again indicating that the pons is a key component of the circuit producing motor inhibition.

The studies just reviewed focused largely on ventral horn and hypoglossal motoneurons. However, the control of jaw muscles also is a critical clinical issue. The success of jaw appliances indicates that reduced jaw muscle activity can contribute to closure of the airway in sleep apnea (see Chapter ••). 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, with use of the other side as a control for changes in behavioral state caused by application of neurotransmitter agonist and antagonists.[139] Using this model, it was determined that tonic glycine release reduces muscle tone in both waking and NREM sleep. Blockade of glycine receptors, however, 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 NREM sleep but did not prevent the suppression of masseter tone[140] or of genioglossus tone in REM sleep.[141] Both of these manipulations, however, 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 relative to the level in NREM sleep. Glutamate also contributes to the phasic motor activity during REM sleep. Reduction in glutamate alone, however, is not sufficient to account for the suppression of muscle tone in REM sleep, because stimulation of NMDA and non-NMDA glutamate receptors does not appear to restore muscle tone in REM sleep.[142]

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.[143] 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, but not by reduced serotonin release.[144] In the context of previous microdialysis analysis of transmitter release, these studies suggest that the reduction of norepinephrine release may a key factor regulating muscle tone, along with the aforementioned changes in amino acid release. These conclusions are consistent with earlier work indicating that cataplexy was linked to a reduction in the activity of noradrenergic neurons (see further on).[145] Although the current literature suggests that trigeminal, hypoglossal, and ventral horn motoneurons are subjected to similar neurochemical control across the sleep cycle, direct comparison 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 has been 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 serotoninergic neurons, although earlier studies in vagotomized and anesthetized rats had shown an effect of serotonin on muscle tone under these aphysiologic conditions.[146-148]

Subsequent work suggested that inhibition of motor output is accompanied by a neurochemically similar inhibition of sensory relays during REM sleep.[149] Such sensory inhibition may be important in preserving sleep and, in particular, in 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 pathologic states.

In contrast with the 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.[111] Dopamine release in the amygdala measured by dialysis does not significantly vary across the sleep cycle.[150] In disagreement with this finding, a Fos study indicted that dopaminergic neurons within the ventral portion of the mesencephalic tegmentum were activated during periods of increased REM sleep.[151] 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.[113] Other work using the Fos labeling technique identified a wake-active dopaminergic cell population in the ventral periaqueductal gray.[116] In dialysis measurements of dopamine release, dopamine release was reduced in the dorsal horn of the spinal cord during the REM sleep–like state triggered by carbachol. Such a decrease was not seen in the ventral horn or hypoglossal nucleus.[134] These data suggest either heterogeneity in the behavior of sleep cycle activity of dopaminergic neurons or presynaptic control of dopamine release independent of action potentials in the cell somas.

Figure 8-9 illustrates some of the anatomic and neurochemical substrates of the brainstem generation of REM sleep.

NARCOLEPSY AND HYPOCRETIN

Narcolepsy has long been characterized as a disease of the REM sleep mechanism. Narcoleptic patients often enter REM sleep within 5 minutes of sleep onset, in contrast with normal persons, who rarely show such "sleep-onset REM sleep." Most narcoleptics experience cataplexy,[152] 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.[145] 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 normals, become active during cataplexy in narcoleptics including cells in the medial medullary inhibitory region that are selectively active in relation to the atonia of REM sleep.[17,132] Likewise, cells in the locus coeruleus, which cease discharge only in REM sleep in normal animals, invariably cease discharge in cataplexy.[153] 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 noted previously, in the normal animal, noradrenergic, serotoninergic, and histaminergic cells are all tonically active in waking, reduce discharge in NREM sleep, and cease discharge in REM sleep.[145,153] Unlike noradrenergic cells, however, serotoninergic cells do not cease discharge during cataplexy, only reducing discharge to quiet waking levels. Histaminergic cells actually increase discharge in cataplexy relative to quiet waking levels[154] (Figure 8-10). These findings allow identification of some of

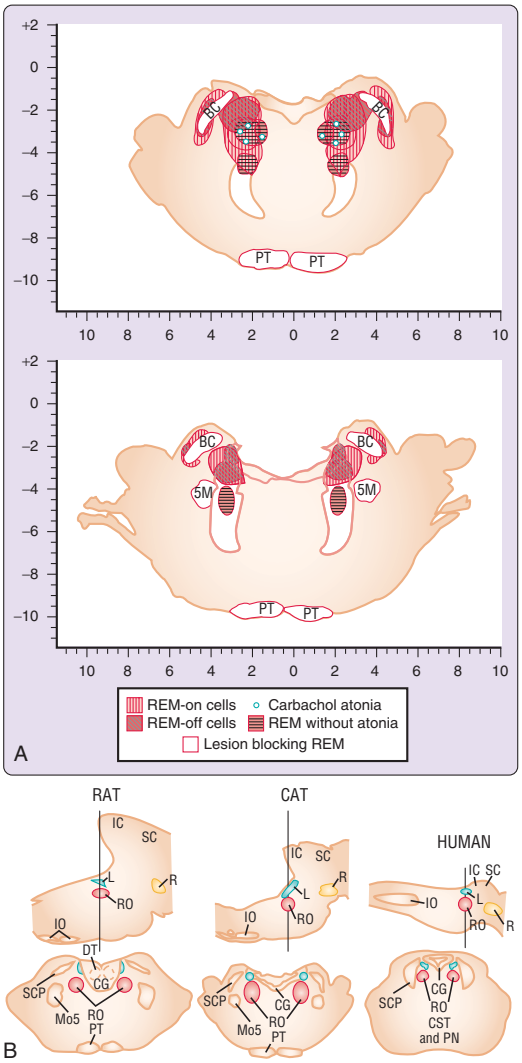

Figure 8-9 A, B, Anatomic relation of "REM sleep–on" and "REM sleep–off" cells, carbachol-induced atonia sites, lesions blocking atonia but not preventing REM sleep, and lesions completely blocking REM sleep. **A,** ••. BC, ••; 5M, ••; PT, ••. **B** shows anatomic locations of REM on areas in cat and rat brains and projected location in the human in sagittal and coronal views. CG, Central gray; CST, corticospinal tract; DT, dorsal tegmental; IC, inferior colliculus; IO, inferior olive; L, locus coeruleus; Mo5, motor nucleus of the trigeminal nerve (5M); PN, pontine nuclei, PT, ••; R, red nucleus; RO, reticularis oralis nucleus; SC, superior colliculus; SCP, superior cerebellar peduncle (brachium conjunctivum). (**A** from Siegel JM, Rogawski MA. A function for REM sleep: regulation of noradrenergic receptor sensitivity. *Brain Res* 1988;13:213-33. **B** from Siegel JM. The stuff dreams are made of: anatomical substrates of REM sleep. *Nat Neurosci* 2006;9:721–2.)

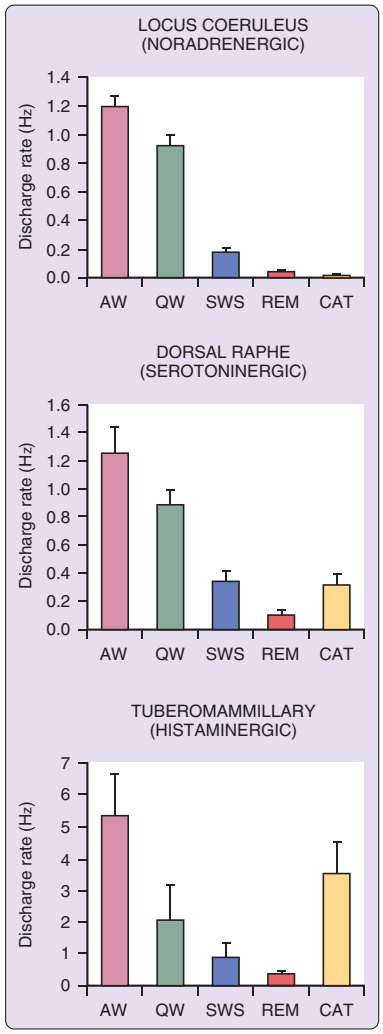

Figure 8-10 Comparison of mean discharge rates in sleep-waking states and cataplexy for REM-off cells recorded from three brain regions. Posterior hypothalamic histaminergic neurons remain active, whereas dorsal raphe serotoninergic neurons reduced discharge, and locus coeruleus noradrenergic neurons ceased 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. AW, Active waking; CAT, cataplexy; QW, quiet waking; REM, REM sleep; SWS, slow wave (NREM) sleep. (From John J, Wu MF, Boehmer LB, SiegelJM. Cataplexy-active neurons in the posterior hypothalamus: implications for the role of histamine in sleep and waking behavior. *Neuron* 2004;42:619–34.).

the cellular substrates of cataplexy. Medullary inhibition and noradrenergic disfacilitation are linked to cataplexy's loss of muscle tone. By 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 insight into both narcolepsy and the normal role of these cell groups in maintaining consciousness and muscle tone.

In 2001 it was discovered that most human narcolepsy was caused by a loss of hypothalamic cells containing the peptide hypocretin[23,24] (Figure 8-11). On average, 90% of these cells are lost in narcolepsy. Subsequently it was discovered that a lesser reduction in the number of hypocretin cells was seen in Parkinson disease, with a loss of up to 60% of hypocretin cells.[155,156] It was found that administration of the peptide to genetically narcoleptic dogs reversed symptoms of the disorder[157] and that nasal administration reversed sleepiness in monkeys,[158] suggesting that similar treatment could be uniquely effective for narcolepsy and perhaps for other disorders characterized by sleepiness.[159-161] Recently it also has been found that in human narcoleptics, the number of detectable histamine cells is increased more than 65%.[162,163] It has been speculated that because this change is not seen in any of four different animal genetic models of narcolepsy, the increase may be related to the presumed immune activation that causes human narcolepsy.[162]

In further work in normal animals, it was determined that identified hypocretin neurons discharge at their highest rates during active waking[35,164] (Figure 8-12). This discharge was reduced or absent during aversive waking situations, even if the EEG indicated high levels of alertness.[35] The hypocretin level in normal dogs is nearly doubled when they are let out into a yard to play with other dogs. By contrast, when these same dogs run at maximal speed on a treadmill, hypocretin levels are unchanged, demonstrating that motor activity and associated changes in respiratory rate, heart rate, and body temperature do not by themselves determine the release of hypocretin. Findings in studies of hypocretin release in the cat[165] also are consistent with this hypothesis. Hypocretin cells send ascending projections to cortical and basal forebrain regions, in addition to their descending projection to locus coeruleus and other brainstem regions. In the absence of hypocretin-mediated facilitation of forebrain arousal centers, waking periods are truncated, resulting in the sleepiness of narcolepsy.[166]

The functions of hypocretin have been investigated in genetic knockout animals lacking the peptide and in their wild-type littermates, using operant reinforcement tasks. Hypocretin-knockout mice are deficient in the performance of bar presses to secure food or water reinforcement. However, they do not differ from their normal littermates in their performance when trained to bar press to avoid foot shock. Periods of poor performance on the positive reinforcement tasks are characterized by EEG deactivation.[167] This deficit is restricted to the light phase, suggesting that hypocretin neurons mediate the arousing and mood-elevating effects of light,[167] effects that are central to the current understanding of depression. Fos labeling studies in normal littermates showed that the positive reinforcement task used in this study is characterized by activation of hypocretin neurons. However, hypocretin neurons are not activated in the negative reinforcement task or during the same positively motivated task in the dark phase, despite high levels of EEG activation, indicating that nonhypocretin systems mediate arousal during these behaviors.

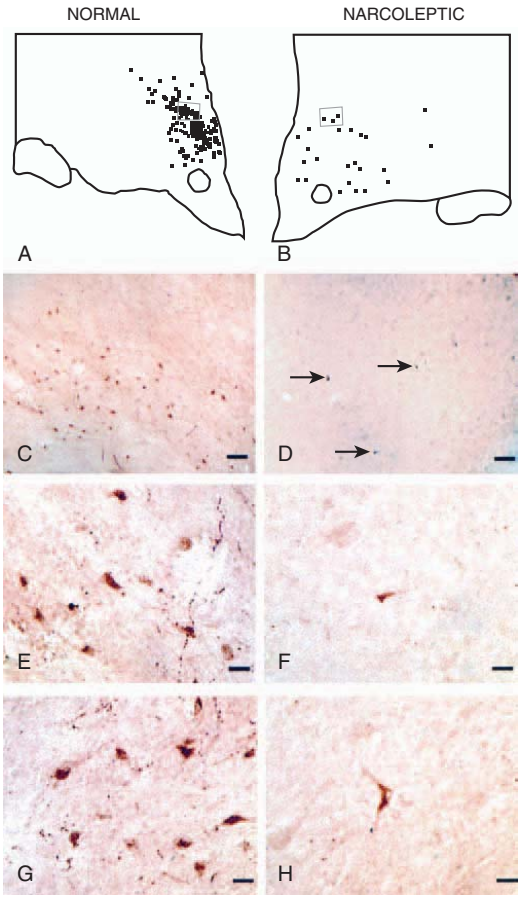

Figure 8-11 Loss of hypocretin cells in human narcolepsy. Distribution of cells in perifornical and dorsomedial hypothalamic regions of normal (**A, C, E, G**) and narcoleptic (**B, D, F, H**) humans. (From Thannickal TC, Moore RY, Nienhuis R, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 2000;27:469-74.)

The conclusions of these animal studies were extended in the first study of hypocretin release within the human brain. Hypocretin levels were shown to be maximal during positive emotion, social interaction, and anger, behaviors that induce cataplexy in human narcoleptics. This finding is consistent with the hypothesis that release of hypocretin facilitates motor activity during emotionally charged activities of the sort that trigger cataplexy in narcoleptics.[166,168,169] Even normal persons experience weakness at these times, seen in the "doubling over" that often accompanies laughter or the weakness that can result from other strong emotions of sudden onset. In the absence of the hypocretin-mediated motor facilitation of locus coeruleus and other brainstem regions, muscle tone is lost at

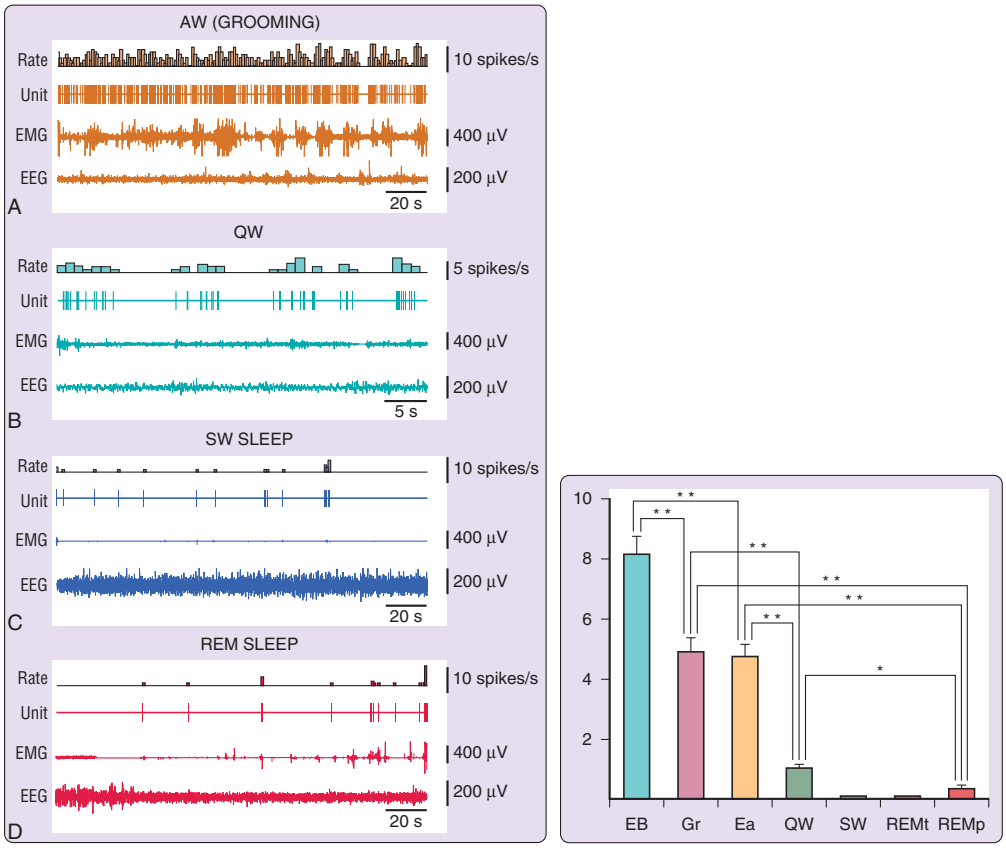

Figure 8-12 Firing rate of hypocretin cells in waking and sleep behaviors in freely moving rats. *Left:* The discharge pattern of a representative hypocretin neuron across the sleep-waking cycle in the freely moving rat. **A,** High firing rates are seen during active waking (AW) withgrooming. **B,** Reduced firing rate or cessation of activity is seen in quiet waking (QW) and drowsiness. **C,** A further decrease or cessation of firing is seen during slow wave (NREM) sleep. **D,** Minimal firing rate is seen during the tonic phase of REM sleep. Brief hypocretin cell discharge bursts are correlated with muscle twitches during the phasic events of REM sleep. *Right:* Summary data from identified hypocretin cells: exploratory behavior (EB), grooming (Gr), eating (Ea), QW, SW sleep (SW), and tonic (REMt) and phasic (REMp) sleep. Maximal discharge is seen during exploration-approach behavior. (From Mileykovskiy BY, Kiyashchenko LI, Siegel JM. Behavioral correlates of activity in identified hypocretin (orexin) neurons. *Neuron* 2005;46:787-98.)

these times. By contrast, the release in humans of melanin-concentrating hormone, a peptide produced by neurons intermixed in the hypothalamus with the hypocretin neurons, is minimal during social interaction but is increased after eating. Both peptides are at minimal levels during periods of postoperative pain despite high levels of arousal. Melanin-concentrating hormone levels increase at sleep onset, consistent with a role in sleep induction,[170] whereas hypocretin-1 levels increase at wake onset, consistent with a role in wake induction. Levels of these two peptides in humans are not simply linked to arousal but rather are correlated with specific emotions and state transitions[171] (Figure 8-13).

The findings that hypocretin is released and hypocretin neurons are active only during arousal linked to certain emotions suggests a new approach to the understanding of arousal systems. Hypocretin is clearly related to arousal linked to certain generally positive emotions. Other arousal systems must mediate arousal during aversive situations. An analysis of the differential activation of arousal systems as a function of emotion, light level, and other variables might provide important clinical and basic science insights into the unique roles of each arousal system.

Hypocretin appears to act largely by modulating the release of amino acid neurotransmitters.[172] Systemic injection of hypocretin causes a release of glutamate in certain hypocretin-innervated regions, producing a potent postsynaptic excitation.[139,173] In other regions it facilitates GABA release, producing postsynaptic inhibition.[165,174] The loss of these competing inhibitory and facilitatory influences in narcolepsy appears to leave brain motor regulatory and arousal systems

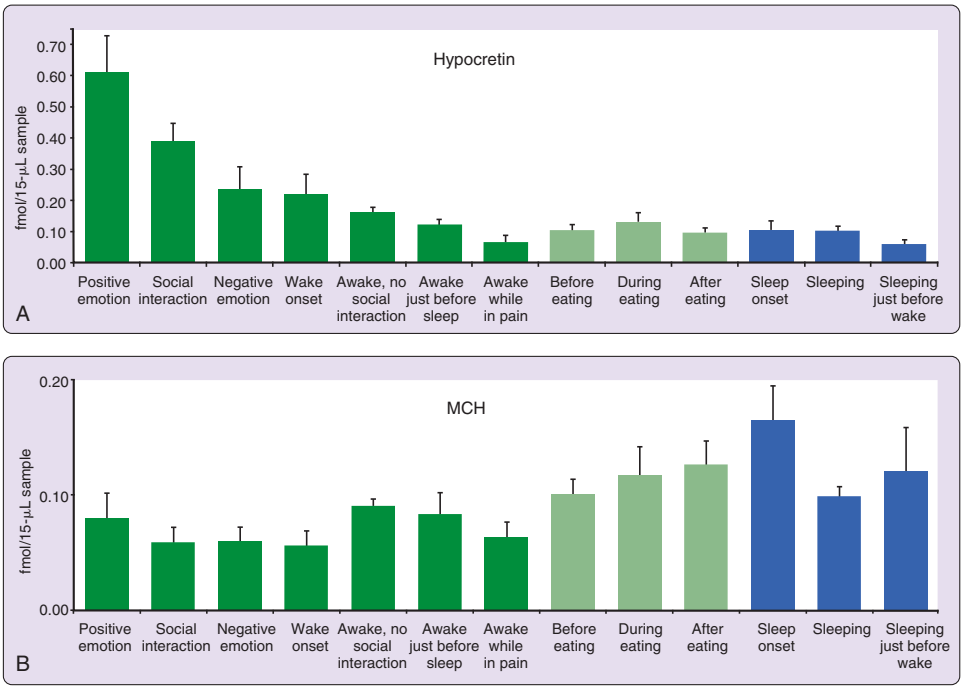

Figure 8-13 Hypocretin and melanin-concentrating hormone (MCH) levels across waking and sleep activities in humans. **A,** Maximal hypocretin levels in waking are seen during positive emotions and social interactions and on awakening; minimal levels are seen before sleep and in alert waking associated with reported pain. Changes during and after eating are smaller than those during monitored non–eating-related activities. Waking values are shown in *shades of green*; sleep values, in *blue*. For all awake samples, subjects were awake but were not exhibiting social interaction or reporting emotion. **B,** Maximal MCH levels are seen at sleep onset and after eating. Minimal levels are seen during wake onset, social interaction, and pain. Error bars represent ±S.E.M. (From Blouin AM, Fried I, Wilson CL, et al. Human hypocretin and melanin-concentrating hormone levels are linked to emotion and social interaction. *Nat Commun* 2013;4:1547.)

less stable than the tightly regulated balance that can be maintained in the presence of hypocretin (Figure 8-14). 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 in muscle tone during sleep, resulting in a striking *increased* incidence of REM sleep behavior disorder in narcoleptics (Chapter ••). In the same manner, although a principal symptom of narcolepsy is intrusions of sleep into the waking period, narcoleptic persons sleep poorly at night, with frequent awakenings.[175-177] In other words, narcoleptics are not simply weaker and sleepier than normal subjects. Rather, their muscle tone and sleep-waking state regulation is less stable than in normal persons as a result of the loss of hypocretin function.

THE FUNCTIONS OF RAPID EYE MOVEMENT SLEEP

Research into the control of REM sleep turns into a seemingly infinite regression, with REM-on cells inhibited by REM-off cells, which in turn may be inhibited by other REM-on cells. It is very difficult to identify the sequence in which these cell groups normally are activated because the axonal condition and synaptic delays could not be more than a few milliseconds between these cell groups, yet REM sleep onset occurs over a period of minutes in the human and cat and at least 30 or more seconds in the rat. It also does not completely enlighten researchers with respect to the ultimate functional question: What is REM sleep for? To answer this question requires determining what if any physiologic process is altered over REM sleep periods. Is some toxin excreted or some protein synthesized? If so, how can the widely varying durations of the typical REM sleep be accounted for? In the human, REM sleep typically lasts from 5 to 30 minutes, whereas in the mouse, it typically lasts 90 seconds.[178] What can be accomplished in 90 seconds in the mouse but requires an average of approximately 15 minutes in humans? If a vital process is accomplished, why do drug treatments that abolish REM sleep have no discernable effect on any vital process, even when such drugs are taken continuously for many years? The biologic need that initiates REM sleep remains unknown, as well as the source of the REM sleep "debt" that accumulates during REM sleep deprivation.[179] Why do some marine mammals have no apparent REM sleep (see Chapter 10). 17

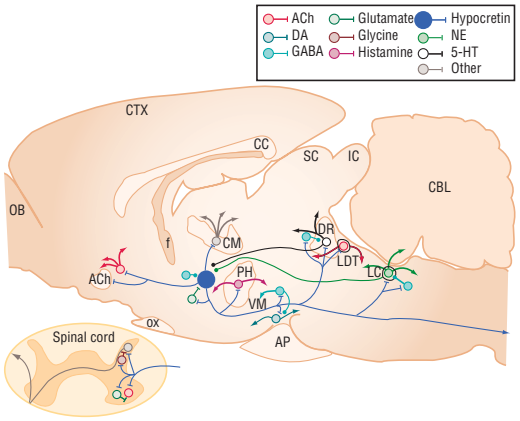

Figure 8-14 Major identified synaptic interactions of hypocretin neurons. Lines terminated by *perpendicular* lines denote excitation; *circular* terminations indicate inhibition. Acb, Nucleus accumbens; ACh, acetylcholine; AP, anterior pituitary; CBL, cerebellum; CC, ••; CM, centromedian nucleus of the thalamus; CTX, cortex; DA, dopamine; DR, dorsal raphe; f, fornix; 5-HT, 5-hydroxytryptamine (serotonin); 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.

Why is REM sleep present in homeotherms (i.e., birds and mammals) but apparently absent in the reptilian ancestors of homeotherms?

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

Clearly, increased brain activity in REM sleep consumes considerable amounts of metabolic energy. The intense neuronal 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. Such a state would be unlikely to 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 received much media attention is that REM sleep has an important role in memory consolidation. However, the evidence for such a role is poor.[180] 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.[181] A leading proponent of a sleep and memory consolidation relationship has concluded that sleep has no role in the consolidation of declarative memory,[182] 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 NREM sleep is important and others stating just the reverse, and still others claiming that both sleep states are essential.[180] Millions of people have taken monoamine oxidase (MAO) 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. Of note, however, not a single report of memory deficits attributable to such treatment has emerged. Likewise, well-studied patients with permanent loss of REM sleep resulting from pontine damage show normal learning abilities; the best-studied of these patients completed law school after his injury[183] and was last reported to be the puzzle editor of his city newspaper. People with multiple systems atrophy can have a complete loss of slow wave sleep and disruption of REM sleep without manifesting any substantial memory deficit.[184] A recent well-controlled study showed that REM sleep suppression with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors was associated with no significant decrement in memory consolidation on any task and even produced a small but significant improvement in a motor learning (i.e., procedural) task.[185]

Another idea that has been suggested repeatedly is that REM sleep serves to stimulate the brain.[186-188] According to this theory, the inactivity of NREM sleep causes metabolic processes to slow down to an extent that the animal would be unable to respond to a predator, capture prey, or meet other challenges upon awakening. Such alterations would leave mammals functioning like reptiles, with slow response after periods of inactivity. This hypothesis explains the appearance of REM sleep after NREM sleep under most conditions. It also explains the well-documented increased proportion of sleep time in REM sleep as the sleep period nears its end in humans and other animals. Humans are more alert when aroused from REM sleep than from NREM sleep, as are rats[189]—findings consistent with this idea. The very low amounts or absence of REM sleep in dolphins, in which the brainstem is continuously active and which never show 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 cannot substitute for REM sleep in terrestrial mammals. REM sleep–deprived persons experience a REM sleep rebound even if they are kept in an active waking state for extended periods, although this effect may be a result of stress, rather than REM sleep loss.[181]

A 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 the awake state, so waking would not be expected to substitute for this aspect of REM sleep.[190] REM sleep rebound may therefore 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 also may potentially benefit from periods of inactivity. Some but not all studies have supported this hypothesis.[191-195]

Further 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.

CLINICAL PEARL

The loss of hypocretin neurons is responsible for most cases of 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 explanation 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, as well as for depression.

SUMMARY

REM sleep was first identified by its most obvious behavior: rapid eye movements during sleep. In most adult mammals the EEG of the neocortex is low in voltage during REM sleep. The hippocampus has regular high-voltage theta waves throughout REM sleep. The tone of the postural muscles is greatly reduced or abolished during this state.

The key brain structure for generating REM sleep is the brainstem, particularly the pons and adjacent portions of the midbrain. Considerable progress has been made in identifying the neurons most closely linked to REM sleep within these regions and the transmitters that they employ. Massive damage to the REM-generating region can abolish REM sleep. Small lesions can cause REM sleep without atonia in animals or REM sleep behavior disorder in humans

Narcolepsy is characterized by abnormalities in the regulation of REM sleep. Most cases of human narcolepsy are caused by a loss of hypocretin (orexin) neurons, a cell group whose somas are localized to the hypothalamus. Hypocretin neurons have potent effects on alertness and motor control and normally are activated in relation to particular, generally positive emotions in humans as well as in animals. In the absence of this cell group, cataplexy, a REM sleep–like loss of muscle tone, occurs.

ACKNOWLEDGEMENTS

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REVIEW QUESTIONS

1. Human sleep is unusual in comparison with that of other mammals because of:
   A. The high amount of REM sleep
   B. The high amount of REM sleep as a percentage of total sleep time
   C. The low amount of REM sleep
   D. None of the above
2. A good way to prove that a substance is involved in REM sleep generation is to:
   A. Inject it in the pons or other candidate area and note if REM sleep increases
   B. Measure its release in the pons or other region and see if it is selectively released in REM sleep
   C. Block it with an antagonist and see if REM sleep is blocked
   D. Apply the manipulations in A to C to control areas adjacent to the areas of interest
   E. All of the above
3. Transection and lesion studies have localized the critical REM sleep generation mechanisms to:
   A. The pons and adjacent midbrain
   B. The medulla
   C. The hypothalamus
   E. The cerebral cortex
4. *Choose all that apply:* Which of the following statements regarding GABA is/are correct?
   A. GABA is the sleep chemical, promoting sleep throughout the brain.
   B. Profound arousal results when it is injected into certain pontine areas.
   C. GABA has actions outside of the brain and nervous system.
   D. GABA is unrelated to sleep onset or maintenance.
5. Narcolepsy is due to:
   A. Generalized degeneration of the hypothalamus.
   B. Localized cell-specific cell losses within the hypothalamus
   C. Amygdala dysfunction
   D. Frontal cortex damage
   E. All of the above
6. In the egg-laying mammals echidna and platypus, REM sleep is:
   A. Nonexistent
   B. Largely restricted to brainstem structures
   C. Largely restricted to forebrain structures
   D. Much greater in hours/day than in other mammals
   E. B and D
7. *True or false:* Studies in animals have shown that the isolated forebrain can generate a REM sleep-like state.
8. *True or false:* Narcolepsy is due to generalized degeneration of the hypothalamus.
9. *True or false:* The cessation of activity in monoaminergic neurons, including the histamine and noradrenergic neurons of the tuberomammillary nucleus and the locus coeruleus, is linked to GABA release.

ANSWERS

1. **D.** Amounts of total sleep time, total non-REM sleep time, REM sleep, and REM sleep time as a percentage of total sleep time are not unusual in humans.
2. **E.** Because REM sleep generation mechanisms are located in the pons, excitatory substances may trigger or increase REM sleep even if they have no substantial normal role in the control of this state. It is important to show the normal release of the substance in question and that blocking the effects of normal release blocks REM sleep. The same strategy applies to NREM sleep–related substances injected in forebrain regions.
3. **A.** However, the "REM sleep" aspects that appear in the isolated pons or pons connected to medulla but disconnected from rostral structures are not normal in physiologic form. This finding and other data point to a two-way interaction between forebrain, medullary, and pontine structures in normal REM sleep.
4. **B** and **C.** GABA is released in some regions selectively during sleep, but in others selectively during waking or just in REM sleep or just in NREM sleep. Any pharmacologic manipulation that activates GABA receptors throughout the brain (as benzodiazepines do) would be expected to produce an abnormal mixture of aspects of sleep-waking states. GABA also acts on receptors in the heart, kidney, T cells, and many other nonneural tissues.
5. **B.** Current evidence suggests that damage is limited to hypocretin (orexin) neurons, with adjacent melanin concentrating neurons intact. At this point it appears that only hypocretin neurons are lost in human narcolepsy, making the damage the most restricted of any neurologic disease. This conclusion is subject to future modification as other systems are examined more closely! Of course, even localized cell loss will produce changes throughout the brain, including up- and downregulation of receptors, sprouting of new connections, and so on.
6. **E.**
7. **False.** The caudal midbrain and pons are required for REM sleep. If the midbrain and pons are attached to the forebrain, a REM sleep—like state with PGO waves and EEG aspects of REM sleep is seen, even though structures caudal to the pons are disconnected from the forebrain.
8. **False.** Current evidence suggest that damage is limited to hypocretin (orexin) neurons, with adjacent melanin-concentrating neurons intact. At this point it appears that only hypocretin neurons are lost in human narcolepsy, making the damage the most restricted of any neurologic disease. This conclusion is subject to future modification as other systems are examined more closely!
9. **True.** Microdialysis studies have shown increased GABA release onto these neuronal groups during REM sleep.