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REM Sleep

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ABSTRACT

Rapid eye movement (REM) sleep was first identified by its most obvious behavior: rapid eye movements during sleep. In most adult mammals, the electroencephalogram (EEG) of the neocortex is low in voltage during REM sleep. The hippocampus has regular high-voltage theta waves throughout REM sleep.

The key brain structure for generating REM sleep is the brainstem, particularly the pons and adjacent portions of the midbrain. These areas and the hypothalamus contain cells that are maximally active in REM sleep, called REM-on cells, and cells that are minimally active in REM sleep, called REM-off cells. Subgroups of REM-on cells use the transmitters gamma-aminobutyric acid (GABA), acetylcholine, glutamate, or glycine. Subgroups of REM-off cells use the transmitters norepinephrine, epinephrine, serotonin, and histamine. It is likely that interactions between REM-on and REM-off cells control the key phenomena of REM sleep.

Destruction of the entire area of midbrain and pons responsible for REM sleep generation can prevent the occurrence of this state. Damage to portions of the brainstem can cause abnormalities in certain aspects of REM sleep. Of particular interest are manipulations that affect the regulation of muscle tone in REM sleep. Lesions in the pons and medulla cause REM sleep to occur without the normal loss of muscle tone. In REM sleep without atonia, animals exhibit locomotor activity, appear to attack imaginary objects, and execute other motor programs during a state that otherwise resembles REM sleep. This syndrome may have some commonalties with the REM sleep behavior disorder seen in humans. Stimulation of portions of the REM sleep–controlling area of the pons can produce a loss of muscle tone in antigravity and respiratory musculature.

Hypocretin neurons, located in the hypothalamus, contribute to the regulation of the activity of norepinephrine, serotonin, histamine, and acetylcholine cell groups and have potent effects on arousal and motor control. Most cases of narcolepsy are caused by a loss of hypocretin neurons.

OVERVIEW

In this chapter I discuss the defining characteristics of rapid eye movement (REM) sleep, including its physiology and neurochemistry. I review how the amounts of REM sleep differ across the animal kingdom. I consider the advantages and disadvantages of the techniques used to investigate the mechanisms generating REM sleep, and discuss the conclusions of these investigations. I examine the mechanisms responsible for the suppression of muscle tone during REM sleep and the pathologic effects of the disruption of these mechanisms. I discuss narcolepsy and its link to mechanisms involved in REM sleep control and especially to the peptide hypocretin. Finally, I speculate about the functions of REM sleep.

WHAT IS REM SLEEP?

REM sleep was discovered by Aserinsky and Kleitman in 1953.[1] They found that it was characterized by the periodic recurrence of rapid eye movements, linked to a dramatic reduction in the amplitude of the electroencephalogram (EEG). They found that the EEG of REM sleep closely resembled the EEG of alert waking and reported that subjects awakened from REM sleep reported vivid dreams. Dement identified a similar state of low-voltage EEG with eye movements in cats.[2] Jouvet then repeated this observation, finding in addition a loss of muscle tone (atonia) in REM sleep and using the name *paradoxical sleep* to refer to this state. The "paradox" was that the EEG resembled that of waking, whereas behaviorally the animal remained asleep and unresponsive.[3] Subsequent authors have described this state as "activated" sleep, or "dream" sleep. Recent work in humans has shown that some mental activity can be present in non-REM sleep but has supported the original finding linking our most vivid dreams to the REM sleep state.[1]

Most early work was done in cats, and it is in the cat that most of the "classic" signs of REM sleep and their generating mechanisms were discovered. Figure 10–1, top, shows the principal electrical signs of REM sleep. These include the reduction in EEG amplitude, particularly in the amplitude of its lower-frequency components. REM sleep is also characterized by a suppression of muscle tone (atonia), visible in the electromyogram (EMG). Erections tend to occur in men and clitoral enlargement in women. Thermoregulation largely ceases, and animal body temperatures drift toward environmental temperatures, as in reptiles.[4] 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 large electrical potentials that can be most easily recorded in the lateral geniculate nucleus.[5] These potentials originate in the pons, appear after a few milliseconds in the lateral geniculate nucleus, and can be observed with further delay in the occipital cortex, leading to the name *ponto-geniculo-occipital* (PGO) spikes. They occur as large-amplitude, isolated potentials appearing 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 to 10 waves usually correlated with rapid eye movements. PGO-linked potentials can also be recorded in the motor nuclei of the extraocular muscles, where they trigger the rapid eye movements of REM sleep. They are present, in addition, in thalamic nuclei other than the geniculate and in neocortical regions other than the occipital cortex. In humans, rapid eye

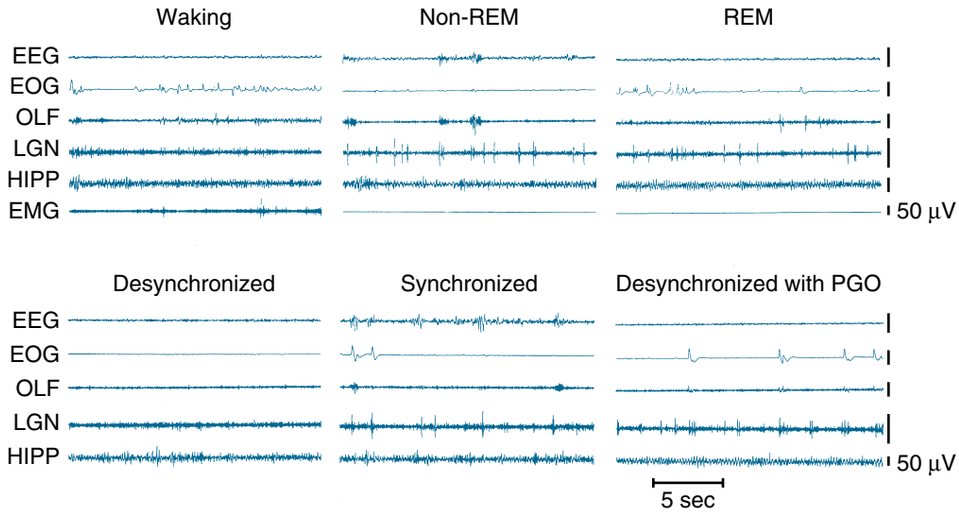

Figure 10–1. *Top,* Polygraph tracings of states seen in the intact cat. *Bottom,* States seen in the forebrain 4 days after transection at the pontomedullary junction. EEG, sensorimotor electroencephalogram; EOG, electrooculogram; OLF, olfactory bulb; LGN, lateral geniculate nucleus; HIPP, hippocampus; EMG, dorsal neck electromyogram. (From Siegel JM, Nienhuis R, Tomaszewski KS: REM sleep signs rostral to chronic transections at the pontomedullary junction. Neurosci Lett 1984;45:241-246, with permission.)

movements are loosely correlated with contractions of the muscles of the middle ear of the sort that accompany speech generation and that are part of the protective response to loud noise.[6] Other muscles also contract during periods of rapid eye movement, briefly breaking through the tonic muscle atonia of REM sleep. There are periods of marked irregularity in respiratory and heart rates during REM sleep, in contrast to non-REM sleep, during which respiration and heart rate are highly regular. There does not appear to be any single pacemaker for all of this irregular activity. Rather, the signals producing twitches of the peripheral or middle ear muscles may lead or follow PGO spikes and rapid eye movements. Bursts of brainstem neuronal activity may likewise lead or follow the activity of any particular recorded muscle.[7-9] These changes that occur episodically in REM sleep have been called its *phasic* features.

As we will see later, certain manipulations of the brainstem can eliminate only the phasic events of REM sleep, whereas others can cause the phasic events to occur in waking; yet other manipulations can affect tonic components. These tonic and phasic features are also expressed to varying extents in different species, and not all of these features are present in all species that have been observed to have REM sleep.

THE DISTRIBUTION OF REM SLEEP IN THE ANIMAL KINGDOM

The identification of REM sleep in the cat indicated that it was not necessarily a correlate of some uniquely human mental state. It soon became apparent that REM sleep was widespread, perhaps even universal in mammals and birds[10] (see Chapter 8). However, a few important exceptions have been identified. Early work investigated the sleep of an egg-laying monotreme mammal, the echidna, an anteater found only in Australia. A thorough study of the echidna EEG by Allison and coworkers showed that this animal did not have any periods of sleep with a low-voltage cortical EEG.[11] This led to the hypothesis that primitive mammals did not have REM sleep, which must therefore have evolved after the divergence of the monotremes from the placental and marsupial mammalian lines. We reexamined this question, looking at brainstem neuronal activity in addition to the EEG for signs of REM sleep. Although we confirmed Allison and colleagues' observation of no low-voltage EEG during sleep, we found that brainstem neurons exhibited the phasic pattern of activation characteristic of REM sleep while the EEG voltage was elevated.[12] A similar conclusion was reached by Nicol et al.[13]

We then went on to examine the only other available monotreme species, the platypus. We found that most of the sleep time in this animal was also characterized by a high-voltage EEG, as in non-REM sleep. However, dramatic phasic motor activity was visible almost continuously throughout sleep in the platypus. (A video of this activity can be seen at our web site [http://www.npi.ucla.edu/sleepresearch] and at the PPSM web site). The platypus has more REM sleep, approximately 8 hours per day, than any other any other animal.[14] An altered distribution of monoaminergic and particularly cholinergic cells in the brainstems and forebrains of monotreme mammals may be the anatomic substrate of this unusual REM sleep pattern.[15–17] Other animals with high amounts of REM sleep are the ferret, armadillo, and possum (see Chapter 8).

Marine mammals also have unusual sleep patterns that may provide an insight into the evolution and function of REM sleep. Dolphins and other cetaceans have slow waves in only one hemisphere at a time, never showing the bilateral slow waves characteristic of non-REM sleep in terrestrial mammals.[18] This EEG pattern is often present while they swim, avoid obstacles, and appear generally responsive to the environment. If they are disturbed whenever slow waves appear on one side of the brain, they display a rebound of slow waves in that hemisphere when they are subsequently left undisturbed, that is, they have a unihemispheric slow wave sleep (SWS or non-REM sleep) rebound.[19] It is unclear whether dolphins or other cetaceans have REM sleep. One approach to detecting REM sleep in these mammals is to look for signs of phasic

events during rest states, although determining which phasic events might correspond to REM sleep twitches and which might be the cetacean equivalent of myoclonic jerks occurring in non-REM sleep is a difficult task. What is already clear is that very few such jerks occur, on the order of 10 to 100 per day, compared with approximately 3000 in the rat. If these events are the correlates of REM sleep in the dolphin, then these animals have some of the smallest amounts of REM sleep observed in any mammalian species, perhaps less than 15 minutes/day.

The fur seal also has an unusual sleep pattern. When quiescent in the water, it assumes an asymmetrical posture, paddling with one flipper while the contralateral flipper remains immobile. The EEG of the hemisphere contralateral to the immobile flipper shows slow waves. Very little REM sleep is seen while the seal is in the water, although REM sleep is apparent on land, when bilateral cortical EEG sleep is seen.[20] Despite the suppression of REM sleep in the water, there is no rebound of REM sleep beyond baseline levels when the seal returns to land.

The average daily amount of REM sleep for a given species appears to be strongly related to how immature it is at birth[21] (see Chapter 8). Animals that are born in a helpless state, as is the case with the platypus, ferret, possum, and armadillo, have high amounts of REM sleep at birth, suggesting that REM sleep may have some role in the development of the brain and body. However, although amounts of REM sleep decrease with age, these animals also have higher amounts of REM sleep as adults, for reasons that remain unclear. In contrast, animals that are born relatively mature, such as the dolphin, which must swim and defend itself from birth, and grazing animals such as the horse or cattle (see Chapter 8), have very little REM sleep either at birth or later in life. Humans fall in the middle, with moderate amounts of REM sleep corresponding to their intermediate level of immaturity at birth.

Birds have REM sleep, although in much smaller amounts than mammals, with REM sleep episodes often lasting only a few seconds.[10] Because birds and mammals diverged from a common reptilian ancestor, we examined sleep in the turtle, using the same neuronal recording technique we had used to detect REM sleep in the echidna. We found no evidence for phasic neuronal activity during sleep.[22] Together, these results suggest a link between REM sleep and homeothermy, but the nature of the link remains unclear.

REM GENERATION MECHANISMS

Technical Considerations: Lesions

More has been learned about brain function and sleep control from brain damage caused by stroke, injury, or infection in patients and by experimentally induced brain lesions in animals, than by any other technique. However, some basic principles need to be borne in mind when interpreting such data.

Brain lesions can result from ischemia, pressure, trauma, and degenerative or metabolic changes. In animals, experimental lesions are most commonly induced by aspiration, transection of the neuraxis, electrolysis, local heating by radiofrequency currents, or by the injection of cytotoxins. The latter include substances such as *N*-methyl-D-aspartate (NMDA) and kainate that cause cell death by excitotoxicity as well as targeted cytotoxins such as saporin coupled to particular ligands, which kill only cells containing receptors for that ligand. Cytotoxic techniques have the considerable advantage of sparing axons passing through the region of damage, so that deficits are attributable to the loss of local neurons, rather than axons of passage.

If damage to a particular region causes the loss of a sleep state, one cannot conclude that this is where a "center" for the state resides. Lesion effects are usually maximal immediately after the lesion is created. Swelling and circulatory disruption make the functional loss larger than will be apparent from standard postmortem histologic techniques. The loss of one brain region can also disrupt functions that are organized elsewhere. For example, spinal shock is a well known phenomenon in which severing the spinal cord's connection to more rostral brain regions causes a loss of functions known to be mediated by circuits intrinsic to the spinal cord.

On the other hand, with the passage of time, this sort of denervation-induced shock dissipates. In addition, adaptive changes occur that allow other regions to take over lost functions. This is mediated by sprouting of new connections to compensate for the loss. A striking phenomenon seen after placement of lesions aimed at identifying the brain regions responsible for REM and non-REM sleep is that even massive lesions often produce only a transient disruption of sleep.

A particularly useful approach to the understanding of REM sleep generation has been the transection technique. In this approach, the neuraxis is severed at the spinomedullary junction, at various brainstem levels, or at various forebrain levels by passing a knife across the coronal plane of the neuraxis. Regions rostral to the cut may be left in situ or may be removed. One might expect that such a manipulation would completely prevent sleep phenomena from appearing on either side of this cut, as in the phenomenon of spinal shock. However, to a surprising extent this is not the case. As I review later, REM sleep reappears within hours after some of these lesions. When both parts of the brain remain, signs usually appear on only one side of the cut. This kind of positive evidence is much more easily interpreted than loss of function, because one can with certainty state that the removed regions are not essential for the signs of REM sleep that survive.

Technical Considerations: Stimulation

Sites identified by lesion or anatomic data can be stimulated to identify their roles in sleep control. Older studies used electrical stimulation and were successful in identifying the basal forebrain as a sleep-inducing region (see Chapter 13) and the medial medulla as a region mediating the suppression of muscle tone.[23] Electrical stimulation is an obviously aphysiologic technique, involving the forced depolarization of neuronal membranes by ion flow at a frequency set by the stimulation device, rather than by the patterned afferent impulses that normally control neuronal discharge. For this reason, it has largely been supplanted by administration of neurotransmitter agonists, either by direct microinjection or by diffusion from a microdialysis membrane that is placed in the target area and perfused with high concentrations of agonists. One cannot, however, assume that responses produced by such agonist administration demonstrate a normal role for the applied ligand. For example, many transmitter agonists and antagonists have been administered to the pontine regions thought to trigger REM sleep. In some cases this administration has increased REM sleep. But we can conclude from this only that cells in the region of infusion have receptors for the ligand and

have connections to REM sleep–generating mechanisms. Under normal conditions these receptors may not have a role in triggering the state. Only by showing that the administration duplicates the normal pattern of release of the ligand in this area, and that blockade of the activated receptors prevents REM sleep, can a reasonable suspicion be raised that a part of the normal REM sleep control pathway has been identified. Because it is far easier to inject a substance than to collect and quantify physiologically released ligands, there have been many studies implying that various substances are critical for REM sleep control based solely on microinjection. These results must be interpreted with caution.

Technical Considerations: Recording

Observation of the normal pattern of neurotransmitter release and neuronal activity can help determine the neurochemical correlates of sleep states. The natural release of ligands can be most easily determined by placing a tubular dialysis membrane 1 to 5 mm in length in the area of interest and circulating artificial cerebrospinal fluid through it. Neurotransmitters released outside the membrane diffuse through the membrane and can be collected. Each sample is collected at intervals typically ranging from 2 to 10 minutes. The collected dialysates can be analyzed by chromatography, radioimmunoassay, or other means.

Recording the activity of single neurons in vivo can provide a powerful insight into the precise time course of neuronal discharge. Unit activity can be combined with other techniques to make it even more useful. For example, electrical stimulation of potential target areas can be used to identify antidromically the axonal projections of the recorded cell. Intracellular labeling of neurons with dyes, with subsequent immunolabeling of their transmitter, can be used to determine the neurotransmitter phenotype of the recorded cell. Combined dialysis and unit recording or iontophoresis of neurotransmitter from multiple-barrel recording and stimulating micropipettes can be used to determine the transmitter response of the recorded cell, although one cannot easily determine if the effects seen are the direct result of responses in the recorded cell or are mediated by an adjacent responsive cell projecting to the recorded cell. Such distinctions can be made in in vitro studies by blocking synaptic transmission or physically dissociating studied cells, but in this case their role in sleep may not be easily determined.

Although the role of a neuron in fast, synaptically mediated events can be traced by inspection of neuronal discharge and comparison of that discharge with the timing of motor or sensory events, such an approach may be misleading when applied to the analysis of sleep generation. The sleep cycle consists of a gradual coordinated change in EEG, EMG, and other phenomena over a period of seconds to minutes, as waking turns into non-REM sleep and then as non-REM sleep is transformed into REM sleep. Neuronal activity can traverse the human brain in as little as 5 msec. Despite this mismatch of time courses, the "tonic latency," a measure of how long before REM sleep onset activity in a recorded cell changes, has been computed. Neurons purported to show a significant change in activity many seconds or even minutes before REM sleep onset have been reported. However, such a measure is of little utility because at the neuronal level, the activity of key cell groups can best be seen as curvilinear over the sleep cycle, rather than changing abruptly in the way that activity follows discrete sensory stimulation. A major determinant of the tonic latency, computed as defined previously, is the level of "noise" or variability in the cell's discharge, which affects the difficulty of detecting a significant underlying change in rate. It is therefore not surprising that cell groups designated as "executive neurons" for REM sleep control on the basis of their tonic latencies were later found to have no essential role in the generation of REM sleep.[24] The more appropriate comparison of the unit activity cycle to state control is to compare two different cell types to see what the phase relation is. This kind of study is difficult, involving the simultaneous long-term recording of multiple cells, and is rarely performed. Even in this case, a phase lead does not by itself prove that the "lead" neuron is driving activity seen in the "following" neuron.

Technical Considerations: Summary

Clearly there is no perfect technique for determining the neuronal substrates of sleep states. Nevertheless, there are certain common pitfalls that must be kept in mind in interpreting experimental manipulations designed to analyze sleep states. The next sections explore the major findings derived from lesion, stimulation, and recording studies of REM sleep control mechanisms.

Transection Studies

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 (Fig. 10–2, level A). This decerebrate rigidity was visible as soon as anesthesia was discontinued. Bard and Macht first reported that animals with decerebrate rigidity would show periodic limb relaxation.[25] 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,[2] Jouvet found that this state of EEG desynchrony was normally accompanied by muscle atonia.[3] Jouvet then examined the decerebrate cat preparation used by Sherrington and Bard, now adding measures of muscle tone, eye movement, and EEG. One might have expected that the "dream state" originated in the forebrain, but Jouvet found something quite different. When he recorded in the forebrain after separating the forebrain from the brainstem at the midbrain level (Fig. 10–2, 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, but when low-voltage activity appeared, the PGO spikes that help identify REM sleep in the intact animal were absent from the thalamic structures, particularly the lateral geniculate, where they can be most easily recorded. Thus, it appeared that the isolated forebrain had SWS 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.

An interesting feature of REM sleep in the decerebrate animal is that its frequency and duration varied with the

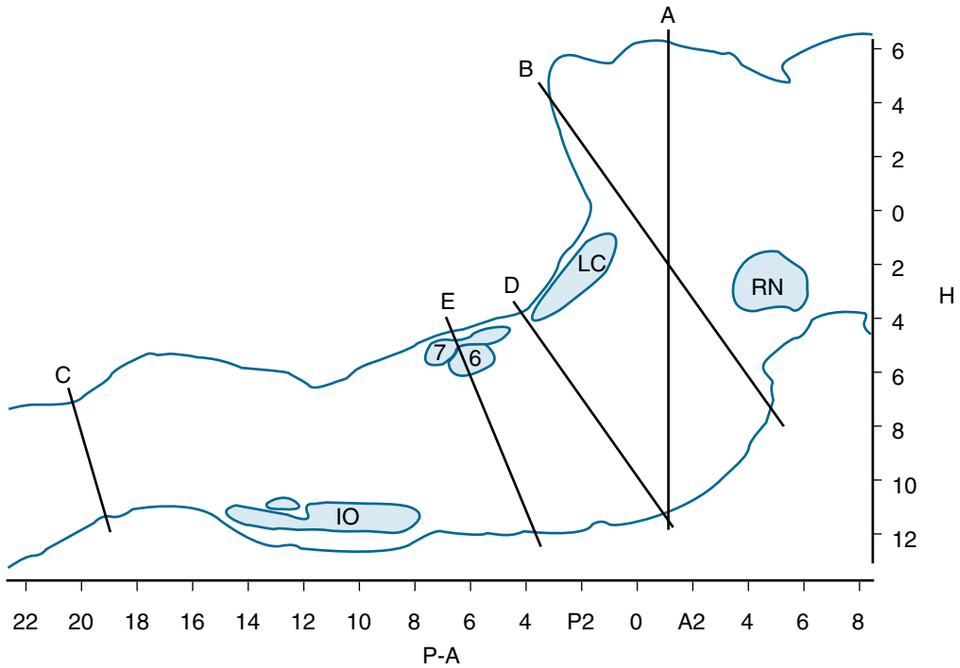

Figure 10–2. Outline of a sagittal section of the brainstem of the cat drawn from level L = 1.6 of the Berman atlas, indicating the level of key brainstem transection studies. A and B, midbrain-pontine junction; D, caudal pons; E, ponto-medullary junction; C, spino-medullary junction; RN, red nucleus; LC, locus coeruleus; 6, abducens nucleus; 7, genu of the facial nerve; IO, inferior olive. H (horizontal) and P-A (posterior-anterior) scales are drawn from the atlas. (From Siegel JM: Pontomedullary interactions in the generation of REM sleep. In McGinty DJ, Drucker-Colin R, Morrison A, Parmeggiani PL [eds]: Brain Mechanisms of Sleep. New York, Raven Press, 1985, pp 157-174, with permission.)

temperature of the animal. In the decerebrate animal, the forebrain thermoregulatory mechanisms are disconnected from their brainstem effectors. Shivering and panting do not occur at the relatively small temperature shifts that trigger them in the intact animal. For this reason, if the body temperature is not maintained by external heating or cooling, it tends to drift toward room temperature. Arnulf et al.[26] found that if body temperature was maintained at a normal level, little or no REM sleep appeared. But if temperature was allowed to fall, REM sleep amounts increased to levels well above those seen in the intact animal. This suggests that REM sleep facilitatory mechanisms are on balance less impaired by reduced temperature than are REM sleep inhibitory mechanisms. Another way of looking at this phenomenon is that brainstem mechanisms are set to respond to low temperatures by triggering REM sleep, perhaps to stimulate the brainstem, and that high brainstem temperatures inhibit REM sleep. In the absence of forebrain control, major increases in REM sleep can be seen with temperature shifts that do not normally occur in the intact animal. However, a more sensitive mechanism may be operative in the intact animal.

A further localization of the REM sleep control mechanisms can be achieved by examining the sleep of humans or animals in which the brainstem–spinal cord connection has been severed (Fig. 10–2, level C). In this case, normal REM sleep in all its manifestations, except for spinally mediated atonia, is present.[27] Thus, we can conclude that the region between the caudal medulla and rostral midbrain is sufficient to generate REM sleep.

A further localization of REM sleep–generating mechanisms can be achieved by separating the caudal pons from the medulla (Fig. 10–2, level D or E). In such animals no atonia is present. 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 highly periodic rate modulation that is linked to the phasic events of REM sleep in the intact animal[28] (Fig. 10–3). This demonstrates that the medulla and spinal cord together are not sufficient to generate this aspect of REM sleep.

In contrast, the regions rostral to the cut show aspects of REM sleep[29] (Fig. 10–1, bottom; Fig. 10–4). 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.[30]

To summarize, this work shows that when pontine regions are connected to the medulla, atonia, the rapid eye movements of REM sleep, and the associated unit activity patterns 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 comes from the studies of Matsuzaki.[31] 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.

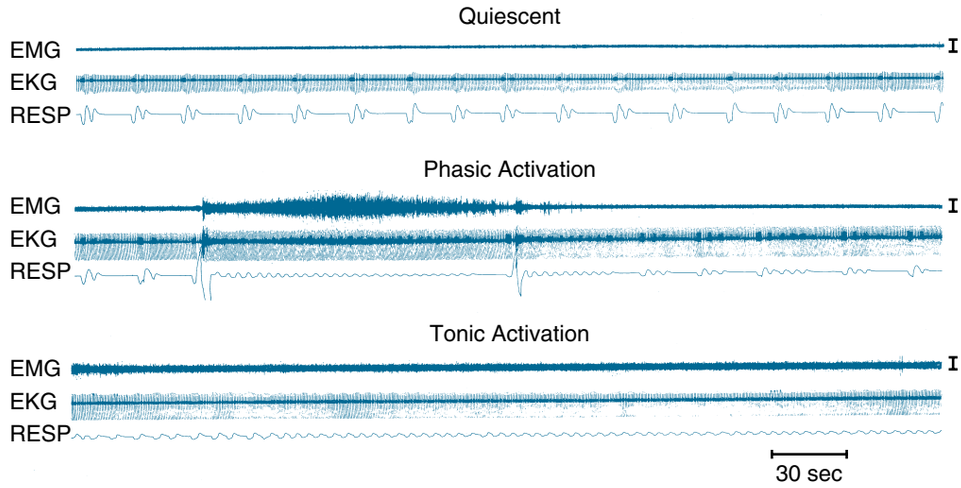

Figure 10–3. States seen in the chronic medullary cat. Note the absence of periods of atonia. EKG, electrocardiogram; EMG, electromyogram; RESP, thoracic strain gauge. Calibration, 50 μV. (From Siegel JM, Tomaszewski KS, Nienhuis R: Behavioral states in the chronic medullary and mid-pontine cat. Electroencephalogr Clin Neurophysiol 1986;63:274-288, with permission.)

These transection studies demonstrate, by 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 characterize REM sleep. One can fairly characterize the pons as the crucial region for the generation of REM sleep.

However, it is also clear that the pons alone does not generate REM sleep. Atonia requires 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.[32] Extrapolating to human dream imagery, one can hypothesize that because 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.

Lesion Studies

The transection studies point to a relatively small portion of the brainstem, the pons and caudal midbrain, as critical for REM sleep generation. Further specification of the critical regions can be achieved by destroying portions of the pons in

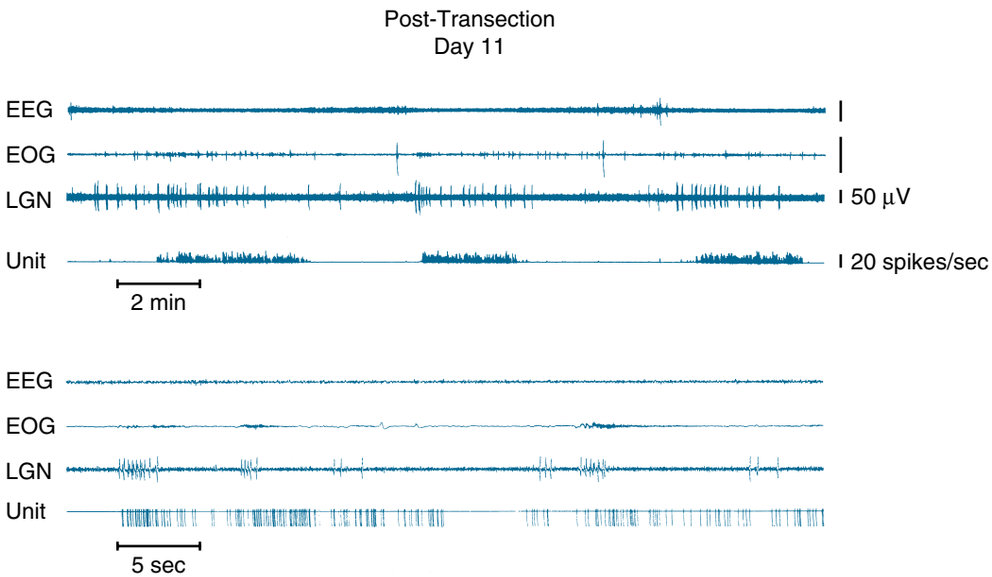

Figure 10–4. Midbrain unit: electroencephalographic (EEG), electrooculographic (EOG), and lateral geniculate nucleus (LGN) activity rostral to chronic transections at the pontomedullary junction. In the upper portion of the figure, the unit channel displays the output of an integrating digital counter resetting at 1-second intervals. In the lower portion, one pulse is produced for each spike by a window discriminator. The figure shows that bursts of PGOs are correlated with increased neuronal ("unit") activity. PGO, ponto-geniculo-occipital. (From Siegel JM: Pontomedullary interactions in the generation of REM sleep. In McGinty DJ, Drucker-Colin R, Morrison A, Parmeggiani PL [eds]: Brain Mechanisms of Sleep. New York, Raven Press, 1985, pp 157-174, with permission.)

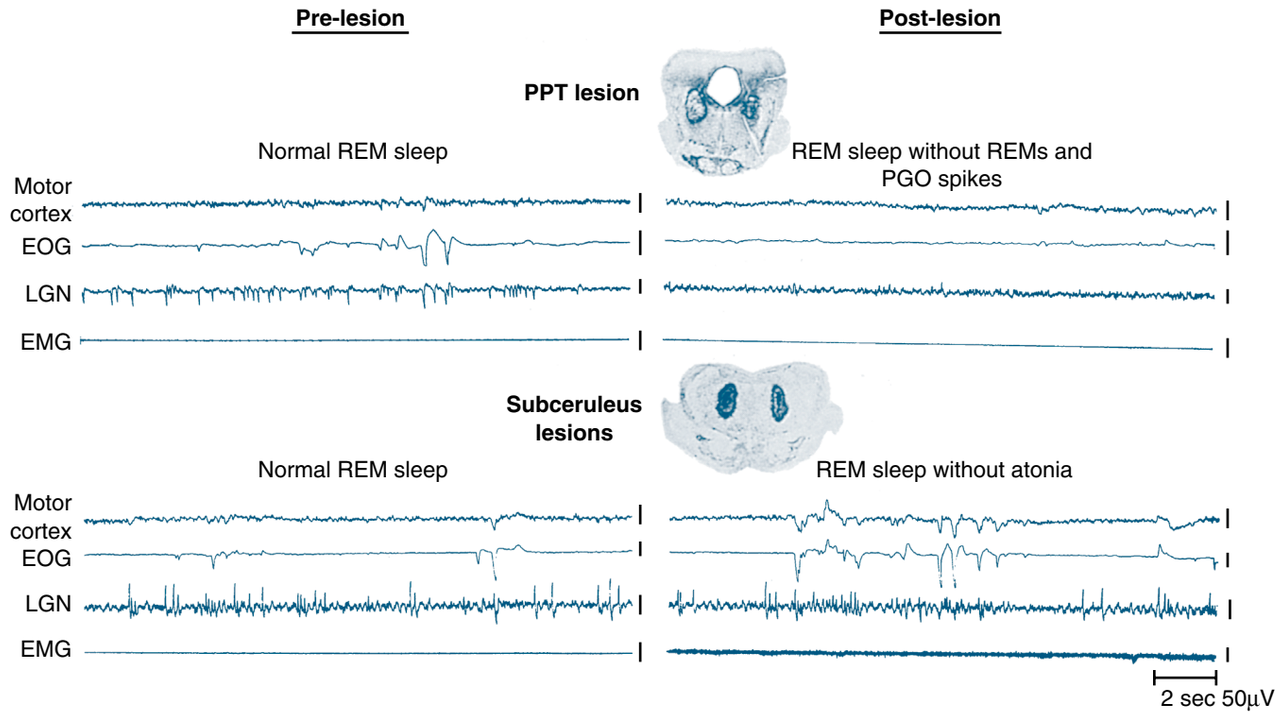

Figure 10–5. Twenty-second polygraph tracings of REM sleep before and after lesions, together with a coronal section through the center of the pontine lesions. Electroencephalographic voltage reduction of REM sleep (recorded from motor cortex) was present after both lesions. *Top,* Radiofrequency lesions of the pedunculopontine 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, Siegel JM: Pontine regulation of REM sleep components in cats: Integrity of the pedunculopontine tegmentum [PPT] is important for phasic events but unnecessary for atonia during REM sleep. Brain Research, vol 571, 50-63, Copyright 1992, with permission from Elsevier Science.)

an otherwise intact animal and seeing which areas are necessary and which are unnecessary for REM sleep generation. An early, exhaustive study by Carli and Zanchetti[33] and other subsequent studies emphasized that lesions of the locus coeruleus[34] and the dorsal raphe[35] nuclei did not block REM sleep. Carli and Zanchetti concluded that lesions that destroyed the region ventral to the locus coeruleus, called the nucleus reticularis pontis oralis or the subcoeruleus region, eliminated or produced a massive decrease in the amount of REM sleep. In their studies, Carli and Zanchetti used the electrolytic lesion technique, in which a current is passed depositing metal that kills cells and axons of passage. As cytotoxic techniques that allowed poisoning of cell bodies without the mechanical damage to the brain substance and axons of passage came into use, these initial conclusions were confirmed and refined. It was shown that neurons in medial 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.[36] However, lesions of the subcoeruleus and adjacent regions produced with cytotoxins did cause a prolonged loss 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.[37]

Although large lesions may eliminate all aspects of REM sleep, small, bilaterally symmetrical lesions in 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 rapid eye movements are absent when lesions include the region surrounding the superior cerebellar peduncle[38] (Fig. 10–5, top). This points to the role of this lateral region in the generation of PGO waves and the associated phasic activity of REM sleep.

Lesions confined to portions of the subcoeruleus regions identified as critical for REM sleep by Carli and Zanchetti, or to the medial medulla,[39] 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[40] (Fig. 10–5, bottom). During "REM sleep without atonia," these animals appear to act out their dreams, attacking objects that are not visible, exhibiting unusual affective behaviors and ataxic locomotion. When "awakened," normal waking behavior resumes. The critical region, termed the *pontine inhibitory area* (PIA), appears to be responsible for the normal coupling of atonia to REM sleep.

Stimulation Studies

The first study showing that stimulation could elicit REM sleep was carried out by George et al.[41] They found that application

of the acetylcholine agonist carbachol could elicit REM sleep, but only when it was applied to specific regions of the pons ventral to the locus coeruleus. An impressive proof that a unique REM sleep generation mechanism was being activated was the long duration of the elicited REM sleep periods. Later studies showed that, depending on the exact site, either REM sleep or just atonia could be triggered by such stimulation.[42,43] 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. More recent studies have found that other chemicals can also trigger atonia or REM sleep when applied to pontine regions. However, the potency of cholinergic agonists in triggering REM sleep remains unique among the tested neurotransmitters.

Neuronal Activity

The transection, lesion, and stimulation studies all point to the same regions of the pons in the control of the state of REM sleep as a whole, and smaller subregions in 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 refine further the dissection of REM sleep mechanisms.

Most cells in 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.[7,8,44-46] 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 and neck, with other cell types linked to equally specific movement of the tongue, face, or limbs. 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 motor movement that is blocked by the muscle tone suppression of REM sleep. Lesions of these cells have little or no effect on REM sleep duration or periodicity, but do dramatically prevent movements of the head and neck.[47]

Monoamine-containing cells have a very different discharge profile. Most, if not all noradrenergic[48,49] and serotonergic[50] cells of the midbrain and pontine brainstem and histaminergic[51] 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 (Fig. 10–6). As was pointed out earlier, these cell groups are not critical for REM sleep generation, but it is likely that they modulate REM sleep parameters. As is discussed later, the cessation of activity in these cells may be important in the function of REM sleep. The cessation of discharge in monoaminergic cells during REM sleep has been linked to release of GABA onto these cells,[52-55] presumably by REM sleep–active GABAergic brainstem neurons.[56] Administration of a GABA agonist to the raphe cell group increases REM sleep duration,[53] demonstrating a modulatory role for this cell group in REM sleep control.

In contrast to norepinephrine, serotonin, and histamine cell groups, most dopaminergic neurons do not appear to alter their discharge rate across the sleep cycle.[57,58]

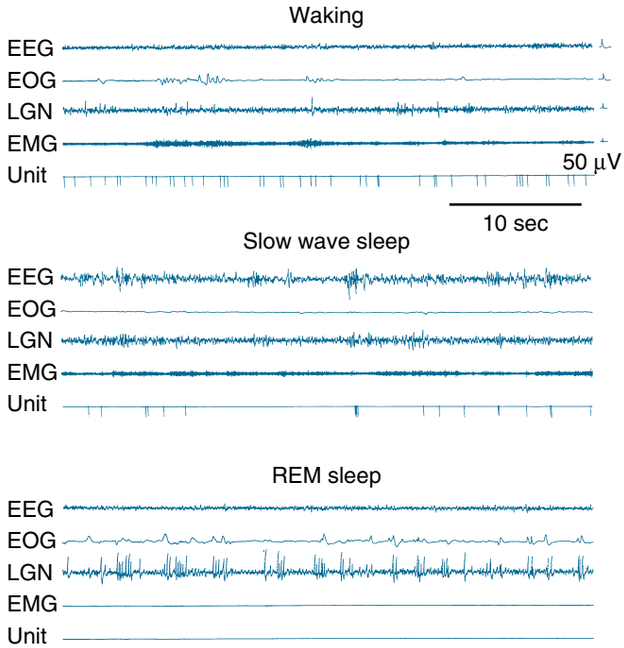

Figure 10–6. Activity of an "REM sleep-off" cell recorded in the locus coeruleus. (From Siegel JM: REM sleep control mechanisms: Evidence from lesion and unit recording studies. In Mayes A [ed]: Sleep Mechanisms and Functions. New York, Van Nostrand Reinhold, 1983, with permission.)

Cholinergic cell groups have an important role in REM sleep control. As was pointed out previously, microinjection of cholinergic agonists into the pons triggers long REM sleep periods. Microdialysis studies show that pontine acetylcholine release is greatly increased during REM sleep compared with either non-REM sleep or waking.[59] Recordings of neuronal activity in 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, as is the case with most reticular cells.[60] Presumably the REM-on cholinergic cells project to the acetylcholine-responsive region in the subcoeruleus area.[61] Other cholinergic cells in lateral pontine regions discharge in bursts before each ipsilateral PGO wave.[62,63] These cells may therefore participate in the triggering of these waves. We know from other studies that PGO waves are tonically inhibited in waking by serotonin input.[64,65] 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.

CONTROL OF MUSCLE TONE

The normal suppression of muscle tone during sleep in general and REM sleep in particular and the failure of the muscle tone suppression system in certain disorders are both of immense clinical importance. During REM sleep, central motor systems are highly active, whereas motoneurons are hyperpolarized (see Chapter 12). The suppression of tone in the tongue and laryngeal muscles is a major contributing factor in sleep apnea (see Chapter 82).

The normal role of the REM sleep atonia system is most dramatically apparent in REM sleep without atonia in animals and in the REM sleep behavior disorder (RBD) in humans (see Chapter 75). However, despite the similarity of RBD to REM sleep without atonia, humans with RBD do not usually have lesions in the areas implicated in feline REM sleep without atonia. One clue to the locus of damage in humans is the progression of RBD to Parkinson's disease in a high percentage of patients. The link between Parkinson's and degenerative changes in the ventral midbrain suggests that the locus for RBD may also be in this region. We have found that lesions in ventral midbrain can release motor activity during REM sleep,[66] consistent with this hypothesis.

Recent work has identified the mechanisms operating at the motoneuronal level to produce muscle tone suppression in REM sleep. Early work using intracellular recording and microiontophoresis had shown that motoneuron hyperpolarization during REM sleep was accompanied by the release of glycine onto motoneurons (see Chapter 12). In recent work it has been shown that both GABA and glycine are released onto motoneurons during atonia.[67] This release occurs in ventral horn motoneurons as well as in hypoglossal motoneurons. In related work it has been shown that norepinephrine and serotonin release onto motoneurons is decreased during atonia.[68] Because these monoamines are known to excite motoneurons and GABA and glycine are known to inhibit them, we can see the coordinated activity of these cell groups as combining disfacilitation and inhibition to produce motoneuron hyperpolarization and hence atonia in REM sleep.

The inhibitory and facilitatory systems are strongly and reciprocally linked. Electrical stimulation of the PIA produces muscle tone suppression. Even though this region is within a few millimeters of the noradrenergic locus coeruleus, stimulation in the PIA that suppresses muscle tone always causes a *cessation* of activity in the noradrenergic neurons of the locus coeruleus[69] and other facilitatory cell groups.[69] 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 (Fig. 10–7).

The release of GABA and glycine during REM sleep atonia is most likely mediated by a pathway from the PIA to the medial medulla.[70,71] The pontine region triggering this release not only is sensitive to acetylcholine, but responds to glutamate[72,73] (Fig. 10–8). 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.[74,75] The medullary interaction with pontine structures is critical for muscle tone suppression because inactivation of pontine regions greatly reduces the suppressive effects of medullary stimulation on muscle tone.[76,77] This ascending pathway from medulla to pons may mediate the inhibition of the 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 by interrupting ascending and descending portions of the pontomedullary inhibitory system.[78]

Recent work suggests that inhibition of motor output is accompanied by a neurochemically similar inhibition of sensory relays during REM sleep.[79] Such sensory inhibition may be important in preserving sleep in the face of sensory activation produced by twitches breaking through the motor inhibition of REM sleep.

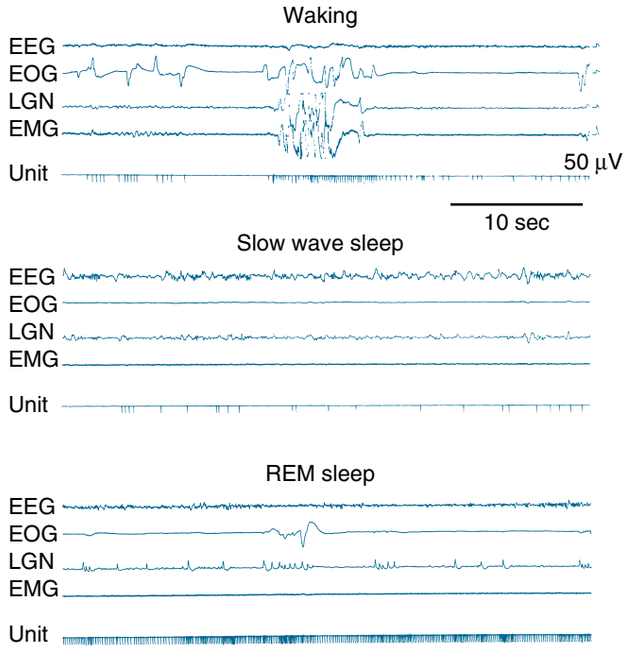

Figure 10–7. Activity of medullary "REM sleep-on" cell. Note the tonic activity during REM sleep. In waking, activity is usually absent even during vigorous movement. However, some activity is seen during movements involving head lowering and postural relaxation. (From Siegel JM, Wheeler RL, McGinty DJ: Activity of medullary reticular formation neurons in the unrestrained cat during waking and sleep. Brain Res 1979;179:49-60, with permission.)

Figure 10–9 illustrates some of the anatomic and neurochemical substrates of the brainstem generation of REM sleep.

NARCOLEPSY

Narcolepsy has long been characterized as a disease of the REM sleep mechanism. Narcoleptics often have REM sleep within 5 minutes 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 present in cataplexy.[80] 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 that are tonically active only during REM sleep in normal individuals, become active during cataplexy in narcoleptics.[9,81] Likewise, cells in the locus coeruleus, which cease discharge only in REM sleep in normal animals, invariably cease discharge in cataplexy.[82]

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 explained previously, 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,[80,83]

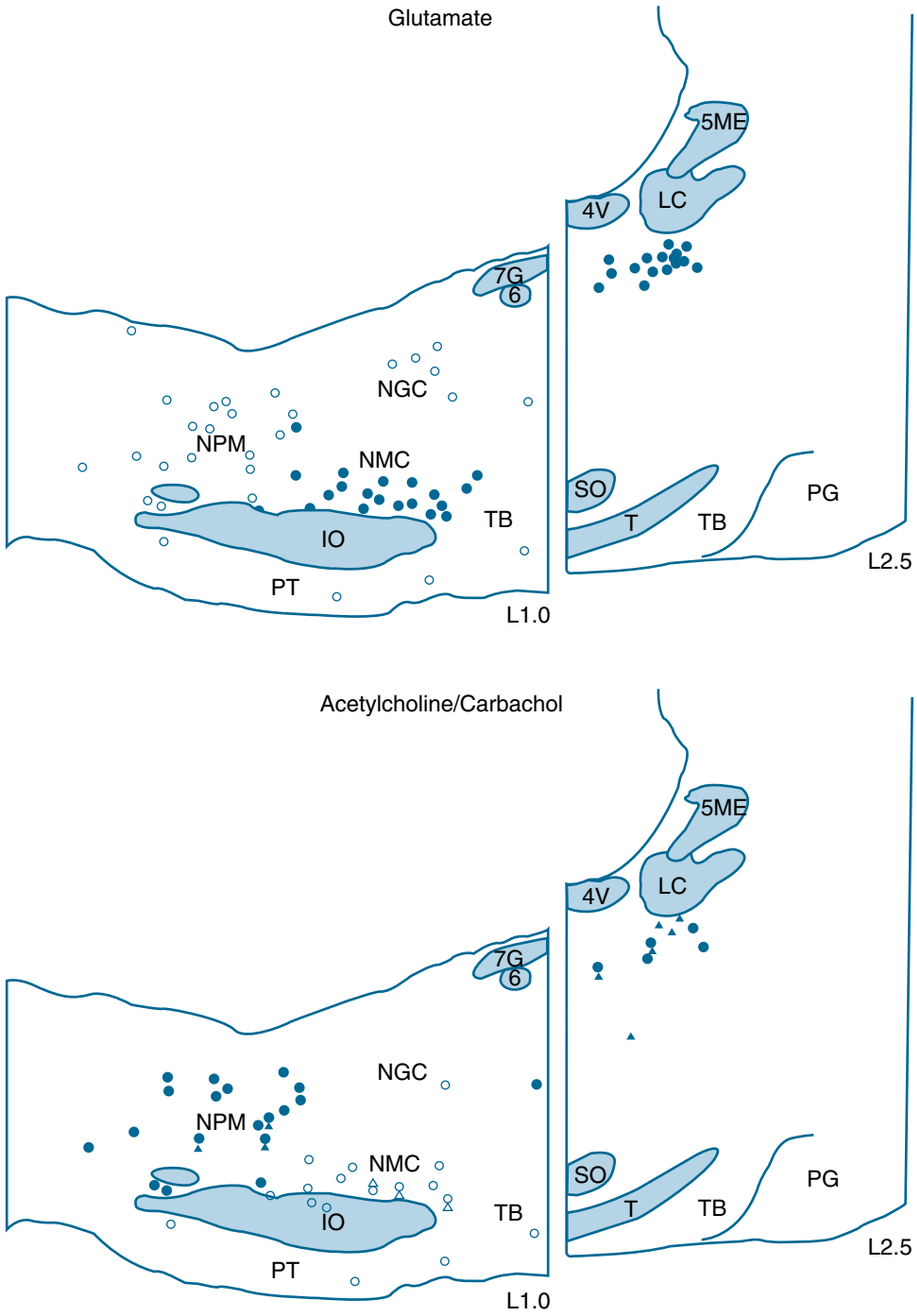

Figure 10–8. Sagittal map of pontomedullary inhibitory areas. Electrical stimulation produced atonia at all the points mapped. All electrically defined inhibitory sites were microinjected with glutamate or cholinergic agonists. *Filled symbols* represent points at which microinjections decreased muscle 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, pyramidal tract; SO, superior olivary nucleus; T, nucleus of the trapezoid body; TB, trapezoid body. (From Lai YY, Siegel JM: Medullary regions mediating atonia. J Neurosci 1988;8: 4790-4796, with permission.)

only reducing discharge to quiet waking levels. Histaminergic cells actually increase discharge in cataplexy relative to quiet waking levels.[80] 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 (Hcrt, also called orexin).[84,85] It was found that administration of the peptide to genetically narcoleptic dogs reversed symptoms of the disorder,[86] suggesting that similar treatment could be uniquely effective for human narcolepsy.

In further work in normal animals, it was determined that Hcrt was released maximally during motor activity,[87] leading to the hypothesis that release of Hcrt facilitates motor activity during emotionally charged activities of the sort that trigger cataplexy in narcoleptics.[88,89] Even normal individuals

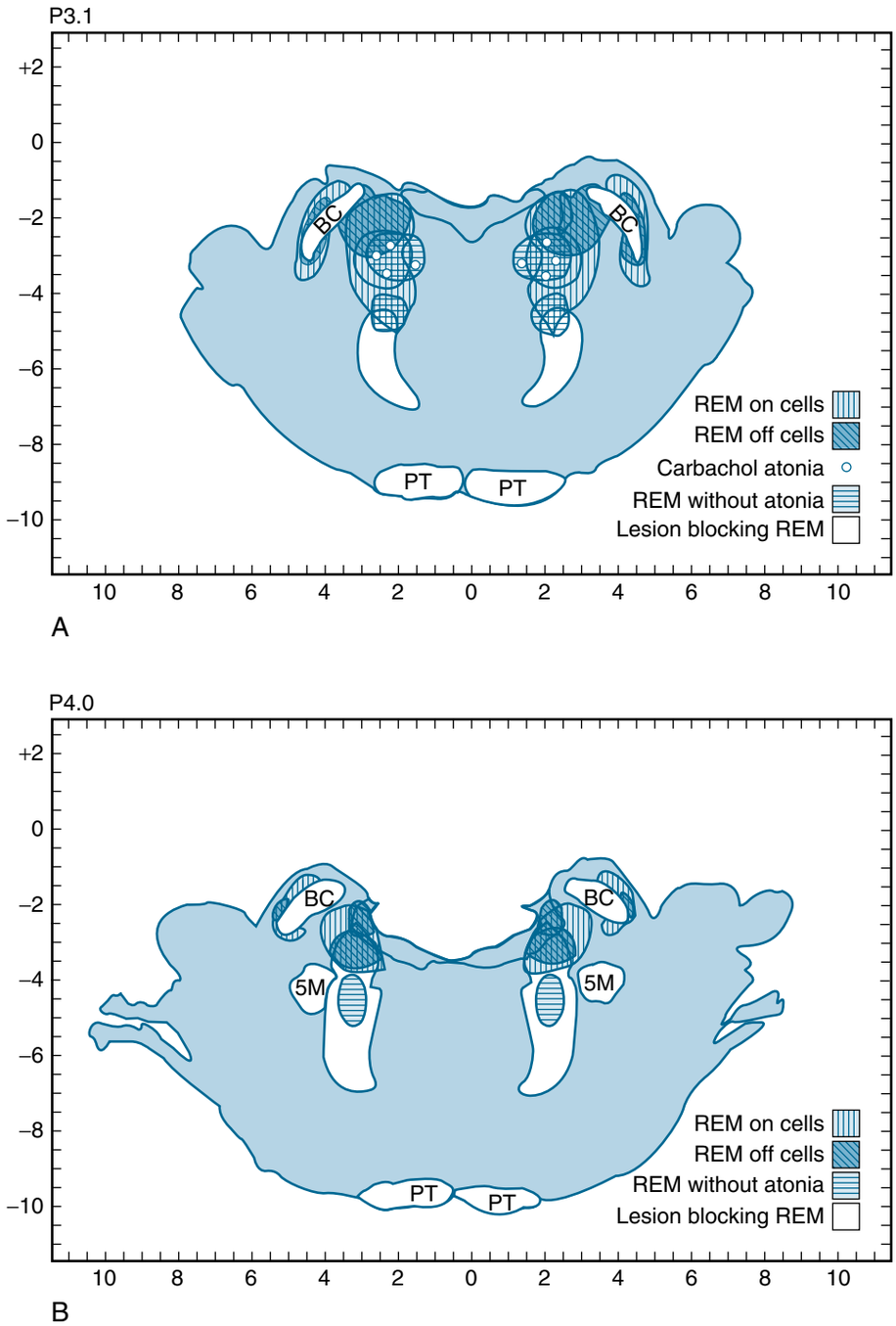

Figure 10–9. A, B, Anatomic relation of "REM sleep-on" and "REM sleep-off" cells, carbachol-induced atonia sites, lesions blocking atonia but not preventing REM sleep, and lesions completely blocking REM sleep. BC, brachium conjuctivum; PT, pyramidal tract; 5M, motor nucleus of the trigeminal nerve. Units are stereotaxic coordinates in mm. (From Siegel JM, Rogawski MA: A function for REM sleep: Regulation of noradrenergic receptor sensitivity. Brain Res 1988;13: 213-233, with permission.)

experience weakness at these times, seen in the "doubling over" that often accompanies laughter or the weakness that can result from sudden-onset, strong emotions. In the absence of the Hcrt-mediated motor facilitation, muscle tone is lost at these times. Hcrt cells also send ascending projections to cortical and basal forebrain regions. In the absence of Hcrt-mediated facilitation of forebrain arousal centers, waking periods are truncated, resulting in the sleepiness of narcolepsy.[88]

Hcrt appears to act largely by modulating the release of amino acid neurotransmitters.[90] Systemic injection of Hcrt causes a release of glutamate in certain Hcrt-innervated regions, producing a potent postsynaptic excitation.[91,92] In other regions it

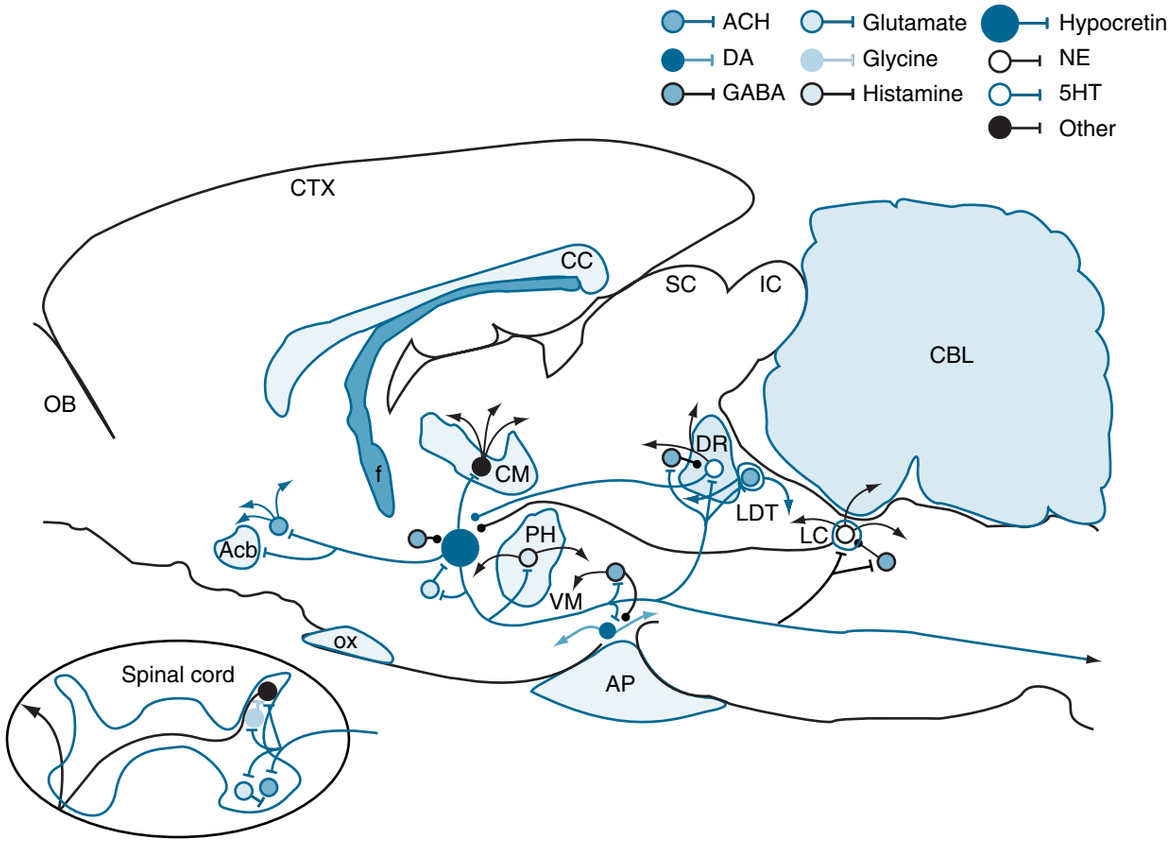

Figure 10–10. Major identified synaptic interactions of hypocretin (Hcrt) neurons. Lines terminated by *perpendicular lines* denote excitation; *circular terminations* indicate inhibition. Arrows indicate direction of projections. CC, corpus callosum; CTX, cortex; 5HT, serotonin; Acb, nucleus accumbens; ACH, acetylcholine; AP, anterior pituitary; CBL, cerebellum; CM, centromedian nucleus of the thalamus; DA, dopamine; DR, dorsal raphe; f, fornix; IC, inferior colliculus; LC, locus coeruleus; LDT, laterodorsal tegmental and pedunculopontine; NE, norepinephrine; OB, olfactory bulb; ox, optic chiasm; PH, posterior hypothalamus; SC, superior colliculus; VM, ventral midbrain. (From color figure in Siegel JM, Ann Rev Psych 2004;55:125-148, with permission.)

facilitates GABA release, producing postsynaptic inhibition.[87,93] 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 Hcrt (Fig. 10–10). 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 REM behavior disorders in narcoleptics (see Chapter 75). 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.[94-96] In other words, narcoleptics are not simply weaker and sleepier than normal individuals. Rather, their muscle tone and sleep–waking state regulation is less stable than that in normal subjects as a result of the loss of Hcrt function.

THE FUNCTION OF REM SLEEP

Great progress has been made in localizing the mechanisms that generate REM sleep. As described previously, we know many of the key neurotransmitters and neurons involved. The recent discovery of the role of Hcrt in narcolepsy serves as a reminder that there may still be key cell groups that need to be identified before we can gain fundamental insights into the generation mechanism and functions of REM sleep. Yet despite this caveat, we already understand a substantial amount about what goes on in the brain during REM sleep.

However, the mystery exposed by the discovery of REM sleep remains. We do not know the biologic need that initiates REM sleep. We do not know the source or the REM sleep "debt" that accumulates during REM sleep deprivation.[97]

What is clear is that increased brain activity in REM sleep consumes considerable amounts of metabolic energy. The intense activity shown by most brain neurons, similar to or even more intense than that seen during waking, extracts a price in terms of energy consumption and "wear and tear" on the brain. It is unlikely that such a state would have produced a darwinian advantage and remained so ubiquitous among mammals if it did not have benefits compensating for its obvious costs. But what might these benefits be?

One idea that has gained a great deal of publicity recently is that REM sleep has an important role in memory consolidation. However, the evidence for this is poor. A recent review[98]

concludes that a major role for sleep in memory consolidation is unproven and unlikely. Although early animal work suggested that REM sleep deprivation interfered with learning, subsequent studies showed that it was the stress of the REM sleep deprivation procedure rather than the REM sleep loss itself that was critical. A leading proponent of a sleep and memory consolidation relationship has recently concluded that sleep has no role in the consolidation of declarative memory,[99] which would exclude a role for sleep in rote memory, language memory, and conceptual memory, leaving only the possibility of a role in procedural memory, the sort of memory required for learning to ride a bicycle or play a musical instrument. However, studies supporting a role for sleep in the consolidation of human procedural learning have made contradictory claims about similar learning tasks, with some concluding that REM but not non-REM sleep is important, others stating just the reverse, yet others claiming that both sleep states are essential.[98] Millions of humans have taken monoamine oxidase inhibitors or tricyclic antidepressants, often for 10 to 20 years. These drugs profoundly depress or in many cases completely eliminate all detectable aspects of REM sleep. However, there is not a single report of memory deficits attributable to such treatment. Likewise, well-studied individuals with permanent loss of REM sleep resulting from pontine damage show normal learning abilities; the best-studied such individual completed law school after his injury and was last reported to be the puzzle editor of his city newspaper.[100]

Another idea that has been repeatedly suggested is that REM sleep serves to stimulate the brain.[26,101,102] According to this theory, the inactivity of non-REM sleep causes metabolic processes to slow down to an extent that the animal would be unable to respond to a predator or capture prey if one became available. This would leave mammals functioning like reptiles, with slow response after periods of inactivity. This hypothesis explains the appearance of REM sleep after non-REM sleep under most conditions. It also explains the well-documented increased proportion of sleep time in REM sleep as morning approaches in humans. Humans are more alert when aroused from REM sleep than non-REM sleep, consistent with this idea. The very low amounts or absence of REM sleep in dolphins, whose brainstem is continuously active and which never have bilateral EEG synchrony, can be explained by this hypothesis. If one hemisphere is always active, there is no need for the periodic stimulation of REM sleep to maintain the ability to respond rapidly. However, the brain stimulation hypothesis of REM sleep function does not explain why waking does not substitute for REM sleep in terrestrial mammals. REM sleep–deprived individuals have an REM sleep rebound even if they are kept in an active waking state for extended periods.

One phenomenon that may explain REM sleep rebound is the cessation of activity of histamine, norepinephrine, and serotonin neurons during REM sleep. This cessation does not occur during waking and therefore waking would not be expected to substitute for this aspect of REM sleep.[103] Thus, REM sleep rebound may be due to an accumulation of a need to inactivate these aminergic cell groups. Several cellular processes might benefit from the cessation of activity in aminergic cells. Synthesis of these monoamines and their receptors might be facilitated during this period of reduced release. The receptors for these substances might be resensitized in the absence of their agonist. The metabolic pathways involved in the reuptake and inactivation of these transmitters might also benefit from periods of inactivity. Some, but not all studies have supported this hypothesis.[104-108]

Investigation at the cellular level may lead to an "inside out" explanation of REM sleep function, deriving a functional explanation from a better understanding of the neuronal basis of REM sleep control.

Further relevant literature can be found at http://www.npi.ucla.edu/sleepresearch.

Clinical Pearl

The loss of hypocretin (orexin) neurons is responsible for most human narcolepsy. It is thought that this cell loss may be the result of an immune system attack on these neurons, but convincing evidence for this is lacking. Administration of hypocretin is a promising future avenue for the treatment of narcolepsy. Because the hypocretin system has potent effects on arousal systems, including the norepinephrine, serotonin, acetylcholine, and histamine systems, manipulation of the hypocretin system with agonists and antagonists is likely to be important in further pharmacotherapies for narcolepsy, insomnia, and other sleep disorders.

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