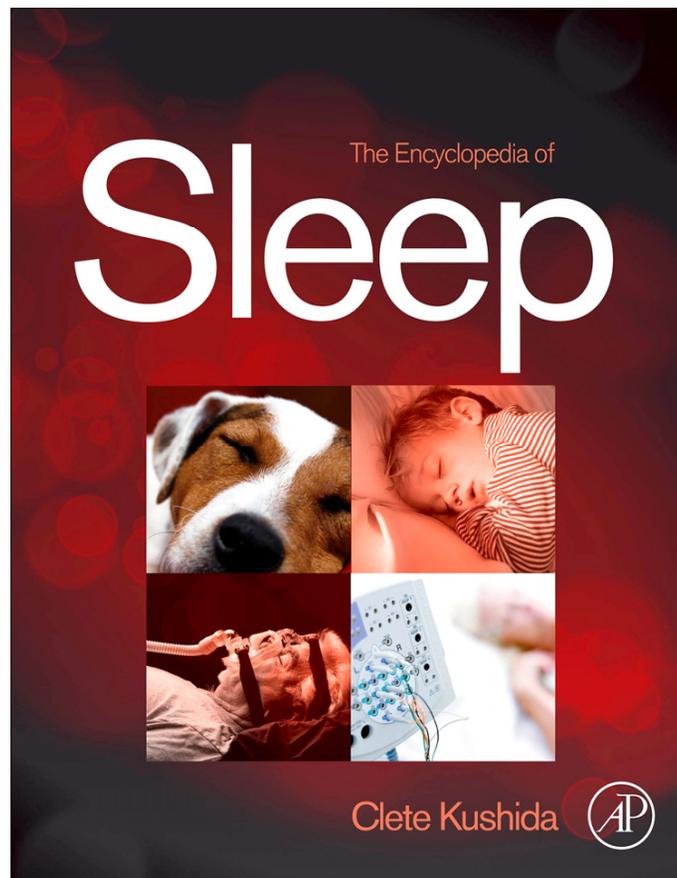


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## REM Sleep Anatomy and Physiology

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Discussions on dreaming probably coincided with the development of speech in humans. It was likely obvious even to some preverbal humans that dreaming was a sleep-related hallucination and that companion animals such as cats and dogs had motor behavior in sleep suggesting that they too dreamed. In the nineteenth and twentieth centuries, Freud and others introspected about the function and meaning of dreams. However, it was not until 1953 that rapid eye movement (REM) sleep was discovered as a physiological phenomenon linked to dreaming by Aserinsky and Kleitman. Their short paper not only provides the first documentation of the key phenomena of REM sleep, but also presents a scholarly discussion of the earlier hints at the existence of this state, generously crediting their predecessors.

Most early work on REM sleep control was done in cats. **Figure 1**, top, shows the principal electrical signs of REM sleep. These include a reduction in cortical electroencephalogram (EEG) amplitude, particularly in the power of its lower frequency components. A theta rhythm is generated in the hippocampus during REM sleep. REM sleep is also characterized by a suppression of muscle tone (called atonia), visible in the electromyogram (EMG). Erections tend to occur in males. Thermoregulation (e.g., sweating and shivering) largely ceases in most animals and body temperatures drift toward environmental temperatures, as in reptiles. Pupils constrict, reflecting a parasympathetic dominance in the control of the iris. These changes that are present throughout the REM sleep period have been termed its 'tonic' features.

Also visible are electrical potentials that can be most easily recorded in the lateral geniculate nucleus of the cat. These potentials originate in the pons, appear after a few milliseconds in the lateral geniculate nucleus and can be observed with some delay in the occipital cortex, leading to the name pontogeniculo-occipital (PGO) spikes. They occur as large amplitude, isolated potentials 30 or more seconds before the onset of REM sleep as defined by EEG and EMG criteria. After REM sleep begins, they arrive in bursts of 3–10 waves usually correlated with REMs. PGO linked potentials can be recorded in the motor nuclei of the extraocular muscles, where they trigger the rapid eye movements of REM sleep. They are also present in thalamic nuclei other than the geniculate and in neocortical regions other than the occipital cortex. In humans, REMs are loosely correlated with contractions of the middle ear muscles of the sort that accompany speech generation and that are part of the protective response to loud noise. Other muscles also contract during periods of REM, briefly breaking through the muscle atonia of REM sleep. There are periods of marked irregularity in respiratory and heart rates during REM sleep, in contrast with non-REM sleep, during which respiration and heart rate are highly regular. No single pacemaker for all of this irregular activity has been identified. Rather, the signals producing twitches of the peripheral or middle ear muscles may lead or

follow PGO spikes and REMs. Bursts of brainstem neuronal activity may likewise lead or follow the activity of any particular recorded muscle. These changes that occur episodically in REM sleep have been called its 'phasic' features.

### Transection Studies

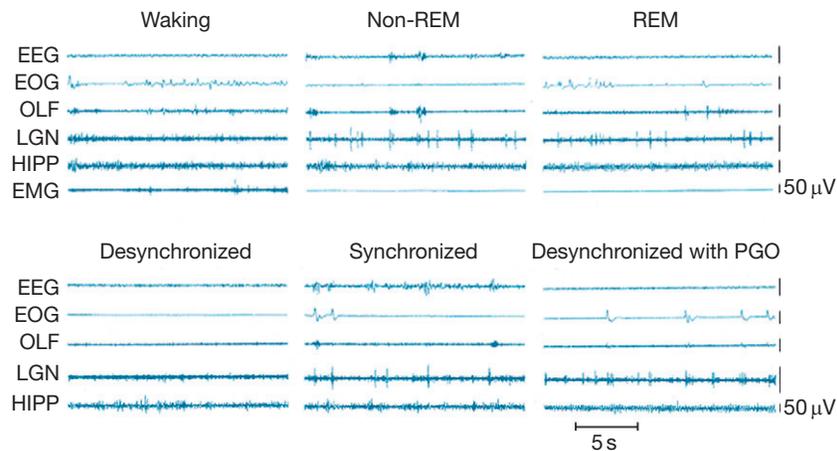
The most radical types of lesion studies are those that slice through the brainstem, severing the connections between regions rostral and caudal to the cut. Sherrington discovered that animals in which the forebrain is removed after transecting the neuraxis in the coronal plane at the rostral border of the superior colliculus, showed tonic excitation of the 'antigravity muscles' or extensors (**Figure 2**, level A). This decerebrate rigidity was visible as soon as anesthesia was discontinued. Bard reported in 1958 that animals with decerebrate rigidity would show periodic limb relaxation. We now know that Bard and Macht were observing the periodic muscle atonia of REM sleep.

After the discovery of REM sleep in the cat, Jouvet found that this state of EEG desynchrony was normally accompanied by muscle atonia. Jouvet then examined the decerebrate cat preparation used by Sherrington and Bard, now adding measures of muscle tone, eye movement, and EEG. When he recorded in the forebrain after separating the forebrain from the brainstem at the midbrain level (**Figure 2**, levels A or B), he found no clear evidence of REM sleep. In the first few days after transection, the EEG in the forebrain was always high voltage as in non-REM sleep, but when low voltage activity appeared, the PGO spikes that help identify REM sleep in the intact animal were absent from the lateral geniculate where they can be most easily recorded. Thus it appeared that the isolated forebrain had slow-wave sleep states and possibly waking, but no clear evidence of REM sleep.

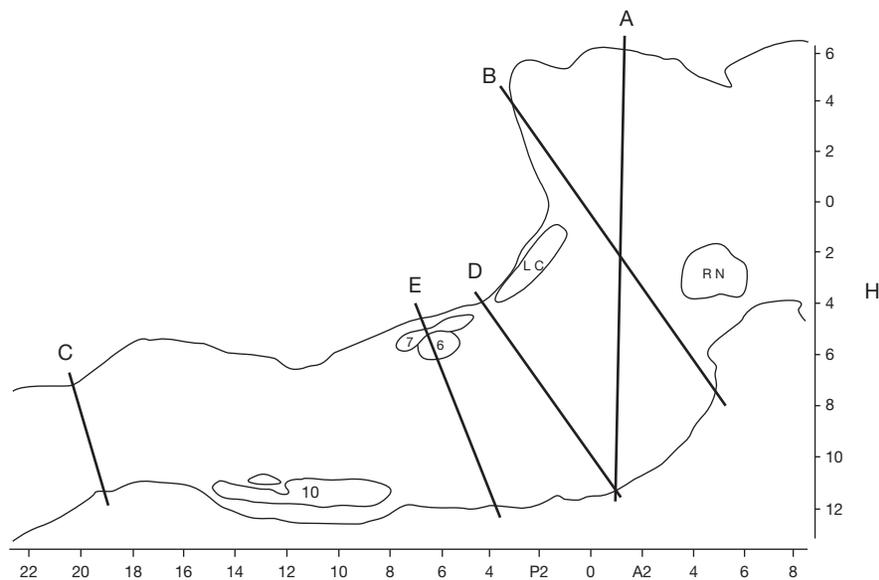
In contrast, the midbrain and brainstem behind the cut showed clear evidence of REM sleep. Muscle atonia appeared with a regular periodicity and duration, similar to that of the intact cat's REM sleep periods. This atonia was accompanied by PGO spikes with a similar morphology to those seen in the intact animal. The pupils were highly constricted during atonic periods, as in REM sleep in the intact cat.

A further localization of the REM sleep control mechanisms can be achieved by examining the sleep of humans or animals where the brainstem–spinal cord connection has been severed (**Figure 2**, level C). In this case, normal REM sleep in all its manifestations, except for spinally mediated atonia is present. Thus we can conclude that the region between the caudal medulla and rostral midbrain is sufficient to generate REM sleep.

This approach can be continued by separating the caudal pons from the medulla (**Figure 2**, level D or E). In such animals no atonia is present in musculature controlled by the



**Figure 1** Top: Polygraph tracings of states seen in the intact cat. Bottom: States seen in the forebrain 4 days after transection at the pontomedullary junction. EEG, sensorimotor electroencephalogram; EOG, electrooculogram; OLF, olfactory bulb; LGN, lateral geniculate nucleus; HIPP, hippocampus; EMG, dorsal neck electromyogram.



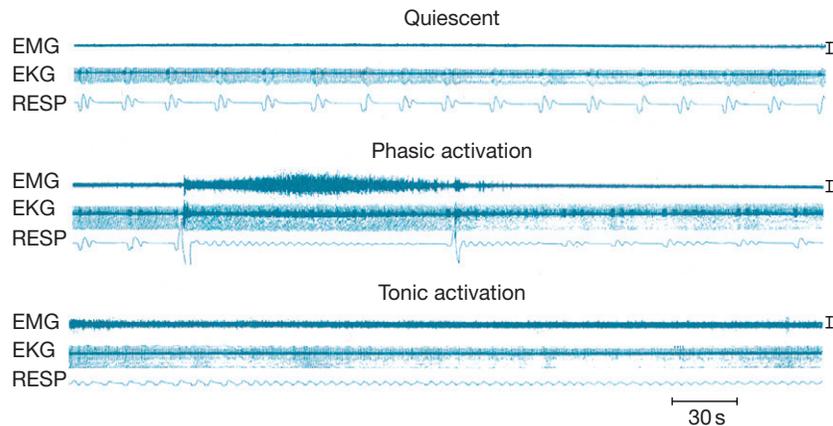
**Figure 2** Outline of a sagittal section of the brainstem of the cat drawn from level L1.6 of the Berman atlas indicating the level of key brainstem transection studies. RN, Red nucleus; LC, locus coeruleus; 6, abducens nucleus; 7, genu of the facial nerve; IO, inferior olive. H (horizontal) and A–P (anterior–posterior) scales are drawn from the atlas.

spinal cord, even though electrical or chemical stimulation of the medial medulla in the decerebrate animal suppresses muscle tone. Furthermore neuronal activity in the medulla does not resemble that seen across the REM–non-REM sleep cycle, with neuronal discharge very regular for periods of many hours, in contrast to the periodic rate modulation that is linked to the phasic events of REM sleep in the intact animal (Figure 3). This demonstrates that the medulla and spinal cord together, although they may contain circuitry whose activation can suppress muscle tone, are not sufficient to generate this aspect of REM sleep when disconnected from more rostral brainstem structures and they are also not sufficient to generate the phasic bursts of activity that characterize REM sleep.

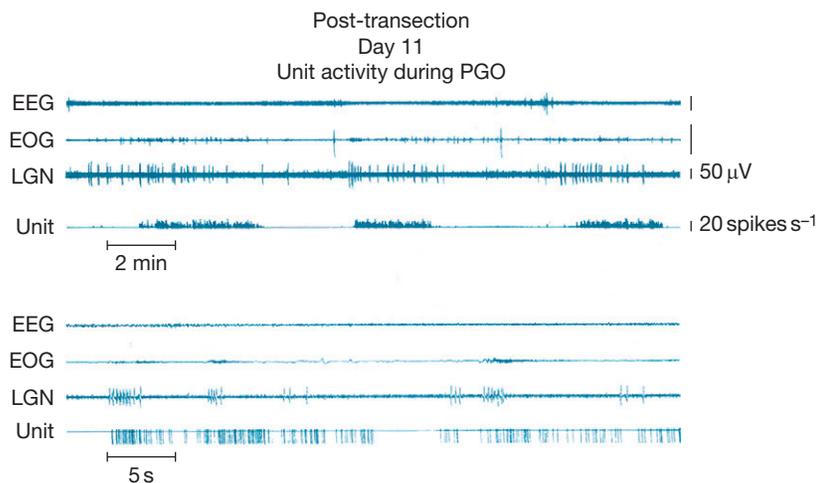
In contrast, the regions rostral to this cut show aspects of REM sleep (Figures 1 (bottom) and 4). In these regions we can

see the progression from isolated to grouped PGO spikes and the accompanying reduction in PGO spike amplitude that occurs in the pre-REM sleep period and the REM sleep periods in the intact animal. We also see increased forebrain unit activity, with unit spike bursts in conjunction with PGO spikes, just as in REM sleep.

To summarize, this work shows that when pontine regions are connected to the medulla, atonia, REMs and the associated unit activity of REM sleep occur, whereas the medulla and spinal cord together, disconnected from the pons, are not sufficient to generate these local aspects of REM sleep. When the pons is connected to the forebrain, forebrain aspects of REM sleep are seen, but the forebrain without attached pons does not generate these aspects of REM sleep. Further confirmation of the importance of the pons and caudal midbrain



**Figure 3** States seen in the chronic medullary cat. Note the absence of periods of atonia. EKG, electrocardiogram; EMG, electromyogram; RESP, thoracic strain gauge. Calibration,  $50 \mu\text{V}$ . Reproduced from Siegel JM, Tomaszewski KS, and Nienhuis R (1986) Behavioral states in the chronic medullary and mid-pontine cat. *Electroencephalography and Clinical Neurophysiology* 63: 274–288.



**Figure 4** Midbrain unit: electroencephalographic (EEG), electro-oculographic (EOG), and lateral geniculate nucleus (LGN) activity rostral to chronic transections at the pontomedullary junction. In the upper portion of the figure, the unit channel displays the output of an integrating digital counter resetting at 1 s intervals. In the lower portion, one pulse is produced for each spike by a window discriminator. Reproduced from Siegel JM (1985) Pontomedullary interactions in the generation of REM sleep. In: McGinty DJ, Drucker-Colin R, Morrison A, et al. (eds.) *Brain Mechanisms of Sleep*, pp. 157–174. New York, NY: Raven Press.

comes from the studies of Matsuzaki et al. They found that when two cuts were placed, one at the junction of the midbrain and pons and the other at the junction of the pons and medulla, one could see periods of PGO spikes in the isolated pons, but no signs of REM sleep in structures rostral or caudal to the 'pontine island.'

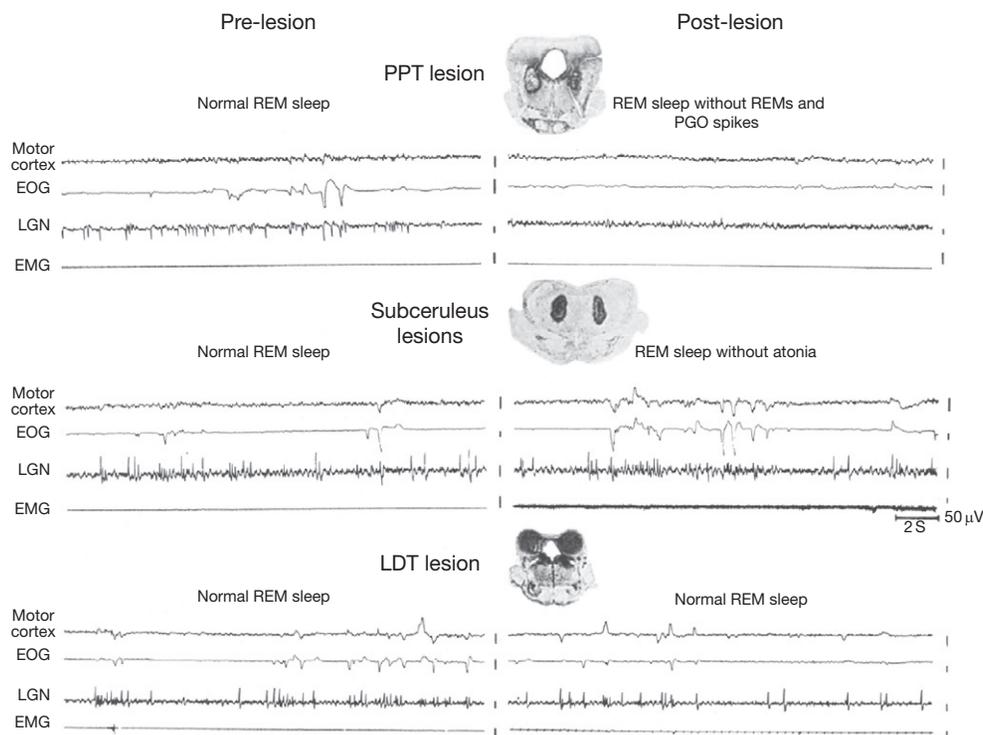
These transection studies demonstrate, by persuasive positive evidence, that the pons is sufficient to generate the pontine signs of REM sleep, that is, the periodic pattern of PGO spikes and irregular neuronal activity that characterizes REM sleep. One can conclude that the pons is the crucial region for the generation of REM sleep. Below, we will consider in more detail the structures within this region that synthesize the core elements of REM sleep.

However, it is also clear that the pons alone does not generate all the phenomena of REM sleep. Atonia requires the inactivation of brainstem systems facilitating muscle tone and the activation of motor inhibitory systems in the medulla.

In the intact animal, forebrain mechanisms interact with pontine mechanisms to regulate the amplitude and periodicity of PGO spikes, which in turn is linked to the twitches and rapid eye movements of REM sleep. We know from cases of human REM sleep behavior disorder (RBD) that the motor activity expressed in dreams is tightly linked to the imagery of the dream. Extrapolating to dream imagery in normal humans, one can hypothesize that since the structure of REM sleep results from an interaction of forebrain and brainstem mechanisms, the dream itself is not just passively driven from the brainstem, but rather represents the result of a dynamic interaction between forebrain and brainstem structures.

### Localized Lesion Studies

The transection studies point to a relatively small portion of the brainstem, the pons, and caudal midbrain as critical for



**Figure 5** Twenty-second polygraph tracings of rapid eye movement (REM) sleep before and after lesions, together with a coronal section through the center of the pontine lesions. EEG voltage reduction of REM sleep (recorded from motor cortex) was present after both lesions. Top: radiofrequency lesions of the pedunclopontine region diminished ponto-geniculo-occipital (PGO) spikes and eye movement bursts during REM sleep. Bottom: lesions in the region ventral to the locus coeruleus produced REM sleep without atonia without any diminution of PGO spike or REM frequency. Reprinted from Shouse MN and Siegel JM (1992) Pontine regulation of REM sleep components in cats: integrity of the pedunclopontine tegmentum [PPT] is important for phasic events but unnecessary for atonia during REM sleep. *Brain Research* 571: 50–63, Copyright 1992, with permission from Elsevier Science.

REM sleep generation. Further specification of the core regions can be achieved by destroying portions of the pons in an otherwise intact animal and seeing which areas are necessary and which are unnecessary for REM sleep generation. It was shown that neurons in medial pontine regions including the giant cell region were not important in REM sleep control, because near total destruction of these cells was followed by normal amounts of REM sleep as soon as anesthesia dissipated. However, lesions of the subcoeruleus (the region below the locus coeruleus, a nucleus which contains cells that release noradrenalin) and adjacent regions with cytotoxins did cause a prolonged reduction in the amount of REM sleep. According to one study, the extent of this loss was proportional to the percentage of cholinergic cells lost in subcoeruleus and adjacent regions of the brainstem of the cat, although this correlation is difficult to separate from the overall size of the lesion. In rats, lesion or inactivation of the same region below the locus coeruleus, called the sublateralodorsal nucleus in the terminology of Swanson, has been found to reduce REM sleep.

Although large lesions may eliminate all aspects of REM sleep, small bilaterally symmetrical lesions within the pons can eliminate specific aspects of REM sleep. Lesions of lateral pontine structures allow muscle atonia during REM sleep. However, PGO spikes and the associated REMs are absent when lesions include the region surrounding the superior cerebellar

peduncle of the cat (Figure 5, top). This points to a role for this lateral region in the generation of PGO waves and the associated phasic activity of REM sleep.

Small lesions confined to portions of the subcoeruleus regions result in a very unusual syndrome. After non-REM sleep, these animals enter REM sleep as indicated by lack of responsiveness to the environment, PGO spikes, EEG desynchrony, and pupil constriction. However, they lack the muscle atonia that normally characterizes this state (Figure 5, bottom). During 'REM sleep without atonia' these animals appear to act out dreams, attacking objects that are not visible, exhibiting unusual affective behaviors and ataxic locomotion. When they are awakened, normal behavior resumes. More recent studies have demonstrated that lesions of a system extending from the ventral midbrain to the medial medulla can cause REM sleep without atonia and that activation of this system can suppress muscle tone.

This subcoeruleus region is under the control of midbrain regions. A midbrain region located just beneath and lateral to the periaqueductal gray (and called the dorsocaudal central tegmental field in the cat) appears to inhibit REM sleep by inhibiting the critical 'REM-on' subcoeruleus neurons. Muscimol, a GABA<sub>A</sub> receptor agonist, injected into this midbrain region silences these cells and increases REM sleep, presumably by blocking the inhibition. The same phenomena have been

observed when muscimol is injected into the corresponding region of the guinea pig and the rat (in the rat, this midbrain region has been called the deep mesencephalic nucleus).

Increasing the levels of gamma-aminobutyric acid (GABA) in the subcoeruleus region (also called the pontine oralis nucleus in the rat and cat) produces an increase in waking, rather than the increase in REM sleep seen with GABA injection into the midbrain regions indicated above. This is another reminder that, despite the sleep inducing effect of systemic administration of GABA receptor activating hypnotic medications, local manipulation shows that the effect of GABA on sleep and waking states varies across brain regions. Blocking GABA in the subcoeruleus has been reported to increase REM sleep in the cat.

### Stimulation Studies

The first study showing that stimulation could elicit REM sleep was carried out by George et al. They found that application of the acetylcholine agonist carbachol to specific regions of the pons ventral to the locus coeruleus could elicit REM sleep in the cat. An impressive proof that a unique REM sleep generation mechanism was being activated was the long duration of the elicited REM sleep periods with aspects of REM sleep persisting for hours or even days after injection. Microinjection of acetylcholine into this region in the decerebrate cat produces an immediate suppression of decerebrate rigidity. Later studies showed that, depending on the exact site, either REM sleep or just atonia in a waking state could be triggered by cholinergic. When stimulation was applied to the lateral regions whose lesion blocked PGO waves, continuous PGO spikes were generated even though the animal was not always behaviorally asleep. Increased REM sleep has been reported in the rat after microinjection of cholinergic agonists into the subcoeruleus region, although this effect is certainly not as robust as it is in the cat.

The first study demonstrating a role for glutamate in the control of REM sleep was done in the cat. It was found that a profound suppression of muscle tone could be elicited by the injection of glutamate into the subcoeruleus region or into the ventral medullary region. Further work has demonstrated that the pontine cells in this inhibitory region receiving this cholinergic input use glutamate as their transmitter and project directly to glutamate responsive regions of the medial medulla.

Work in the rat has emphasized the strong triggering of REM sleep by glutamatergic excitation of this region. However, glutamatergic excitation of this region in the cat also increases REM sleep, suggesting that the difference in response in the two species does not indicate a fundamental difference in control features, although it does suggest species differences in the relative potency of these transmitters or perhaps in the pattern of distribution of receptors for them.

### Neuronal Activity, Transmitter Release

The transection, lesion, and stimulation studies, all point to the same regions of the pons and caudal midbrain as the critical regions for the generation of the state of REM sleep as

a whole, and smaller subregions in the brainstem and forebrain for the control of its individual components. The pons contains a complex variety of cells differing in their neurotransmitter, receptors, and axonal projections. Unit recording techniques allow an analysis of the interplay between these cell groups and their targets to further refine our identification of REM sleep mechanisms.

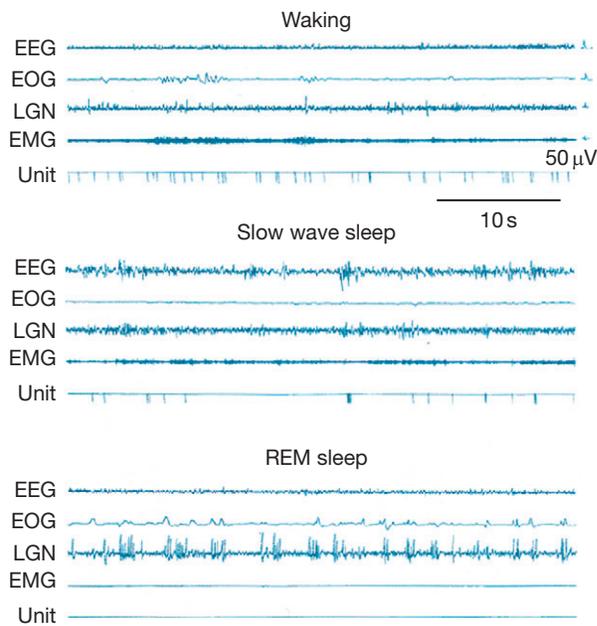
Most cells within the medial brainstem reticular formation are maximally active in waking, greatly reduce discharge rate in non-REM sleep, and increase discharge rate back to waking levels in REM sleep. Discharge is most regular in non-REM sleep and is relatively irregular in both waking and REM sleep. The similarity of the waking and REM sleep discharge pattern suggests a similar role of these cells in both states. Indeed, most of these cells have been shown to be active in waking in relation to specific lateralized movements of the head, neck, tongue, face, or limbs. For example, a cell may discharge only with extension of the ipsilateral forelimb or abduction of the tongue. The twitches that are normally visible in facial and limb musculature during REM sleep and the phenomenon of REM sleep without atonia suggest that these cells command movements that are blocked by the muscle tone suppression of REM sleep. Lesion of these cells has little or no effect on REM sleep duration or periodicity, but does dramatically prevent movements of the head and neck in waking.

Microinjection of cholinergic agonists into the pons triggers REM sleep. Microdialysis studies show that pontine acetylcholine release is greatly increased during natural REM sleep when compared to either non-REM sleep or waking. Recordings of neuronal activity within the cholinergic cell population demonstrate the substrates of this release. Certain cholinergic cells are maximally active in REM sleep (REM-on cells). Others are active in both waking and REM sleep. Presumably the REM sleep-on cholinergic cells project to the acetylcholine responsive region in the subcoeruleus area.

Cells with activity selective for REM sleep can be identified within the subcoeruleus area in both cats. Anatomical studies using Fos labeling and tract tracing suggest that these neurons are glutamatergic and that some of them project to the ventral medullary region involved in the triggering of the muscle atonia of REM sleep.

Monoamine containing cells have a very different discharge profile. Most, if not all, noradrenergic, and serotonergic cells of the midbrain and pontine brainstem and histaminergic cells of the posterior hypothalamus are continuously active during waking, decrease their activity during non-REM sleep, and further reduce or cease activity during REM sleep (Figure 6). As was pointed out above, these cell groups are not critical for REM sleep generation, but it is likely that they modulate the expression of REM sleep. The cessation of discharge in monoaminergic cells during REM sleep appears to be caused by the release of GABA onto these cells, presumably by REM sleep-active GABAergic brainstem neurons. Administration of a GABA agonist to the raphe cell group increases REM sleep duration, demonstrating a modulatory role for this cell group in REM sleep control.

Other cholinergic cells in lateral pontine regions discharge in bursts before each ipsilateral PGO wave. These cells may therefore participate in the triggering of these waves. We know



**Figure 6** Activity of a 'REM sleep-off' cell recorded in the locus coeruleus.

from other studies that PGO waves are tonically inhibited in waking by serotonin input. Therefore, it is likely that certain groups of cholinergic cells receive direct or perhaps indirect serotonergic inhibition in waking and that the decrease of this inhibition in non-REM sleep and REM sleep facilitates PGO wave and REM sleep generation.

A more global mapping of neurons active in REM sleep can be achieved by using the Fos labeling to identify neurons active within the 20 (or more)-minute period before sacrifice. Quattrochi et al. demonstrated that microinjections of the cholinergic agonist carbachol that triggered episodes of continuous PGO waves in waking activated neurons within the laterodorsal and pedunculopontine nuclei of the cat. Destruction of these nuclei blocks these waves.

More extensive Fos mapping has been done to identify neurons activated during REM sleep in the rat. Verret et al. found that only a few cholinergic neurons from the laterodorsal and pedunculopontine tegmental nuclei were Fos-labeled after REM sleep. In contrast, a large number of noncholinergic Fos-labeled cells were observed in the laterodorsal tegmental nucleus, subcoeruleus region, and lateral, ventrolateral, and dorsal periaqueductal gray of the midbrain. In addition, cells in other regions outside of the brainstem regions critical for REM sleep control were labeled. These included neurons in the alpha and ventral gigantocellular reticular nuclei of the medulla, dorsal and lateral paragigantocellular reticular nuclei and the nucleus raphe obscurus. In a second study, an effort was made to identify the source of the GABAergic input thought to cause the cessation of discharge in locus coeruleus cells during REM sleep. Verret et al. found that the dorsal and lateral paragigantocellular reticular nuclei of the medulla and regions of the periaqueductal gray of the midbrain, regions with large percentages of GABAergic cells, are active in REM sleep. Maloney et al. found GABAergic cells adjacent to the locus coeruleus that expressed Fos during periods of REM sleep.

Because the critical phenomena of REM sleep do not appear to require the medulla, it seems likely that the periaqueductal gray GABAergic neurons and GABAergic neurons adjacent to locus coeruleus and raphe nuclei are sufficient to suppress the activity of noradrenergic and serotonergic neurons, although medullary neurons may participate in the intact animal.

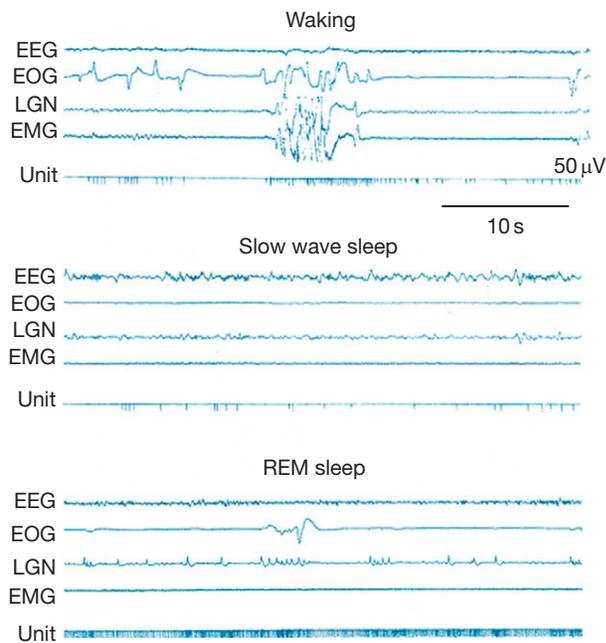
Fos mapping has also been used to identify forebrain regions likely to control REM sleep. The preoptic region, important in non-REM sleep control, contains neurons that express Fos maximally in REM sleep deprived animals, suggesting that these neurons may be related to the triggering or maintenance of REM sleep by brainstem systems, perhaps in coordination with the triggering of non-REM sleep by this region. Fos studies also indicate that melanin-concentrating hormone neurons, which are located in the hypothalamus, express Fos during periods with large amounts of REM sleep and that intracerebroventricular administration of melanin-concentrating hormone increases the amount of subsequent REM sleep. These results suggest that melanin-concentrating hormone neurons are an additional source of forebrain modulation of REM sleep.

### Control of Muscle Tone in Sleep

Abnormalities of muscle tone control underlie many sleep disorders. During non-REM sleep, muscle tone is greatly reduced. During REM sleep, central motor systems are highly active, whereas motoneurons are hyperpolarized, producing a further reduction of muscle tone. The normal suppression of tone in the tongue and laryngeal muscles in non-REM sleep and their further suppression in REM sleep are major contributing factors in sleep apnea. The failure of muscle tone suppression in REM sleep causes RBD. Triggering of the REM sleep muscle tone control mechanism in waking is responsible for cataplexy.

Early work using intracellular recording and microiontophoresis had shown that motoneuron hyperpolarization during REM sleep was accompanied by the release of glycine onto motoneurons. Microdialysis sampling showed that both GABA and glycine are released onto motoneurons during atonia induced by carbachol in the cat. This release occurs in ventral horn motoneurons as well as in hypoglossal motoneurons. The glycinergic inhibition during a carbachol-elicited REM sleep-like state was investigated with immunohistochemistry and found to be due to the activation of glycinergic neurons in the nucleus reticularis gigantocellularis and nucleus magnocellularis in the rostro-ventral medulla and the ventral portion of the nucleus paramedianus reticularis, regions whose activation has been shown to suppress muscle tone in the unanesthetized decerebrate animal. A second population was located in the caudal medulla adjacent to the nucleus ambiguus; these neurons may be responsible for the REM sleep-related inhibition of motoneurons that innervate the muscles of the larynx and pharynx.

In related work it has been shown that norepinephrine and serotonin release onto motoneurons is decreased during atonia. Since these monoamines are known to excite motoneurons and GABA and glycine are known to inhibit them, it appears that the coordinated activity of these cell groups



**Figure 7** Activity of medullary 'REM sleep-on' cell. Note the tonic activity during REM sleep. In waking, activity is generally absent even during vigorous movement. However, some activity is seen during movements involving head lowering and postural relaxation.

produces motoneuron hyperpolarization and hence atonia in REM sleep by a combination of inhibition and disfacilitation.

The inhibitory and facilitatory systems are strongly and reciprocally linked. Electrical stimulation of the pontine inhibitory area (PIA), located in the subcoeruleus region, produces muscle tone suppression. Even though the PIA is within a few millimeters of the noradrenergic locus coeruleus, electrical stimulation in the PIA that suppresses muscle tone will always cause a cessation of activity in the noradrenergic neurons of the locus coeruleus and other facilitatory cell groups. This indicates that the process responsible for the suppression of muscle tone causes the linked inhibition and disfacilitation. Cells that are maximally active in REM sleep ('REM-on' cells) are present in the PIA and also in the region of the medial medulla that receives PIA projections (Figure 7).

The release of GABA and glycine onto motoneurons during REM sleep atonia is most likely mediated by a pathway from the PIA to the medial medulla. The pontine region triggering this release is not only sensitive to acetylcholine, but also responds to glutamate (Figure 8). The medullary region with descending projections to motoneurons can be subdivided into a rostral portion responding to glutamate and a caudal portion responding to acetylcholine (Figure 8). The medullary interaction with pontine structures is critical for muscle tone suppression, since inactivation of pontine regions greatly reduces the suppressive effects of medullary stimulation on muscle tone. An ascending pathway from the medulla to the pons may mediate the inhibition of locus coeruleus during atonia and may also help recruit other active inhibitory mechanisms. Thus damage anywhere in the medial pontomedullary region can block muscle atonia (perhaps causing RBD) by interrupting ascending and descending portions of the pontomedullary

inhibitory system as can muscimol injection into the pontine inhibitory region.

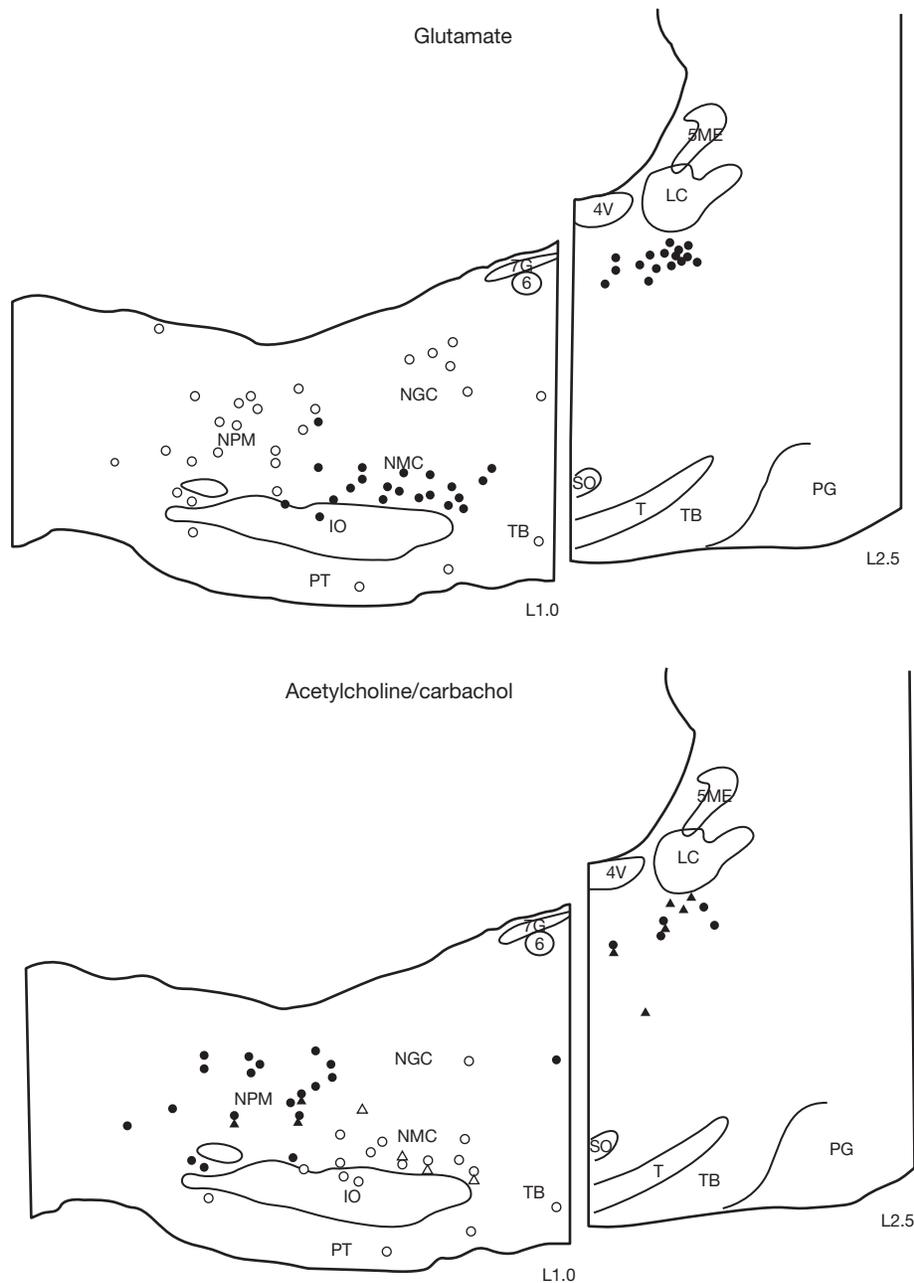
The success of jaw appliances indicates that reduced jaw muscle activity can contribute to closure of the airway in sleep apnea. Jaw muscle relaxation is a common initial sign of cataplexy and tonic muscle activation underlies bruxism. Investigation of the control of masseter motor neurons allows analysis of the regulation of muscle tone on one side of the face, while using the other side as a control for changes in behavioral state caused by application of neurotransmitter agonist and antagonists. Using this model, it was determined that tonic glycine release reduces muscle tone in both waking and non-REM sleep. However, blockade of glycine receptors did not prevent the suppression of muscle tone in REM sleep. In a similar manner, blockade of GABA receptors alone or in combination with glycine receptors increased tone in waking and non-REM sleep, but did not prevent the suppression of masseter tone or of genioglossus tone in REM sleep. However, both of these manipulations increased phasic masseter muscle activity in REM sleep.

Further studies showed that a blockade of glutamate receptors reduces the normal enhancement of muscle tone in waking state relative to the level in non-REM sleep. Glutamate also contributes to the phasic motor activity during REM sleep. However, reduction in glutamate alone is not sufficient to account for the suppression of muscle tone in REM sleep as stimulation of N-Methyl-D-aspartic acid (NMDA) and non-NMDA glutamate receptors does not appear to restore muscle tone in REM sleep.

A study in the anesthetized rat suggested that activation of norepinephrine receptors, in combination with the activation of glutamate receptors was sufficient to potently increase muscle tone in the masseter muscles in REM sleep. A study of the hypoglossal motor nucleus in the unanesthetized rat concluded that the suppression of muscle tone in REM sleep was mediated to a large extent by a reduction in norepinephrine release. Thus this work in the context of prior microdialysis analysis of transmitter release suggests that the reduction of norepinephrine release may be a key factor regulating muscle tone, along with the above described changes in amino acid release. These conclusions are consistent with prior work indicating that cataplexy was linked to a reduction in the activity of noradrenergic neurons. Although the current literature suggests that trigeminal, hypoglossal, and ventral horn motoneurons are subjected to similar neurochemical control across the sleep cycle, direct quantitative comparison of the neurochemical control of these systems has not been made and it is likely that some aspects of control may differ across systems as well as species.

The role of reduced serotonin release in the suppression of muscle tone was investigated in the hypoglossal nucleus of the rat. It was found that the modulation of genioglossus activity across natural sleep-wake states was not greatly affected by endogenous input from serotonergic neurons, although prior studies in vagotomized and anesthetized rats had shown an effect of serotonin on muscle tone under these aphysiological conditions.

Recent work suggests that inhibition of motor output is accompanied by a neurochemically similar inhibition of sensory relays during REM sleep. Such sensory inhibition may be



**Figure 8** Sagittal map of pontomedullary inhibitory areas. Electrical stimulation produced atonia at all the points mapped. All electrically defined inhibitory sites were microinjected with glutamate or cholinergic agonists. Filled symbols represent points at which microinjections decreased muscle tone (to less than 30% of baseline values or to complete atonia). Open circles indicate points at which injections increased or produced no change in baseline values. Glutamate injections are shown at the top, acetylcholine (ACh) and carbachol (Carb) injections at the bottom. At the bottom, circles and triangles represent ACh and Carb injections, respectively. 4V, fourth ventricle; 5ME, mesencephalic trigeminal tract; 6, abducens nucleus; 7G, genu of the facial nerve; IO, inferior olivary nucleus; LC, locus coeruleus nucleus, NGC, nucleus gigantocellularis; NMC, nucleus magnocellularis; NPM, nucleus paramedianus; PG, pontine gray; PT, pyramid tract; SO, superior olivary nucleus; T, nucleus of the trapezoid body; TB, trapezoid body. Reproduced from Lai YY and Siegel JM (1988) Medullary regions mediating atonia. *The Journal of Neuroscience* 8: 4790–4796.

important in preserving sleep, especially by blocking the sensory input produced by twitches breaking through the motor inhibition of REM sleep. The failure of this inhibition may contribute to sleep disruption and increased motor activity in sleep in pathological states.

In contrast to norepinephrine, serotonin, and histamine cell groups, it was reported that mesencephalic dopaminergic

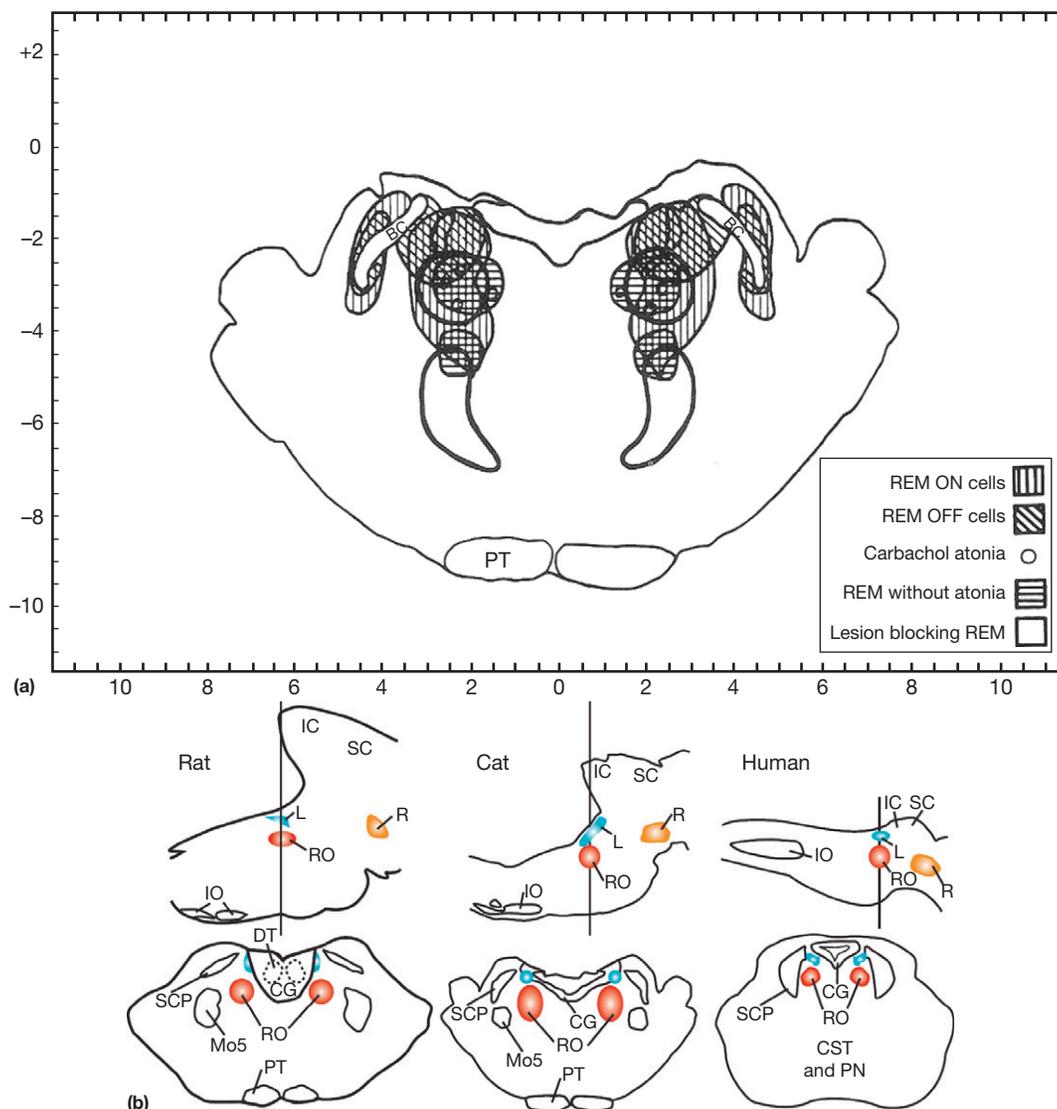
neurons do not appear to alter their discharge rate across the sleep cycle. Dopamine release in the amygdala measured by dialysis does not significantly vary across the sleep cycle. In disagreement with this finding, a Fos study indicated that dopaminergic neurons within the ventral portion of the mesencephalic tegmentum were activated during periods of increased REM sleep. A unit recording study indicated that dopaminergic

neurons in the ventral tegmental area of the midbrain show maximal burst firing in both waking and REM sleep. Other work using the Fos labeling technique identified an active dopaminergic cell population in the ventral periaqueductal gray in the wake state. In dialysis measurements of dopamine release, we have seen reduced dopamine release in the dorsal horn of the spinal cord during the REM sleep-like state triggered by carbachol. We did not see such a decrease in the ventral horn or hypoglossal nucleus. These data suggest either heterogeneity in the behavior of sleep cycle activity of dopaminergic neurons, presynaptic control of dopamine release independent of action potentials in the cell somas or variable vesicle size allowing greater release of transmitters per action potential.

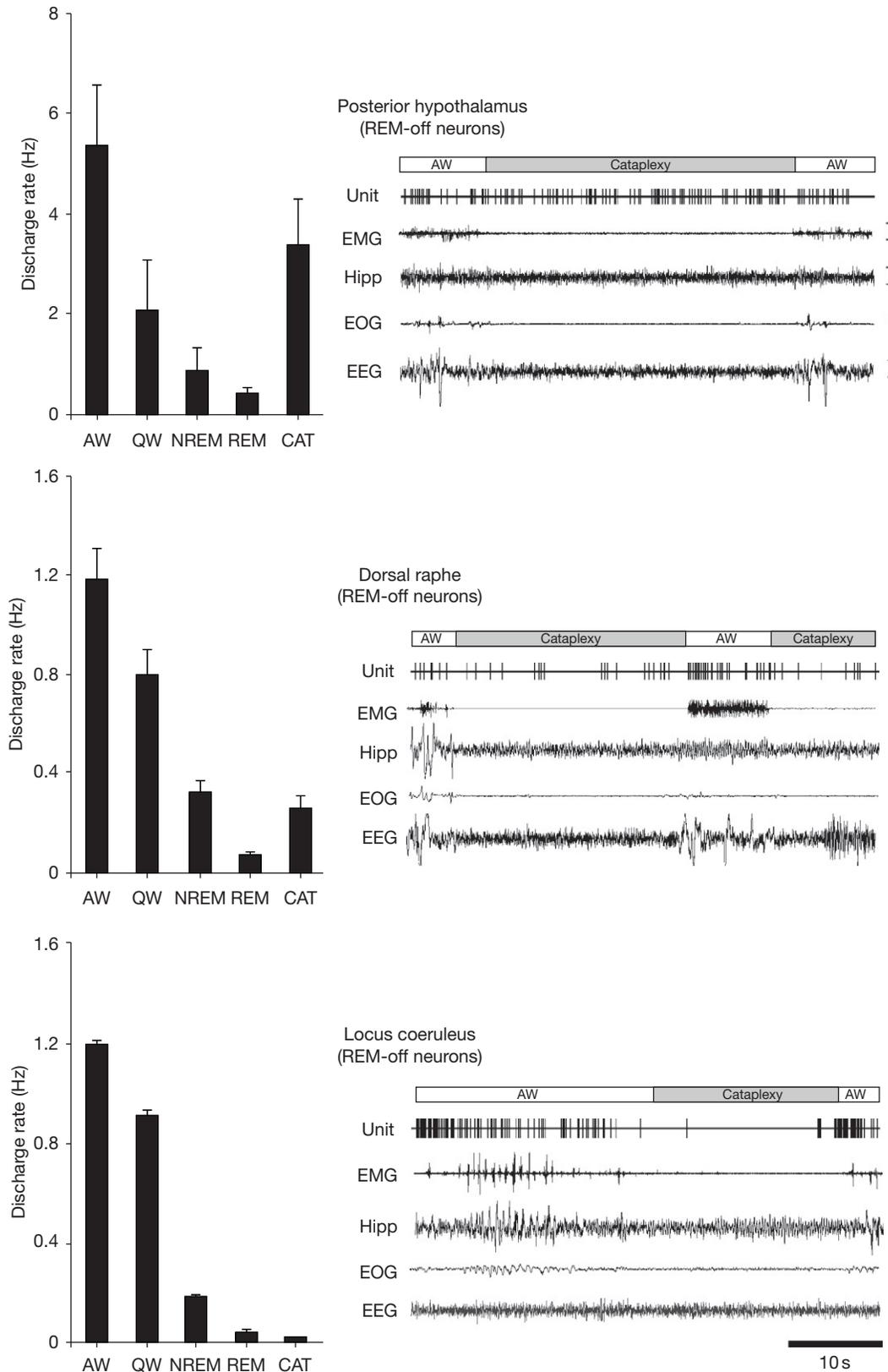
Figure 9 illustrates some of the anatomical and neurochemical substrates of the brainstem generation of REM sleep.

### Narcolepsy and Hypocretin

The persistent sleepiness of narcolepsy appears to be related to activation of sleep-active neurons or disfacilitation of wake-active neurons. Narcolepsy has also been characterized as a disease of the REM sleep mechanism. Narcoleptics often have REM sleep within 5 min of sleep onset, in contrast to normal individuals who rarely show such 'sleep onset REM sleep.' Most narcoleptics experience cataplexy, a sudden loss of muscle tone with the same reflex suppression that is seen in REM sleep. High amplitude theta activity in the hippocampus, characteristic of REM sleep, is also prominent in cataplexy as observed in dogs. Further evidence for links between narcolepsy and REM sleep comes from studies of neuronal activity during cataplexy. Many of the same cell populations in the pons and medulla



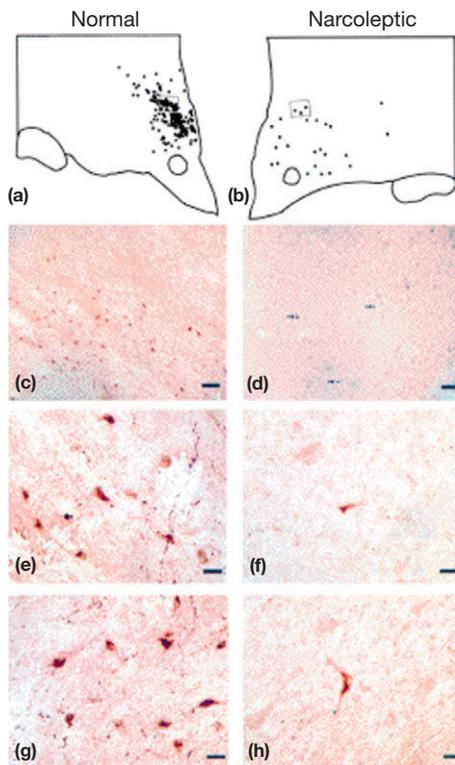
**Figure 9** (a) Top: Anatomic relation of 'REM sleep-on' and 'sleep-off' cells, carbachol-induced atonia sites, lesions blocking atonia but not preventing REM sleep, and lesions completely blocking REM sleep, as indicated by studies in the cat. The REM sleep controlling regions overlap extensively (reproduced from Siegel JM and Rogawski MA (1988) A function for REM sleep: Regulation of noradrenergic receptor sensitivity. *Brain Research* 13: 213–233). (b) Bottom of figure shows anatomical locations of 'REM-on' areas in cat, rat, and projected locations in human, in sagittal and coronal views (reproduced from Siegel JM (2006) The stuff dreams are made of: Anatomical substrates of REM sleep. *Nature Neuroscience* 9: 721–722).



**Figure 10** Comparison of mean discharge rates in sleep-waking states and cataplexy of REM-off cells recorded from three brain regions. Posterior hypothalamic histaminergic neurons remain active, whereas dorsal raphe serotonergic neurons reduced discharge, and locus coeruleus noradrenergic neurons cease discharge during cataplexy. All of these cell types were active in waking, reduced discharge in NREM sleep, and were silent or nearly silent in REM sleep. Reproduced from John J, Wu MF, Boehmer LB, and Siegel JM (2004) Cataplexy-active neurons in the posterior hypothalamus: Implications for the role of histamine in sleep and waking behavior. *Neuron* 42: 619–634.

that are tonically active only during REM sleep in normals, become active during cataplexy in narcoleptics. Likewise, cells in the locus coeruleus, which cease discharge only in REM sleep in normal animals, invariably cease discharge in cataplexy. However, just as cataplexy differs behaviorally from REM sleep in its maintenance of consciousness, not all neuronal aspects of REM sleep are present during cataplexy. As was noted above, in the normal animal, noradrenergic, serotonergic, and histaminergic cells are all tonically active in waking, reduce discharge in non-REM sleep, and cease discharge in REM sleep. However, unlike noradrenergic cells, serotonergic cells do not cease discharge during cataplexy; they only reduce discharge to quiet waking levels. Histaminergic cells actually increase discharge in cataplexy relative to quiet waking levels (Figure 10). These findings allow us to identify some of the cellular substrates of cataplexy. Medullary inhibition and noradrenergic disfacilitation are linked to cataplexy's loss of muscle tone. In contrast the maintained activity of histamine neurons is a likely substrate for the maintenance of consciousness during cataplexy that distinguishes cataplexy from REM sleep. Thus the study of neuronal activity in the narcoleptic animal provides an insight into both narcolepsy and the normal role of these cell groups across the sleep cycle.

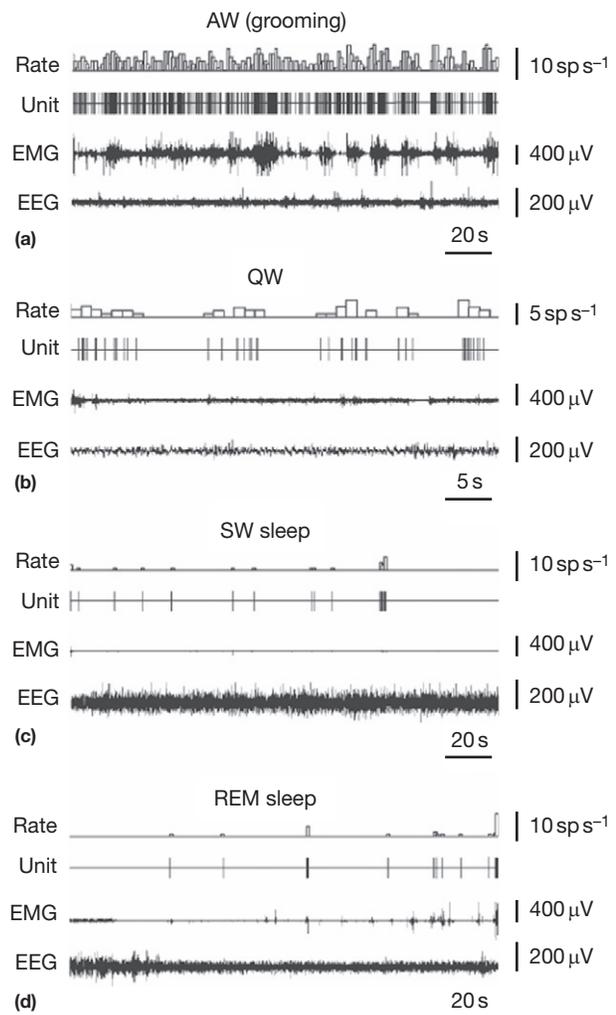
In 2001, it was discovered that most human narcolepsy was caused by a loss of hypothalamic cells containing the peptide hypocretin (Figure 11). On average, 90% of these cells are lost in narcolepsy. Subsequently it was discovered that a lesser



**Figure 11** Loss of hypocretin cells in human narcolepsy. Distribution of cells in perifornical and dorsomedial hypothalamic regions of normal and narcoleptic humans. Reproduced from Thannickal TC, Moore RY, Nienhuis R, et al. (2000) Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 27: 469–474.

reduction in the number of hypocretin cells was seen in Parkinson's disease, with a loss of up to 60% of hypocretin cells. It was found that administration of the peptide to genetically narcoleptic dogs reversed symptoms of the disorder and that nasal administration reversed sleepiness in monkeys, suggesting that similar treatment could be uniquely effective for narcolepsy and perhaps for other disorders characterized by sleepiness.

In further work in normal animals it was determined that identified hypocretin neurons fire maximally during active waking (Figure 12). This discharge was reduced or absent during aversive waking situations, even if the EEG indicated



**Figure 12** Firing Rate of hypocretin cells in waking and sleep behaviors in freely moving rats. The discharge pattern of a representative hypocretin neuron across the sleep-waking cycle in the freely moving rat. (a) High firing rates are seen during AW (active waking–grooming). (b) Reduced firing rate or cessation of activity is seen in QW (quiet waking) and drowsiness. (c) A further decrease or cessation of firing is seen during SW sleep. (d) Minimal firing rate is seen during the tonic phase of REM sleep. Brief Hcrt cell discharge bursts are correlated with muscle twitches during the phasic events of REM sleep. Reproduced from Mileykovskiy BY, Lyudmila I, Kiyashchenko LI, and Siegel JM (2005) Behavioral correlates of activity in identified hypocretin (orexin) neurons. *Neuron* 46: 787–798.

high levels of alertness. This is consistent with the hypothesis that release of hypocretin facilitates motor activity during emotionally charged activities of the sort that trigger cataplexy in narcoleptics such as laughter. Even normal individuals experience weakness at these times, seen in the 'doubling over' that often accompanies laughter or the weakness that can result from other sudden onset of strong emotions. Studies of hypocretin release in the cat and preliminary studies in humans are also consistent with this hypothesis. In the absence of the hypocretin mediated motor facilitation, muscle tone is lost at these times. Hypocretin cells also send ascending projections to cortical and basal forebrain regions. In the absence of hypocretin mediated facilitation of forebrain arousal centers, waking periods are truncated, resulting in the sleepiness of narcolepsy.

Hypocretin appears to act largely by modulating the release of amino acid neurotransmitters. Systemic injection of hypocretin causes a release of glutamate in certain hypocretin innervated regions producing a potent postsynaptic excitation. In other regions it facilitates GABA release, producing postsynaptic inhibition. The loss of these competing inhibitory and facilitatory influences in narcolepsy appears to leave brain motor regulatory and arousal systems less stable than the tightly regulated balance that can be maintained in the presence of hypocretin (Figure 13). According to this hypothesis, this loss of stability is the underlying cause of narcolepsy, with the result being inappropriate loss of muscle tone in waking and inappropriate increases of muscle tone during sleep resulting in a striking increased incidence of RBD in narcoleptics. In the same manner, although a principal symptom of narcolepsy is intrusions of sleep into the waking period, narcoleptics sleep poorly at night with frequent awakenings. In other

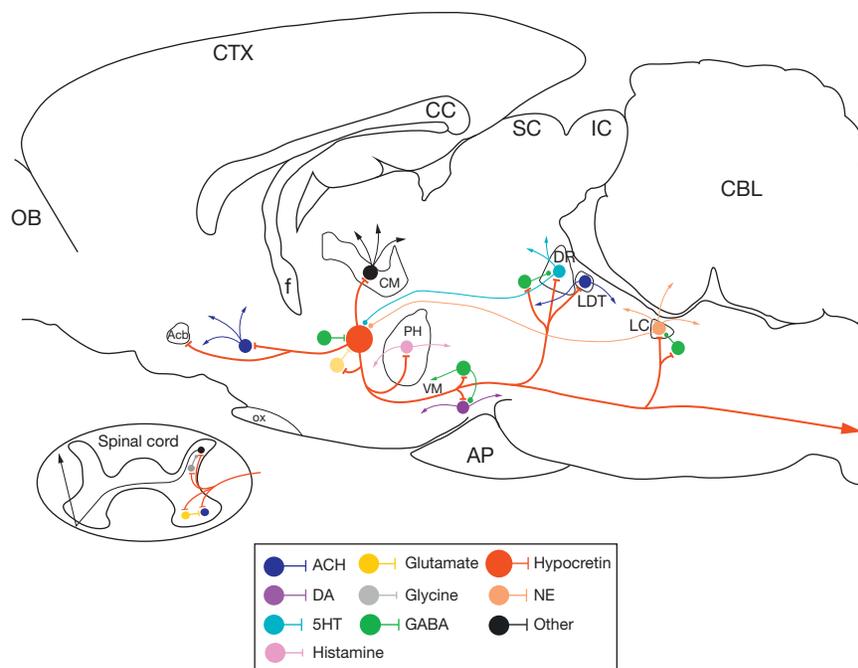
words, narcoleptics are not simply weaker and sleepier than normals. Rather, their muscle tone and sleep-waking state regulation is less stable than that in normals as a result of the loss of hypocretin function.

## The Functions of Sleep

A discussion of the function(s) of REM and non-REM sleep is beyond the scope of this article. However, phylogenetic data and a critical consideration of physiological data suggest that a universal function of sleep is to conserve energy and time – behavior for conditions optimal for acquiring food and escaping predators. Other functions that can be fulfilled in some species in waking may have 'migrated' into sleep in some species. Genetic success is best served by maximizing sleep time when vital needs have been met. This contrasts with the demands and attractions of human society, which values waking activity for entertainment and professional advancement. But, as in other animals, increased wake time in humans does not necessarily produce a genetic advantage in terms of maximizing offspring.

## Acknowledgments

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**Figure 13** Major identified synaptic interactions of hypocretin neurons. Lines terminated by perpendicular lines denote excitation; circular terminations indicate inhibition. ACH, acetylcholine; DA, dopamine; NE, norepinephrine; 5HT, serotonin; OB, olfactory bulb; Acb, nucleus accumbens; f, fornix; OX, optic chiasm; CM, centromedian nucleus of the thalamus; PH, posterior hypothalamus; VM, ventral midbrain; AP, anterior pituitary; SC, superior colliculus; IC, inferior colliculus; DR, dorsal raphe; LDT, laterodorsal tegmental and pedunculopontine; LC, locus coeruleus; CBL, cerebellum. Reproduced from Siegel JM (2004) Hypocretin (orexin): Role in normal behavior and neuropathology. *Annual Review of Psychology* 55: 125–148.

**See also: Background:** Evolution of Sleep (Sleep Phylogeny); Mammalian Sleep; Neurotransmitters and Neuropharmacology of Sleep/Wake Regulations; Sleep in Aquatic Species; Sleep in Birds; **Critical Theoretical and Practical Issues:** The Function of Sleep; **Features, Factors, and Characteristics of Hypersomnias:** The History of Narcolepsy; **Sleep and the Nervous System:** Basic Sleep–Wake Mechanisms; Electrophysiology of Sleep–Wake Systems; Neurochemistry of Sleep; NREM Sleep: Anatomy and Physiology; NREM–REM Sleep Regulation.

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### Relevant Website

<http://www.npi.ucla.edu/sleepresearch> – Center for Sleep Research/UCLA.