation of the NTS produced synchronization of the EEG and behavioural sleep, though high frequency stimulation of the same region produced arousal (14). Inactivation of the lower brain stem regions, including the NTS, produces a profound arousal.

There is some evidence that certain NTS neurons increase their discharge during SWS and that these neurons are reciprocally connected with the cells in the midbrain EEG arousal region. Thus,

these data suggest that the NTS region may constitute a "center" for the regulation of SWS. However, there has been relatively little recent research in this area and the evidence for an NTS role in SWS control is weaker than that for the preoptic basal forebrain region.

Kumar et al (15) have localized the synchronizing structures at the nucleus gigantocellularis at the caudal brain stem. This study fulfilled the lacunae in our knowledge regarding the location of the regions in the caudal brain stem that bring about cortical EEG synchronization on electrical stimulation. It also characterized the features of synchronized waves elicited from those regions. Stimulation of ventromedial regions of the caudal brain stem, with low frequency, elicited stimulus-bound synchronized waves in the cortex, which were more prominent ipsilaterally. On the other hand, low-frequency stimulation of dorsal and lateral areas produced synchronized waves which were either equally prominent on both sides, or more prominent on the contralateral side. The induced synchronized waves showed amplitude modulation and did not outlast the train of stimuli (15). These evidences indicate the strong possibility that these caudal brain stem regions play an important role in the genesis of sleep.

Rapid Eye Movement (REM) Sleep: The primary role for the genesis of SWS is played by structures above the brain stem, but the activity of certain groups of neurons in the brain stem is important in the generation of REM sleep. Some of these neurons are characterized as REM-on neurons because of their selective activity during this state. Many of these neurons are located in the laterodorsal tegmental (LDT) and pedunculopontine tegmental (PPT) nuclei and use acetylcholine as a neurotransmitter. According to Datta (16), the cholinergic neurons involved in sleep-wakefulness are located at the peribrachial area (PBL). The major nuclei of the PBL are the PPT, the LTD, the cuneiform nuclei, and parts of the central tegmental field and paralemniscal tegmental field. The activity of PBL cholinergic and noncholinergic cells are also responsible for the EEG activation process during wakefulness and REM sleep. During wakefulness, together with noradrenergic and serotonergic cells of the brain stem, PBL cholinergic and noncholinergic cells activate the diencephalic EEG desynchronizing structures, which in turn activate cortical neurons. However, during REM sleep, only PBL cholinergic and noncholinergic cells are responsible for activating those diencephalic EEG desynchronizing structures.

Several findings suggest that there are two populations of cholinergic neurons which have different influences on sleep-wakefulness regulation. A population of cholinergic neurons in the brainstem which are most active during paradoxical sleep (PS-on neuron) are inhibited by carbachol and excited by bicuculline. Another population of neurons, which are active both during waking and paradoxical sleep, are inhibited by carbachol and excited by noradrenaline

and histamine. Non-cholinergic PS-on neurons are excited by carbachol and inhibited by noradrenaline (17).

According to McCarley (18) the LDT and PPT neurons activate the neurons located in the pontine reticular formation (PRF) which are the effector neurons for REM sleep phenomena. They begin to depolarize even before the onset of the polysomnographic signs of REM sleep. These neurons begin to discharge (i.e. generate action potentials) as REM sleep is approached, and the high level of discharge is maintained throughout REM sleep (18). PRF neurons are important for the rapid eye movements saccades and the PGO waves, which are the cardinal signs of REM sleep. A group of dorsolateral PRF neurons controls the muscle atonia of REM sleep, and these neurons become active just before the onset of muscle atonia. Neurons in the bulbar reticular formation are also important for muscle atonia.

Neurons in the locus ceruleus (using norepinephrine) and neurons in the dorsal raphe (using serotonin) have an opposite time course of activity compared to the LDT and the PPT neurons. They become selectively inactive during REM. They do suppress REM sleep-promoting activity of the LDT and the PPT neurons. These neurons, with an opposite discharge time course, are called REM-off neurons. REM-off neurons are most active in the waking state. Their discharge declines during slow-wave sleep, and are virtually silent during REM sleep. They resume discharge near the end of the REM sleep episode. This inverse pattern of activity to REM-off neurons has led to the hypothesis that these neurons may be REM-suppressive and interact with REM-on neurons in control of the REM sleep cycle. This concept is indirectly supported by production of REM sleep on cooling (i.e. inactivating) the nuclei where REM-off neurons are found. In vitro data from Luebke and co-workers (19) have provided direct support for the inhibition of cholinergic LDT neurons by serotonin.

Several classes of neurons are REM-off. Apart from norepinephrine-containing neurons in the locus ceruleus, and serotonin-containing neurons located in the raphe system, the midline collection of neurons that extends from the bulb to the midbrain, with serotonin-containing neurons in the more rostral regions, and histamine-containing neurons in the posterior hypothalamus, are REM-off. But transection studies indicate that the histaminergic neurons are not essential for REM sleep.

Role of thalamus in the genesis of sleep

There are three main systems in the brain which may be regarded as responsible for, or at least contributing to, the onset of sleep. They are localized respectively in the basal forebrain, in the lower brain stem, and in the midline nuclei of the thalamus.

According to Koella (20), the thalamamus is the head ganglion of sleep. Koella brings several interesting considerations in support of this hypothesis originally put forward by

Hess. Probably the most important among them is the striking similarity between natural sleep and the sleep induced by stimulation of the thalamus. Koella regards the hypnogenic regions of the basal forebrain, including the anterior hypothalamus, and of the lower brain stem, as subordinate sleep controlling structures. At the same time, he recalls that Hess (21) obtained a syndrome of generalized muscular relaxation, without typical sleep behaviour, from an area closely related to the basal forebrain. According to Steriade (22), brain stem, diencephalic and basal forebrain systems influence the functional modes of thalamic and cortical neurons during the behavioural states of vigilance. The posterior hypothalamus and the preoptico-anterior hypothalamus (PO-AH) can influence the neurons of the midline thalamus. A majority of the influenced neurons of the midline thalamus showed increased firing on stimulation of the posterior hypothalamus. Although the number of neurons showing increased or decreased firing on the preoptico-anterior hypothalamic stimulation were nearly equal, stimulus bound increased firing in many neurons was followed by a prolonged decreased firing. It is likely that the hypothalamo-thalamic circuit constitutes a parallel pathway to the reticulo-thalamic circuit for alteration of the cortical EEG (23).

Stimulation experiments of Hess and electrophysiological investigations on thalamic driving of electrocortical EEG spindles (24,25) had focused the attention of sleep physiologists on the thalamus for several years. Thalamocortical projection exhibits two distinct states of activity (a) synchronized rhythmic activity in the form of delta, spindle, and other slow waves during EEG-synchronized sleep and (b) tonic activity during waking and rapid-eye-movement sleep. Spindle waves are generated largely through a cyclical interaction between thalamocortical and thalamic reticular neurons involving both the intrinsic membrane properties of these cells and their anatomical interconnections (26).

The old literature on the effects of thalamic lesions was reviewed by Knott et al (27). A careful re-examination of these findings showed that the old experiments were contaminated by lesions of the hypothalamus and are therefore of little interest for the physiology of sleep. Naquet et al (28), who were able to follow six completely thalamectomised cats for up to 25 days, showed that the sleep-waking cycle was still present in these animals, although the EEG spindles were absent during behavioural sleep. Clearly sleep may occur even in the absence of the thalamus.

There is as yet no evidence of a marked hyposomnia produced by lesion of the midline thalamic nuclei(29). According to Moruzzi (29) the ARAS and a group of neurons lying in the posterior hypothalamus are probably concerned with the maintenance of wakefulness. The lower brain stem and the basal forebrain area contain structures with an opposing function, which exert a tonic deactivating influence and lead ultimately to sleep.

The role of hypothalamus in sleep-wakefulness

The ability to maintain a state of wakefulness do reappear in the chronic cerveau isole preparation. This shows that structures endowed with an activating influence are present in the cerebrum. They are mainly, though probably not exclusively, localized in the posterior hypothalamus. It is likely that these activating structures coincide with, or are at least strongly related to, the hypothalamic centre which is responsible for the outbursts of sham rage after decortication and for the defense-aggression behaviour of the normal animal.

Though it was known for years that there are centres or regions in the brain which could play an active role in the genesis of sleep, it was never given that much importance as to merit a place in the text books of neuroscience and physiology. In fact it was the statement of Moruzzi himself, in his review article which appeared in 1972, which played a major role in informing the world about the importance of the preoptic area (POA) in the genesis of sleep (29). Attempts have been made to locate within the POA the critical area for genesis of sleep. But the areas involved are not likely to restricted within this area. So, people have referred to this hypnogenic area as the basal forebrain or the anterior hypothalamus. But some others have referred to the area as the preoptic-anterior hypothalamus (PO-AH). In this manuscript, an attempt is made to refer to the areas using the terms mentioned by the authors themselves. Information gathered about the role of the hypothalamus in sleep-wakefulness is listed under different techniques employed in collecting the evidences.

Brain lesions and section studies: von Economo (30) was the first to draw the attention of physiologists to the involvement of the rostral hypothalamus in sleep, on the basis of his observations in some cases of encephalitis. On post-mortem examination of brain material collected from cases of *encephalitis lethargica*, he described two symptomatic patterns of the disease, associated with two different localizations of inflammatory lesions in the nervous system. In those cases in which somnolence was the distinguishing symptom, the lesions were regularly found in the posterior wall of the third ventricle, continuing caudally to the level of the occulomotor nucleus. In contrast to this, there were other cases in which insomnia was observed. Inflammation in these latter patients was associated with the rostral hypothalamus, the tuberal region and the adjacent portion of the striatum. From these observations, von Economo concluded that the rostral hypothalamic zone was a part of a "sleep regulating center" which, when appropriately excited, actively inhibited the thalamus and cerebral cortex and caused "brain sleep". Therefore, he concluded that the rostral hypothalamus is a "sleep center". In 1936, Ingram and co-workers (31) reported that in cats a lesion between mammillary bodies and the third nerves, which involved the caudal hypothalamus and the upper part

of the mesencephalic tegmentum, led to a state that resembled catalepsy. In 1939, Ranson (30) demonstrated in rhesus monkeys, that bilateral lesions in the lateral hypothalamus which extended up to the mammillary bodies, produced a lethargic syndrome. He reported that there was a lack of motor initiative and the symptoms were similar to those observed in catalepsy.

After von Economo's observations (30), several studies were carried out to elucidate the role played by the POA in the regulation of sleep. In 1946, Nauta (33), employing the knife cut lesion technique, showed that the rats became insomniac, restless and irritable after the lesion of the POA. They reacted vigorously even to minor stimuli. Those rats which survived up to 13 days did not show a return to what he called the "capacity of sleeping". He thought that the POA was an important region for sleeping and he termed this area as "sleep centre". Nagel and Satinoff (34) reported hyperactivity in rats after bilateral electrolytic lesion of the mPOA. McGinty and Sterman (35) reported that large bilateral POA lesions produced complete sleeplessness in cats. Smaller lesions resulted in significant reduction in SWS as well as in REM sleep. The severity of sleep suppression was found to be related to the size and localization of the lesions placed specifically within the POA (36). These lesions shortened the mean periodicity of the sleep awake cycle with a decrease in SWS and no alteration in REM sleep (36). Neurotoxic lesion studies provided convincing evidence of the involvement of the POA neurons in the regulation of sleep. Lesions produced by neurotoxins such as kainic acid, which spares the fibres of passage in the medial and lateral POA, reduced both SWS and REM sleep (37,38). Suppression of sleep produced by the NMDA lesion of the medial preoptic area (mPOA) neurons showed the importance of this area in the regulation of sleep (39). Persistence of hyposomnia for three weeks after the lesion further showed that the deficits produced by the mPOA lesions were not compensated for. Insomnia was primarily due to a reduction in the duration of SWS episodes. There was a trend towards a reduction in the frequency and duration of REM sleep episodes. Recovery of sleep in the lesioned rats, after the fetal neural tissue transplantation, indicated the vital role of the mPOA in the regulation of sleep (40).

c-Fos expression studies: c-fos expression is strongly induced by both spontaneous and forced wakefulness in many brain regions. c-Fos expression was considerably increased in regions involved in the regulation of S-W, such as the locus coeruleus and the mPOA. With c-fos antisense injection in the mPOA, it was demonstrated that c-fos expression in this region is causally involved in sleep regulation. c-Fos expression in other areas, such as the cerebral cortex and the hippocampus, are explained as related to the functional consequences of prolonged wakefulness and to the need for sleep (41). Periods of wakefulness result in the induction of immediate-early gene c-fos in the mPOA. Injections in the rat mPOA

of c-fos antisense, oligonucleotides, blocked the expression of Fos protein detected immunocytochemically. Rats receiving bilateral antisense injections showed a higher percentage of wakefulness, the day after the injection, than controls receiving sense or sham injections or antisense injections outside the POA. These results suggest that blocking the expression of fos protein in the POA may interfere with the homeostatic regulation of sleep and wakefulness (42). Immunocytochemistry was used to identify the fos protein, an immediate-early gene product, in a group of ventrolateral POA neurons that is specifically activated during sleep. The retrograde tracer cholera toxin B, in combination with fos immunocytochemistry, was used to show that sleep-activated ventrolateral POA neurons innervate the tuberomammillary nucleus, a posterior hypothalamic cell group, thought to participate in the modulation of arousal. This monosynaptic pathway in the hypothalamus may play a key role in determining sleep-wake states (43).

Stimulation studies: Sterman and Clemente (44), on the basis of behavioural and electrophysiological observations, reported that bilateral stimulation of the POA in unanaesthetised freely moving cats, produced sleep. Low frequency stimulation was effective in inducing sleep. The effect of low frequency stimulation (5-25 cycles/sec) on induction of sleep was confirmed by Hernandez-Peon (45), and Yamaguchi et al (46). In addition, they showed that high frequency stimulation (200-300 cycles/sec) induced cortical EEG desynchronization and some signs indicative of behavioural arousal. Thus, it can be concluded that both sleep and arousal responses can be obtained from electrical stimulation of the POA, depending upon the rate and site of stimulation.

Local intracerebral injection studies: Injection of norepinephrine (NE) at the mPOA produced arousal and the alpha receptors were involved in this response (47,48). Locally applied NE can act on both the presynaptic and postsynaptic receptors (49). It was later shown that the administration of NE did not induce arousal when the noradrenergic fibres in the mPOA were lesioned (49). These findings showed that the NE induces arousal by acting on the presynaptic alpha-2 receptors. Stimulation of alpha-2 receptors by externally applied NE and clonidine, would produce decreased release of endogenous NE from the presynaptic terminals (50). So, it is very likely that the decreased release of endogenous NE produced arousal in normal animals. This assumption was further supported by the finding that the alpha-2 agonist, clonidine, also produced arousal when applied at the mPOA (51). Alpha-2 receptors are primarily present on the presynaptic noradrenergic terminals (50,52). The presynaptic site of the action of clonidine was confirmed by the studies on VNA lesioned animals (53). Similarly, yohimbine, an alpha-2 antagonist, induced sleep by its action on the presynaptic terminals, as the effect was attenuated after the VNA lesion. Thus, the observations in the VNA

lesioned rats further confirmed the contention that these responses are mediated through presynaptic alpha-2 terminals (49,51).

Injection of beta adrenergic blocker, propranolol, at the mPOA was ineffective in changing sleep-wakefulness (47,54). But, beta receptors are also thought to be indirectly involved in the regulation of sleep-wakeful function. Beta agonist, isoproterenol injection into the mPOA induced wakefulness (55). Beta receptors in the mPOA have been shown to be important in inducing sexual arousal (56), which would in turn cause generalized arousal. So, it is possible that the injected isoproterenol would have produced arousal through a stimulatory action on the sexual arousal system. It may be hypothesized that there are different sets of neurons in the mPOA, controlling sleep, sex drive and other functions. It could be possible that the sleep regulating neurons are primarily stimulated through alpha receptors, whereas the neurons controlling the sex drive are activated through beta receptors.

Progesterone has also been reported to induce sleep, when applied directly into the rostral POA or basal forebrain area in cats, whereas no change was observed when it was injected into the caudal or lateral regions (57).

Prostaglandin has been shown to alter sleep by its action at the POA Prostaglandin D2 (PGD2) is present in high concentration in the hypothalamus in the rat brain. Ueno et al (58) reported that PGD2 application into the POA of conscious rats increased SWS. On the other hand prostaglandin E2 (PGE2) produced arousal in rats (59,60). According to Hayaishi (61) PGD2 is the endogenous sleep inducing substance in rats, mice, monkeys and probably in humans. PGD synthase (PGDS), the enzyme that produces PGD2 in the brain, is the key enzyme in sleep regulation. When the enzyme activity is inhibited by its specific inhibitor, SeCl4 in vivo, rats can no longer sleep. PGDS is present mainly in the arachnoid membrane and choroid plexus. It is secreted into the cerebrospinal fluid to become beta-trace. PGD2 thus produced is bound to the receptors on the surface of the ventro-medial region of the rostral basal forebrain. This signal is probably transmitted into the brain parenchyma by adenosine via adenosine A2a receptors. PGE2 plays a major role in the maintenance of wakefulness.

Hernandez-Peon (62) showed that the application of ACh at the POA elicited EEG synchronization and sleep, in cats, whereas carbachol, a cholinergic agonist, when applied at the mPOA, produced a fall in rectal temperature and an injection bound long lasting arousal in rats (63). Administration of GABA at the mPOA did not produce any significant alteration in S-W (64). Application of 5-HT crystals in the POA produced drowsiness and SWS in freely moving rats (46). But, Datta et al (65) showed that 5-HT application at the same site did not have any change in SW. Intracerebral injection of melatonin into the POA has been shown to increase SWS and REM sleep in rats (66).

Single unit recording studies: Mallick et al (67) showed that a majority (55%) of neurons of the POA showed alterations in their firing rate during transient changes in EEG. Among these 62.5% showed increased firing during synchronization and the remaining 37.5% showed increased firing during desynchronization of the EEG. Findlay and Hayward (68) showed that the majority of the neurons in the hypothalamus, including POA in freely moving rabbits, showed an increase in their firing rates during sleep as compared to the awake state. The POA neuronal activity was recorded during all states of sleep and wakefulness, and were classified into five groups according to their firing behaviour in relation to sleep-wakefulness states (69). One third of the neurons showed no clear correlation with the sleep-waking states. Out of the 65 neurons which showed changes in activity with sleep-wakefulness states, 26 were most active during REM sleep. There were 16 neurons which were most inactive during REM sleep, some of which were inactive during SWS also. Those which were specifically active during SWS were 14 in number. Nine were less active during SWS than during wakefulness and REM sleep. About one third of neurons which showed increased discharge with SWS and REM sleep, began to increase their sleep-related activity in advance of the shift of sleep-wakefulness state recognized in EEG. These results suggest that the PO-AH areas are involved, at least in rats, in regulation of not only SWS but also REM sleep.

The role of the mPOA in the maintenance of sleep-wakefulness

There was persistent reduction in sleep (light SWS, deep SWS and REM sleep) and increase in the awake periods in rats after the mPOA neuronal lesion using NMDA (38). In cats, light SWS was not much affected after electrolytic and neurotoxic lesion (35,70). So, there was reduction in deep SWS and REM sleep in both rats and cats, after the mPOA lesion (39,70). The reduction in REM sleep suggests that the integrity of the POA is important for the regulation of this phase of sleep also (70,71). It is worth noting that the majority of the POA neurons show higher firing rates during REM sleep, than during SWS (69,72).

There was a significant decrease in the duration of SWS episodes after the mPOA lesion in rats (39). There was no significant increase in SWS frequency after the mPOA lesion. Thus, the initiation of sleep was not affected significantly by the mPOA lesion. This indicates that it is the maintenance of SWS rather than its initiation, which seems to have been mainly affected after the mPOA lesion. Lucas and Sterman(36) have also reported that there was a decrease in SWS bout duration, and an increase in the number of transitions of sleep stages after the basal forebrain lesions in cats.

There was a reduction in sleep pressure after the mPOA lesion, which shortened the sleep episode duration (39). This produced a reduction in the duration and frequency of deep SWS and REM

sleep episodes. Normally, deep SWS occurred after the animal had spent some time in slow SWS. Similarly REM sleep appeared after the animals had spent some time in deep SWS. Thus, the reduction in sleep episode duration produced a reduction in frequency and duration of deeper stages of sleep, namely deep SWS and REM sleep. Unlike in human beings, in rats and cats, REM sleep forms a part of the deeper stage of sleep. So, the studies on NMDA lesioned rats indicate the possibility that the mPOA neurons are important for the maintenance and initiation of REM sleep.

Marginal increase in the frequency and duration of awake episodes, after the mPOA lesion (39), could be due to a release of the waking mechanism from the inhibitory influence of the POA (73).

Role of the mPOA in circadian and sleep-wake rhythms

Circadian rhythms are major features of the adaptation to our environment (74). In mammals, circadian rhythms are generated and regulated by a circadian timing system. This system consists of entertainment pathway, pace-maker, and pace-maker output to effector systems that are under circadian control. The primary entertainment pathway is the retinohypothalamic tract, which terminates on the circadian pace-maker, the suprachiasmatic nuclei of the hypothalamus. The output of the suprachiasmatic nuclei is principally to the other nuclei of the hypothalamus, the midline thalamus, and the basal forebrain. This provides a temporal organization to the sleep-wake cycle, in addition to many other physiological, endocrine and psychomotor functions (74).

In young adult human beings, the sleep-wake cycle coincides with the circadian cycle. But in cats and rats, and even in children, they do not exactly coincide. They are polycyclic and go through several cycles of sleep during the day and night. But all the same, they do show a circadian variation in the amount of sleep during day and night. The effect of brain lesion on sleep-wakeful cycle could be better studied in polycyclic animals, where the circadian cycle and the sleep-wakeful cycle could be viewed separately.

Many regions of the brain have the ability to produce arousal, or sleep. But it is necessary to locate the brain areas essential to generate the normal pattern of sleep-wake cycle. Neural regulation of sleep is highly incomplete without a proper regulation of sleep-wake cycle itself. Study of the sleep-wakeful cycle would also help in looking at the change in the duration and frequency of sleep episodes, as mentioned in earlier section. The sleep-wake cycle could be due to the slow accumulation and dissipation of chemical products within well defined groups of neurons in the brain (75). Rhythmicity is potentially present both in the cerebrum and in the brain stem, as shown by the experiments on the chronic cerveau isole and chronic decerebrate preparations (29). It is difficult to state where rhythmicity arises in the normal

animal, but several considerations suggest that the cerebrum, especially the hypothalamus, is the most likely location. According to one theory the sleep-waking cycle would normally arise within the cerebrum, and they are controlled by the ascending flow of brain stem impulses from the ARAS and the sleep inducing structures of the lower brain stem. But the important role of the hypothalamus for sleep-wakefulness change is particularly emphasized by Kawamura (76) on the basis of experimental data. According to him the mechanism of sleep-wakefulness change, produced by the forebrain, does not depend on the lower brain stem structures and ARAS. One week after rostral midbrain transection, the isolated forebrain showed sleep-wakefulness change, with circadian rhythm. In this preparation, after additional bilateral preoptic or posterior hypothalamic lesions, ECoG "insomnia" or "coma" pattern appeared, respectively. Hypothalamic sleep-wakefulness mech-anism usually receives strong influence from the suprachiasmatic nucleus, but it can produce its own ultradian "rhythms" (sleep-wakefulness change), though very irregular, even without this input.

The mPOA lesion in rats produced a proportionate reduction in sleep during the day and night, without any obvious change in the day-night sleep ratio (39). Absence of any persistent change in the night-day ratio of sleep would suggest that the mPOA has no role to play in the circadian distribution of sleep. Asala et al (77) have reported an uneven suppression of sleep after the radiofrequency lesion of the mPOA. In those rats the reduction in the light period sleep was compensated for by the dark period sleep. It is difficult to assign any reason for the differences in the observations in the radiofrequency lesioned and the neurotoxic lesioned rats. The damage to the input from suprachiasmatic nucleus in the radiofrequency lesioned rats, could have been instrumental in disrupting the night-day distribution of sleep. Night-day distribution of food and water intake was also not significantly altered after the mPOA lesion. Though there was no alteration in night-day sleep-wakefulness, food and water intake, the rest-activity cycle was disturbed by the mPOA lesion.

Inter-relationship between hypothalamic thermoregulatory and sleep regulatory mechanisms

Roberts and Robinson (78) have suggested that the POA thermoreceptors may provide input to the POA sleep-regulating mechanisms. Stimulation of central receptors by changing blood temperature is likely to be an important source of impulses driving the sleep inducing structures of basal forebrain (30). It was hypothesised that the SWS in mammals and birds is controlled by thermoregulatory mechanisms (79). Local warming of the POA produces sleep (78,79,80). PO-AH warming increases EEG delta frequency activity during SWS (80). So, it was suggested that the PO-AH thermoregulatory mechanisms participate in the regulation of the depth of SWS. According to Nakao et al (81) the SWS is controlled by thermoregulatory mech-

anisms of the PO-AH. Circadian and homeostatic thermoregulatory processes may be integrated in this brain area. Sleep could be induced by radio frequency diathermic warming of the POA in cats and opossum (78). Cooling the POA produces huddled posture (82). Low ambient temperature suppressed sleep and mild environmental warming enhanced sleep in normal rats (83,84). Studies have shown that SWS is facilitated when brain temperature exceeds a threshold level (79). This threshold is hypothesized to be determined by responses of the PO-AH thermosensitive neurons and to be regulated by both circadian and homeostatic processes. SWS-induced brain and body cooling would provide several adaptations including lower energy utilization, reduced cerebral metabolism, protection of the brain against the sustained high temperatures of wakefulness, facilitation of immune defense processes and regulation of the timing of behavioural activity relative to the circadian light-dark cycle. So, it was suggested that the mPOA, anterior hypothalamic and basal forebrain network integrates thermor-egulatory and hypnogenic controls and induces EEG and behavioral deactivation, through suppression of the ARAS.

It has been demonstrated that there are neurons in the mPOA involved in the regulation of sleep and body temperature (85,86,87). Thermosensitive neurons of the PO-AH have been implicated in the regulation of both body temperature and SWS (88). The activation of sleep-related warm-sensitive neurons (WSN) and the deactivation of wake-related cold-sensitive neurons (CSN) may play a key role in the onset and regulation of SWS (89). During SWS, a majority of WSN of the PO-AH exhibit increased discharge compared to wakefulness. CSN exhibit reduced discharge in SWS, compared to wakefulness. WSN with increased discharge in SWS exhibited increased thermosensitivity during SWS compared to wakefulness. CSN with decreased discharge during SWS exhibited decreased thermosensitivity in SWS. In addition, 9 out of 47 neurons that were thermo-insensitive during wakefulness became warm-sensitive during SWS. Changes in PO-AH neuronal thermosensitivity could be a component of the mechanism for stabilization of state after state transition (88).

WSN did not exhibit a significant change in thermosensitivity during REM sleep compared with wakefulness and SWS (90). In contrast, CSN exhibited decreased mean thermosensitivity during REM sleep compared with wakefulness. CSN 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 (90).

The mPOA lesions do increase the rectal temperature (70,71,91,92). Hyperthermia observed during the first week after the mPOA lesion was severe. This was followed by a constant mild hyperthermia during the subsequent weeks (39,92,93). On the other hand, there was

no variation in the magnitude of reduction in sleep throughout the post-lesion period. Thus, there was no temporal correlation between the sleep and temperature changes after the mPOA lesion. Though hyperthermia is the commonly reported observation, hypothermia was also reported after the lesion of the POA (94,95).

Though the possible strong interrelationship between the regulations of body temperature and sleep-wakefulness has been suggested on the basis of single unit and local warming studies (79), they are not supported by intracerebral injection studies. Neurotransmitters and their antagonists, injected at the mPOA, could not always produce simultaneous alterations in sleep and body temperature (48,63,96). Carbachol administration at the mPOA produced hypothermia and arousal. But the changes in these physiological parameters did not have a temporal correlation. The arousal response outlasted far beyond the changes in body temperature (63). Administration of 5-HT at the mPOA produced hyperthermia without any change in sleep-wakefulness (65). So, it is possible that the changes in sleep-wakefulness resulting from the mPOA stimulation and lesion are not 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 is also supported by the observations of Krueger and Takahashi (97).

Effects of noradrenaline (NA) on the activity of sleep-related neurons in the POA and the neighboring basal forebrain were examined in the rat by Osaka and Matsumura (86). Sleep-active neurons were generally inhibited by NA and the alpha 2-agonist clonidine, whereas the alpha 1-agonist methoxamine and the beta-agonist isoproterenol had no effect on them. Thus, alpha 2-receptors mediated the NA-induced inhibition. Waking-active neurons were excited by NA and methoxamine, whereas isopro-terenol and clonidine were without effect. Accordingly, alpha 1-receptors probably mediated the NA-induced excitation. State-indifferent neurons, and REM sleep-active neurons were mostly insensitive to NA. These results suggest that NA promotes wakefulness by inhibiting sleep-active neurons and by exciting waking-active neurons (86).

The noradrenergic terminals, when activated, bring about sleep and hypothermia. On the basis of local application of NA, it has been postulated that there are also two separate groups of afferent noradrenergic inputs, ending on the mPOA neurons. One of them, terminating on sleep inducing neurons, is tonically active during sleep. Those afferents which synapses on the temperature regulatory neurons are suggested to be normally inactive (53). Clonidine administration at the mPOA produced arousal (51), but it was ineffective in producing any change in temperature (98). Clonidine (alpha-2 agonist) injection into the mPOA, in

normal rats, resulted in the activation of presynaptic alpha-2 receptors, on both the groups of noradrenergic afferents, but it brought about decreased release of endogenous NA on those neurons in which there was a tonic release. This decreased release of endogenous NA produced arousal in sleeping animals (51). Clonidine also acted on the inactive terminals which synapse on the temperature regulatory neurons. Since these fibres normally secrete very little NA, there was no change in the body temperature when this drug was applied. Yohimbine, an alpha-2 antagonist, blocks the presynaptic receptors and facilitates the release of endogenous NA. Postsynaptic action of the released NE on alpha-1 receptors, induces sleep in normal animals (51,99,100). Yohimbine failed to exert facilitated release of NA from those fibres which synapse on to the temperature regulatory neurons, since they are normally inactive. Hence, there was no change in the body temperature on application of this drug.

Changes in body weight, food and water intake on sleep regulation

Earlier reports have shown that the alteration in food intake can disrupt sleep (101). There are reports in the literature which indicate that the REM sleep deprivation or total sleep deprivation increases the food intake (102,103,104). But the decrease in SWS and PS, resulting from the mPOA lesion, did not produce any increase in food intake and water intake (39). Food deprivation in birds and squirrels resulted in a lowering of the thermoregulatory set point during sleep along with increased SWS (105).

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 (39,84). Higher locomotor activity and increased body temperature, after the mPOA lesion, would produce 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 recognize low energy reserves, and so it did not bother to conserve energy. Thus, it can be hypothesized that the mPOA lesioned animals had lost the mechanism for the fine tuning of food intake regulation 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 POA would normally facilitate sleep, an energy-conserving state, when energy reserves are at a critical level.

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