

HYPOTHALAMIC REGULATION OF SLEEP AND AROUSAL

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1. ABSTRACT

The hypnogenic function of the rostral hypothalamic region, particularly the preoptic area (POA) was established previously on the basis of lesion, neuronal unit recording, and neurochemical and thermal stimulation studies. Recent studies have mapped the locations of putative sleep-promoting neurons in the POA using c-Fos immunostaining techniques and confirmed these findings with electrophysiological methods. Segregated groups of sleep-active neurons have been localized in the ventrolateral POA (vlPOA) and median preoptic nucleus (MnPN). MnPN and vlPOA sleep-active neurons express the inhibitory transmitter, GABA. In vlPOA neurons, GABA is co-localized with a second inhibitory transmitter, galanin. Descending projections from these sites terminate in putative arousal-promoting cell groups, including histaminergic, serotonergic, orexinergic, noradrenergic, and cholinergic neurons. These findings suggest the hypothesis that non-REM sleep occurs as a consequence of GABAergic and galaninergic inhibition of arousal-promoting neurons resulting from activation of vlPOA and MnPN sleep-promoting neurons. In support of this hypothesis, it was shown that putative sleep-promoting and arousal-promoting neurons exhibit reciprocal changes in discharge across the sleep-wake cycle and that GABA release in wake-promoting sites increases during nonREM sleep. In addition, some POA sleep-active neurons are warm-sensitive. Local POA warming inhibits discharge of multiple arousal-promoting neuronal groups. POA warming, unit recording, and lesion studies also show that POA regulates the amount of delta EEG activity within nonREM sleep, and index of the depth of sleep. Finally, there is evidence that arousal systems inhibit vlPOA and MnPN neurons and the POA hypnogenic mechanism.

Mutually-inhibitory interactions between sleep-promoting and arousal-promoting systems are hypothesized to form a functional sleep-wake switch.

2. INTRODUCTION: EVIDENCE FOR A ROSTRAL HYPOTHALAMIC SLEEP-PROMOTING MECHANISM

The existence of a rostral hypothalamic sleep-promoting mechanism was first proposed by von Economo (1) on the basis of his observations that patients with severe insomnia following encephalitis were found to have inflammatory lesions in this area, *post mortem*. Subsequently, Nauta (2) produced total insomnia in rats with complete frontal hypothalamic transections at the posterior border of the optic chiasm. Focal lesion studies provided further support for a rostral hypothalamic sleep-promoting mechanism. Bilateral lesions, 1-2 mm in diameter, which include portions of both the medial and lateral preoptic area in the rats (3-5) and cats (6) yield significant partial sleep loss, followed by recovery over the course of several weeks. Larger, bilateral lesions that extend into the adjacent basal forebrain induce total, or near total insomnia, sometimes leading to death (7,8). This evidence suggests that *the size of the lesion within this region determines the magnitude of the sleep deficit*. In rats, lesions centered on the ventrolateral POA (vlPOA) produced a 40% reduction in nonREM sleep, leading to a suggestion that this is the primary hypnogenic site (9). However, more dorsolateral POA lesions sparing the vlPOA produced an equivalent nonREM deficit in cats (10). At present, most evidence supports a view that components of the POA hypnogenic mechanism are distributed within the medial and lateral POA, possibly

extending into the adjacent basal forebrain. With lesions that produce partial insomnia, EEG slow wave activity during residual nonREM sleep is reduced compared to baseline (3,6,9,11,12), suggesting that this residual sleep has a reduced intensity and/or depth. Cell-selective neurotoxic lesions induce insomnia (4,6,9,11,12) showing that loss of local neurons rather than fibers of passage is critical. After POA lesions that resulted in partial sleep loss, implantation of healthy fetal POA tissue into the lesion site promoted recovery of normal sleep amount (4). This finding also supports the hypothesis that the hypnogenic process originates in POA neurons.

Following POA lesions, large reductions in REM sleep as well as nonREM sleep have been observed consistently. In cats with POA lesions, administration of pentobarbital induced an increase in REM sleep, leading to a suggestion that REM sleep suppression is secondary to a more general disinhibited state (13). In rats with medial POA lesions, a portion of the REM sleep disturbance is secondary to disturbed thermoregulatory function (5). A recent report described more severe REM sleep loss in rats with lesions centered medially and dorsally to the vlPOA, suggesting that different subpopulations of POA neurons are involved in the regulation of REM sleep and nonREM sleep (9).

The finding that POA lesions, including cell-selective lesions, reduce nonREM sleep leads directly to a hypothesis that this site may contain sleep-promoting neurons, that is, neurons with increased discharge during sleep. Although the criteria for the definition of sleep-active neurons have varied, rather consistent findings from 4 species have confirmed this hypothesis. Within the POA, the percentages of sleep active neurons ranged from 23-32% in the rat (14-17) 17-40% in the cat (18-20), 21% in the rabbit (21) and 33% in kangaroo rats (22). A study targeting sites lateral to the POA, in the magnocellular basal forebrain of cats, identified 24% sleep active neurons in a large sample (23). Given the functional heterogeneity of these brain regions, it should not be surprising that only a minority of neurons are sleep-related. Indeed, in most studies, the discharge of the largest group of neurons was not modulated by changes in state. As will be described below, there is segregation of sleep-active neurons from other cell types in some POA subnuclei. The functional relationship between sleep-active neurons and thermoregulation is also discussed in Section 5.

The identification of sleep-promoting neurochemical agents, or "sleep factors" has been a primary focus of sleep research during the last 20 years. The POA and adjacent brain structures have been identified as potential targets of many sleep factors. Microinjection of a variety of substances directly into the POA will increase nonREM sleep. Using this method, the medial POA was found to be an effective sleep-enhancing site for growth hormone releasing hormone GHRH (24), prostaglandin D₂, (PGD₂) (25) the benzodiazepine, triazolam (26) and, in one study, adenosine agonists (27). The adjacent magnocellular basal forebrain was an effective site for adenosine agonists in other studies

(28,29). The subarachnoid space rostral and ventral to the POA was found to be the most effective hypnogenic site for PGD₂ (30). PGD₂ activates sleep-active neurons (see below) in the vlPOA as well as other specific POA sites (31). After medial POA lesions, the sleep-enhancing effect of PGD₂ administered in the 3rd ventricle is diminished (32). Several additional sleep factors have been identified on the basis of sleep-promoting effects of microinjection into the 3rd or lateral ventricles, including cytokines and related molecules including interleukin-1 (Il-1), tumor necrosis factor (TNF- α), muramyl dipeptide (33), granulocyte-macrophage colony-stimulating factor (34), other peptides such as delta-sleep-inducing peptide (35), corticostatin (36), as well as oxidized glutathione (37), desacetyl- α -melanocyte-stimulating hormone (an ACTH derivative found in brain) (38), insulin (39), a lipid, oleamide (40) and vasoactive intestinal peptide (41).

The cellular targets of these injected substances are not clearly established. In some cases, the relevant receptors are found on glia. In the case of circulating factors, the routes by which substances reach POA targets must be established. However, it is logical to hypothesize that the POA sleep-facilitating neurons lost in lesion studies are the targets of one or more of these neurochemical factors. This hypnogenic neuronal population could be the final common path for several mediators of nonREM sleep. The further identification of the POA "hypnogenic" neuronal populations is a focus of the next sections of this review.

3. SLEEP-RELATED C-FOS ACTIVATION AND THE ANATOMICAL ORGANIZATION OF ROSTRAL

3.1. Hypothalamic Sleep Control

The findings that severity of sleep loss following rostral hypothalamic lesions is proportional to lesion size (see above), and that medial as well as laterally placed damage can yield significant sleep loss, suggests that sleep-regulatory neurons are distributed over several rostral hypothalamic subnuclei. Unit recording studies also suggest a diffuse anatomical organization, as neurons with sleep-related discharge have been described in the lateral preoptic area and substantia innominata, the horizontal limb of the diagonal band of Broca and throughout the medial preoptic area/anterior hypothalamus.

Evidence that sleep-regulatory neurons might, at least partially, be segregated from other cell types was initially achieved through visualization of *c-fos* protein immunoreactivity (IR) during sleep (42). *c-fos* is an immediate-early gene whose expression has been found to be correlated with increased neuronal activity in a variety of cell types (43). Fos protein IR was seen in a small cluster of neurons in the vlPOA in rats that were predominately asleep in the hour prior to sacrifice, whereas few fos-IR neurons were observed in this region in rats that had been predominately awake (42). Comparisons across several animals exhibiting a range of spontaneous sleep times revealed that the number of fos-IR neurons in the circumscribed vlPOA area was positively correlated

with the time spent asleep in the hour prior to sacrifice. Many neurons in the vlPOA co-localized markers for the inhibitory neurotransmitters, GABA and galanin (42). The vlPOA was also found to have a strong afferent projection to the major histaminergic nucleus in the brain, the tuberomammillary nucleus (TMN) in the posterior hypothalamus (42,44,45). Histamine is implicated in the control of arousal and the hypothesis emerged that activation of vlPOA neurons during sleep leads to inhibition of the histamine arousal system (42,44).

Subsequently, we examined neuronal discharge patterns in the rat vlPOA during sleep and wakefulness. The goal was to 1) determine if the concentration of sleep-related fos-IR in this region was correlated with a concentration of neurons with sleep related discharge, and 2) to characterize the activity of vlPOA neurons during nonREM versus REM sleep, since studies of fos-IR cannot temporally resolve such differences (46). First, we found that ~50% of neurons recorded in the ventral most portions of the lateral POA exhibited sleep-related discharge patterns. This was a higher concentration of such cells that we had previously found in other rostral hypothalamic sites (23,47,48). Second, most vlPOA neurons were activated during both nonREM and REM sleep compared to waking; for the group of vlPOA neurons with sleep-related discharge, mean discharge rates during nonREM and REM sleep did not differ significantly (46). Most vlPOA neurons exhibited an increase in activity during the immediate transition periods between waking and sleep onset. They also displayed a progressive increase in discharge rate from light to deep nonREM sleep. In response to 12-16 hours of sleep deprivation, vlPOA neurons exhibited increased activation during sleep, but rates during waking remained the same as in non-sleep-deprived rats. This latter finding was consistent with the observation that fos-IR was plentiful in the vlPOA of sleep-deprived rats only if rats were permitted recovery sleep during the hour prior to sacrifice (42).

Given that we and others had recorded neurons with sleep-related discharge in several rostral hypothalamic subregions outside of the vlPOA, we conducted a systematic examination of sleep-related fos-IR throughout this region to determine if additional, segregated populations of sleep-activated neurons could be localized. We found that within the median preoptic nucleus (MnPN), neurons exhibiting fos-IR were abundant in rats that were predominately asleep during the 2 hours prior to sacrifice, but rare in rats that were kept awake (49). In the rat, the median preoptic nucleus (MnPN) is a midline structure, located immediately dorsal to the rostral-most portions of the third ventricle. Sleep-related fos-IR was observed throughout the rostral to caudal extent of the nucleus. As in the case of the vlPOA, the number of fos-IR neurons in the MnPN was positively correlated with total sleep time recorded during the 2 hours prior to sacrifice. We have recently confirmed that 70-80% of MnPN neurons that exhibit sleep-related fos-IR immunostain for glutamic acid decarboxylase, a marker of GABAergic neurons (50). A similar proportion of vlPOA neurons expressing sleep-related fos-IR were found to be GABAergic (50).

We have examined the discharge of rat MnPN neurons across the sleep-waking cycle, in unanesthetized, unrestrained rats (51). In a sample of 89 MnPN neurons, 76% exhibited highest discharge rate during nonREM sleep and/or REM sleep. The largest population (58% of the sample) exhibited similarly elevated discharge rates during both nonREM and REM sleep, compared to waking. Most of these cells showed a gradual increase in their firing rates prior to sleep onset, elevated discharge rates during nonREM sleep and a small, but significant additional increase in discharge rate during REM sleep. Peak discharge rates were observed early in nonREM sleep episodes that followed sustained episodes of waking. In contrast to vlPOA neurons, which displayed increased activity from early to late in individual nonREM sleep episodes, discharge rates of MnPN declined across sustained nonREM sleep episodes in the absence of intervening waking. Combined with the observed patterns of sleep-related fos-IR in MnPN GABAergic neurons described above, these findings support the hypothesis that MnPN neurons are a potential source of inhibitory modulation during both nonREM and REM sleep.

4. DESCENDING MODULATION OF HYPOTHALAMIC AND BRAINSTEM AROUSAL SYSTEMS BY ROSTRAL HYPOTHALAMIC SLEEP-REGULATORY NEURONS

Anatomical and physiological evidence suggests that the rostral hypothalamic neuronal systems discussed above, exert sleep-promoting effects via descending inhibition of multiple arousal systems. Extensive GABAergic projections from the rostral hypothalamus and adjacent basal forebrain to the posterior hypothalamus have been described in rats (52). The vlPOA has been shown to have dense projections to the histaminergic cell body region of the TMN (42,44,45), and is a major source of afferents to this nucleus. Anterograde tracer injections placed in POA regions adjacent to but not encompassing the vlPOA can also yield significant numbers of labeled axons in the TMN (45). The vlPOA and adjacent medial and dorsal regions are also a source of afferents to the midline and lateral dorsal raphe nucleus containing serotonergic neurons and to noradrenergic neurons in the locus coeruleus (44,45,53,54). The MnPN projects to the dorsal raphe nucleus (55), to cholinergic regions of the magnocellular basal forebrain and to the hypocretin-immunoreactive neuronal field in the perifornical lateral hypothalamus (56). Cholinergic neurons are an important source of ascending neocortical and limbic system activation (see (57) for review). Hypocretin neurons are part of a recently characterized arousal system, implicated in electrographic and behavioral arousal, and in the pathophysiology of narcolepsy (58-61).

There is functional evidence for a descending inhibitory action of rostral hypothalamic sleep-regulatory neurons. Electrical stimulation of the medial and lateral portions of the rostral hypothalamus yield suppression of evoked and spontaneous discharge in midbrain reticular formation neurons (62-64). The insomnia resulting from large POA lesions in the cat can be temporarily "reversed" by microinjections of the GABA-A receptor agonist,

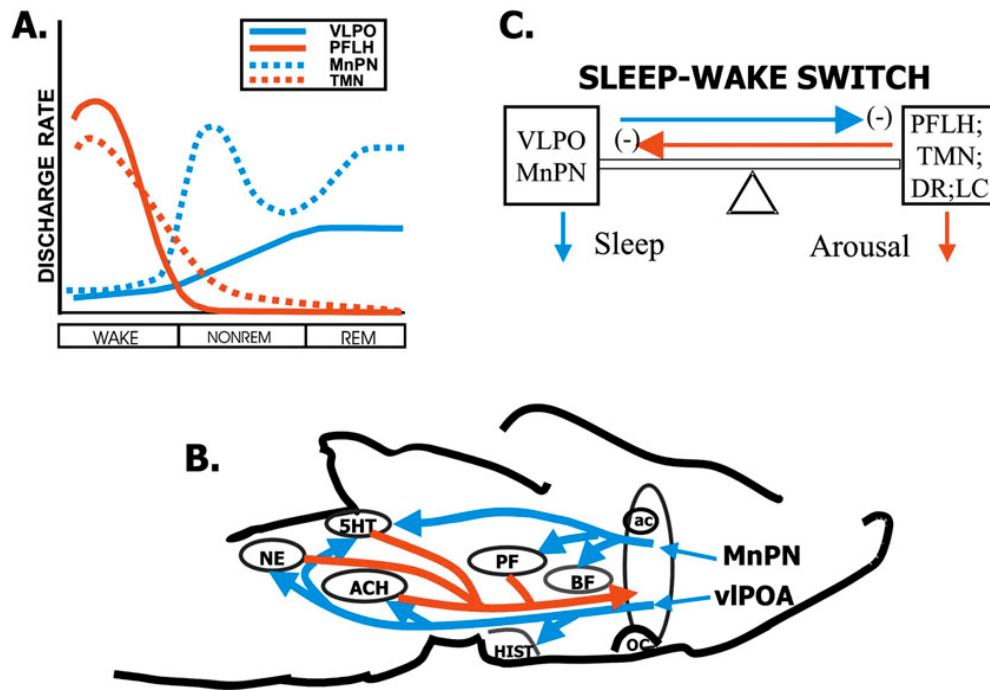


Figure 1. Current conception of the regulation of NREM sleep originating in the preoptic area (POA) of the hypothalamus. **A.** Neurons within the POA, particularly in the median preoptic nucleus (MnPN) and ventrolateral POA (vlPOA) exhibit increases in activity during nonREM sleep and, in some MnPN neurons, further increases during REM sleep. In contrast, putative arousal-promoting neurons in several brain regions, including the perifornical lateral hypothalamus (PFLH), tuberomammillary nucleus (TMN), dorsal raphe nucleus (DRN) and locus coeruleus (LC) exhibit reduced activity at nonREM sleep onset compared to waking and, in the case of DRN and LC neurons, further reductions in activity during REM sleep. **B.** The POA, including particularly the vlPOA and MnPN, contains GABAergic neurons which distribute descending axons to the putative arousal-promoting neuronal groups. Thus, activation of POA GABAergic neurons at sleep onset would be expected to induce inhibition of arousal-promoting neurons in several brain regions. Arousal-promoting neurons project to thalamic, limbic, and neocortical areas where they regulate brain activation (not shown), but some of these neurons also send inhibitory projections back to the POA sleep-active neuronal populations. Thus, activation of arousal systems would be expected to inhibit the POA sleep-promoting system. **C.** The reciprocal inhibitory interactions between the MnPN and vlPOA, on one hand, and the arousal systems, on the other, suggest that sleep-waking may be controlled by a functional “sleep-wake switch”. The mutually inhibitory interactions of these systems provide a mechanism for occurrence of “decisive” transitions between sleep and waking, and the maintenance of stable sleep and waking states (see section 5 for discussion).

muscimol, into the posterior hypothalamus (11). This finding suggests that the insomnia is due to disinhibition of neurons in the posterior hypothalamus as a result of POA cell loss. Extracellular levels of GABA are elevated in the cat posterior hypothalamus during sleep compared to waking (65). Stimulation of the vlPOA region in a horizontal slice containing rostral and caudal portions of the rat hypothalamus, evokes GABA-mediated inhibitory postsynaptic potentials in histaminergic neurons in the TMN (66).

In several of the posterior hypothalamic and brainstem regions identified as afferent targets of the vlPOA and MnPN, significant subpopulations of neurons exhibit spontaneous sleep-waking discharge profiles that are the reciprocal of that observed in sleep-related neurons (see Figure 1A). In the TMN, the dorsal raphe nucleus and the locus coeruleus, the predominate sleep-wake discharge profile is a “REM-off” one, consisting of tonic

firing during waking, significant reductions during nonREM sleep and further reductions in REM sleep (67-71). This is in contrast with MnPN and vlPOA neurons that exhibit minimal activity during waking, and activation during both nonREM and REM sleep (46,51). Within the hypocretin immunoreactive neuronal field, approximately 25% of recorded cells exhibit a “waking-related” discharge pattern with maximal activation during waking, particularly waking accompanied by movement, and uniformly minimal discharge rates during quiet waking, nonREM sleep and REM sleep (72).

In summary, the anatomical and physiological data suggest the existence of a system of GABAergic neurons in the rostral hypothalamus that are activated during both nonREM and REM sleep compared to waking. In the MnPN and vlPOA, sleep-active, GABAergic neurons are relatively segregated from other cell types. However, medial and dorsal extensions the originally identified

vIPOA cluster of neurons have now been described and partially characterized (9,73,74). MnPN and vIPOA neurons send descending projections to multiple cell groups involved in one or more aspects of waking brain function, including electrographic and/or behavioral arousal. Activation of MnPN and vIPOA neurons during transitions from waking to sleep and during stable nonREM and REM sleep can be hypothesized to evoke GABAergic- and galanergic inhibition of these multiple arousal systems. Suppression of activity in these arousal systems would promote the synchronized EEG patterns characteristic of nonREM sleep via direct projections from arousal systems to the cortex, or indirectly via release of thalamo-cortical synchronizing mechanisms (see Steriade this volume for review). Inhibition of brainstem monoaminergic neurons could determine the timing of REM sleep via disinhibition of brainstem REM sleep-generating circuitry (see Bagdoyhan and Lydic, this volume).

5. INTERACTIONS BETWEEN HYPOTHALAMIC SLEEP-REGULATORY AND THERMOREGULATORY

5.1. Mechanisms

Sleep onset is usually coupled to thermoregulatory processes. Most studies show an evoked fall in body temperature at sleep onset that is superimposed on the circadian temperature rhythm (75). Self-selected human bedtimes are predicted by the maximum rate of decline of core body temperature (76). Depending on ambient conditions, sleep onset evokes heat loss effector processes such as cutaneous vasodilation and sweating (77,78). In humans, sleep onset occurs closely in time after a discrete increase in vasodilation of the hands and feet (79). Vasodilation of these skin surfaces allows heat loss. If “lights-out” is scheduled, sleep latency is shorter if this vasodilation has occurred earlier. These studies are compatible with a hypothesis that sleep onset is coupled to body cooling.

An association between thermoregulation and sleep regulation in the POA was suggested by studies showing that local POA warming triggers nonREM sleep or EEG slow wave activity in cats (80), rabbits (81) and rats (82). Sustained POA warming in kangaroo rats tonically increase nonREM sleep during several hours (83). Many studies have confirmed that POA contains populations of warm-sensitive and cold-sensitive neurons (WSN and CSN respectively) that can be identified *in vivo* and *in vitro* (84). These neurons are characterized by robust changes in neuronal discharge in response to locally-applied mild thermal stimuli ($\pm \sim 2^\circ\text{C}$). In most studies, WSN and CSN constitute 20-25% of the neurons recorded in these areas *in vivo*, a finding congruent with the concept that the POA has multiple functions. The sleep-modulating effects of local POA warming or cooling must be mediated by the responses of these neurons.

In cats, POA warming increases EEG slow wave activity within sustained nonREM (85). This enhanced EEG slow wave activity was not due to changes in sleep continuity, but was like that induced following sleep deprivation. Since the relative proportion of EEG slow

wave activity within sleep is considered to be a measure of sleep depth, this study supports a hypothesis that sleep depth as well as sleep induction is controlled by POA thermosensitive neurons. This finding is congruent with the reduction in EEG slow-wave activity observed following POA lesions. On the other hand, mild POA cooling suppresses both nonREM and REM sleep for 3 hours at circadian time 3-6, when rats normally sleep almost continuously (86). Since local cooling selectively inhibits only WSN and excites only CSN, this study supports the hypothesis that these subsets of POA neurons are critical to the hypnogenic mechanism, at least within the 3 hour time frame of this experiment.

Mild to moderate ambient temperature (T_a) elevation increases coincident sleep (83,87-89) as well as subsequent sleep (32,90-91). Augmentation of sleep by ambient warming in kangaroo rats was prevented by coincident local POA cooling (83). Since POA cooling would prevent activation of WSN, this finding suggests that POA WSN activation mediates the sleep augmentation induced by *ambient* warming. Higher ambient temperatures, that evoke strong thermoregulatory effector responses suppress sleep (90).

We have studied the relationships POA neuronal thermosensitivity and sleep-wake discharge in freely-moving awake and sleeping cats and rats. We found that most WSN exhibit sleep-related discharge, and most CSN are active during waking (47,48,92,93). Sleep-active WSN show nearly a 50% increase in discharge rate during nonREM sleep compared to waking. Wake-active CSN show a 50% reduction in discharge rate during nonREM sleep compared to waking. Increases in WSN discharge and decreases in CSN discharge were found to anticipate EEG changes at sleep onset by several seconds in both species. In our studies, WSN and CSN exhibit mirror-image changes in rate and thermosensitivity in nonREM compared to waking (47,48). This is consistent with the idea of inhibitory interactions between WSN and CSN within the POA.

We also examined the effects of ambient warming on sleep-related c-fos IR in the rostral hypothalamus. The number of fos-IR neurons in the rostral and caudal MnPN was increased in rats sleeping in a warm environment compared to rats exhibiting similar amounts of total sleep at a control environmental temperature (49). Ambient warming did not appear to facilitate sleep-related fos-IR in vIPOA neurons (49). These finding suggests that mild ambient warming may facilitate sleep via activation of MnPN sleep-regulatory neurons.

The ability of local warming to activate a significant subpopulation of POA sleep-active neurons can be used experimentally to examine how activation of sleep-active neurons during waking alters neuronal activity in other brain regions. Studies of this type offer further support for a descending inhibitory modulation of arousal systems by rostral hypothalamic sleep-regulatory neurons. In dogs, local warming of the preoptic area results in

suppression of sensory-evoked responses in midbrain reticular formation neurons (94). In cats, rostral hypothalamic warming evokes suppression of spontaneous waking neuronal activity among arousal-related neurons in cholinergic regions of the magnocellular basal forebrain (95) and in the posterior lateral hypothalamus (96). In rats, rostral hypothalamic warming evokes suppression of waking discharge in putative serotonergic neurons in the dorsal raphe nucleus (71), and reductions in waking discharge rates in perifornical lateral hypothalamic neurons (97). The suppression of waking neuronal activity in these multiple arousal systems can be hypothesized to underlie the sleep-promoting and EEG slow-wave enhancing effects of hypothalamic warming.

6. SUMMARY AND PERSPECTIVE: RECIPROCAL INTERACTIONS BETWEEN SLEEP AND AROUSAL SYSTEMS

Figure 1 summarizes our current understanding of the interactions between sleep-regulatory systems in the rostral hypothalamus and multiple arousal systems in the posterior hypothalamus and brainstem. Neurons that exhibit sleep related *c-fos* protein IR during sleep and neurons that exhibit elevated discharge rates during both nonREM and REM sleep are localized in the vlPOA and MnPN (Figure 1B). Additional sleep-regulatory neurons may be located more diffusely within the rostral hypothalamus. A majority of MnPN and vlPOA neurons that exhibit sleep-related *fos*-IR are GABAergic (50). vlPOA neurons co-localize GABA and galanin (42). Projections from the MnPN and vlPOA to multiple brain regions implicated in the control of arousal have been documented. These include the magnocellular basal forebrain, tuberomammillary nucleus, perifornical lateral hypothalamus, dorsal raphe nucleus and locus coeruleus. Therefore, it can be hypothesized that activation of MnPN and vlPOA neurons at the transition from waking to sleep results in GABA- and galanin-mediated inhibition of neurons in these multiple arousal systems. This hypothesis is supported by the findings that the spontaneous discharge patterns of vlPOA and MnPN neurons across the sleep waking cycle are largely reciprocal to that observed in targeted arousal systems (Figure 1A; see Section 4).

Many hypothalamic sleep-regulatory neurons are also thermosensitive and are activated by local increases in temperature. Thus, rostral hypothalamic warming, via activation of GABAergic sleep-active neurons would be expected increase inhibitory modulation of neurons in targeted arousal systems. This prediction has been experimentally confirmed (see Section 5). Similarly, destruction of rostral hypothalamic sleep-regulatory neurons should result in tonic disinhibition of arousal systems, leading to insomnia. This has been experimentally confirmed, and POA lesion-induced insomnia can be temporarily reversed by delivering exogenous GABAergic agonist to the posterior hypothalamus (11).

There is also evidence that functional relationships between sleep and arousal systems are

reciprocal. Regions of the rostral hypothalamus implicated in sleep regulation receive dense projections from histaminergic neurons in the TMN, serotonergic neurons in the dorsal raphe nucleus, and hypocretin neurons in the lateral hypothalamus (58,73,98,99). The locus coeruleus projects to the MnPN (100) and to vlPOA (73). Microinjection of exogenous histamine (101) and hypocretin (102) into the lateral POA evoke insomnia. POA injections of norepinephrine have acute wake-promoting effects (103). Serotonin and nor-epinephrine evoke inhibitory responses in GABAergic neurons in the vlPOA recorded *in vitro* (104). Nor-epinephrine has been shown to have similar effects on MnPN neurons recorded *in vitro* (105).

Taken together, these findings suggest that the interactions between rostral hypothalamic sleep regulatory neurons and multiple arousal systems form a functional “sleep-wake switch” (42,74,106). Activation of MnPN and vlPOA neurons at the transition from wake to sleep simultaneously suppress activity in several arousal systems. The deactivation of arousal systems removes excitatory input to thalamus, resulting in functional sensory deactivation of the cortex and the generation of synchronous activity in thalamocortical circuits (see Steriade this volume). This deactivation of arousal systems would also progressively remove inhibitory input to vlPOA and MnPN neurons, reinforcing sleep onset. This process would provide a mechanism for the production of rapid transitions from wake to sleep and the maintenance of consolidated sleep episodes, once sleep is initiated. These mechanisms could also contribute to the timing of REM sleep, as inhibition of serotonergic and noradrenergic neurons by vlPOA and MnPN neurons would release brainstem REM sleep-promoting circuitry (see Bagdoyan and Lydic, this volume). In contrast, any stimuli or factors that would strongly activate one or more arousal systems would evoke suppression of activity in hypothalamic sleep-regulatory neurons, leading to a rapid transition to stable waking.

Certain details of this model, as summarized in Figure 1, remain to be confirmed. Although the MnPN and vlPOA give rise to descending GABAergic projections and contain GABAergic sleep-active neurons, it has not been shown that these are the same neurons. The reciprocal patterns of activity in POA sleep-active neurons and arousal-related neurons has not been described in detail, particularly with respect to predictions concerning the sequence of neuronal activity changes at state transitions. Sleep propensity is strongly regulated by the circadian clock localized in the suprachiasmatic nucleus in the ventromedial POA. This nucleus sends projections to several POA nuclei, but the exact pathways for control of sleep active neuronal activity are not established. A more general problem is the identification of the interface between the hypnogenic neurochemical sleep factors which act in the POA and the control of sleep-promoting neuronal activity. It has been proposed that the key to understanding the homeostatic control of sleep will be found in the actions of these sleep factors. Detailed analyses of the mechanisms by which sleep factors control sleep-promoting neurons should shed light on this process.

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