The Neurobiology of Sleep

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ABSTRACT

Purpose of Review: The basic circuitries that regulate wake-sleep cycles are described, along with how these are affected by different disease states and how those alterations lead to the clinical manifestations of those disorders.

Recent Findings: The discovery of both sleep-promoting neurons in the ventrolateral preoptic nucleus and wake-promoting neurons, such as the lateral hypothalamic orexin (also called hypocretin) neurons, has allowed us to recognize that these two populations of neurons are mutually antagonistic (ie, inhibit each other) and form a ''flip-flop switch,'' a type of circuit that results in rapid and complete transition in behavioral state. The same principle applies to the circuitry controlling transitions between REM sleep and non-REM (NREM) sleep.

Summary: The flip-flop switch circuitry of the wake-sleep regulatory system produces the typical sleep pattern seen in healthy adults, with consolidated waking during the day and alternation between NREM and REM sleep at night. Breakdown in this circuitry both results in and explains the manifestations of a variety of sleep disorders including insomnia, narcolepsy with cataplexy, and REM sleep behavior disorder.

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CLINICAL OBSERVATIONS FIRST DEFINED WAKE-SLEEP

The subject of sleep has fascinated both philosophers and clinicians since the earliest times. It was not until neurologists began thinking about the brain systems that support wakefulness and how damage to them causes coma, however, that a mechanistic basis for sleep and wakefulness was established.[1,2] The first neurologist to produce a cogent theory about the origins of wakefulness was John Hughlings Jackson, who argued in the late 19th century that consciousness was the sum total of the activity of the cerebral cortex and that loss of consciousness occurred when this activity was prevented. By the early days of the 20th century, however, it became apparent that some patients with upper brainstem lesions who had intact cerebral hemispheres nevertheless fell into comatose states. This issue was addressed by Baron Constantin von Economo, a neurologist practicing in Vienna who witnessed the onset of a new type of encephalitis in an epidemic of encephalitis lethargica that began around 1915. During this epidemic, he found that his patients fell into two groups.

One group became excessively sleepy, sometimes sleeping as many as 20 hours a day. The patients would wake up to eat and remain cognitively intact during that time but would then fall back to sleep. Many of these patients also had eye movement abnormalities. Von Economo recognized this combination of signs from the work of Ludwig Mauthner, who had reported in 1890 that patients with Wernicke

KEY POINT

- von Economo was the first neurologist to recognize that specific brain lesions could identify brain circuitry controlling wake-sleep cycles.

encephalopathy also developed sleepiness and impaired eye movements. Mauthner's patients had had lesions along the caudal third ventricle and the cerebral aqueduct; von Economo found that his patients had lesions in a similar distribution. Based on these observations, von Economo proposed that an ascending arousal system originating in the upper brainstem kept the forebrain awake in an intact brain.

The second group of patients who emerged in this same epidemic had the opposite syndrome. They had a great deal of difficulty falling asleep, slept fitfully, awoke early, and could not fall back to sleep. These patients might be awake 20 or more hours per day, and many of them had movement disorders. The lesions in these patients were found to include the area around the rostral third ventricle and extend into the basal ganglia. These cases caused von Economo to posit that a sleep-promoting influence existed that arose from the region of the rostral third ventricle. Finally, as the epidemic of encephalitis lethargica waned after World War I, a third group of patients emerged. These patients had survived the encephalitis but had persistent difficulty maintaining wakefulness. Many of these patients, when told a joke, would lose muscle tone and fall helplessly to the ground. In the early 1920s, neurologists in London and Philadelphia also reported seeing more of these patients, whom they diagnosed with narcolepsy. In the few cases that ended in autopsy, lesions were found in the posterior part of the hypothalamus. These cases convinced S.A. Kinnier Wilson, who examined them at Queen Square Hospital in London, that the pathologic basis of narcolepsy resided in the posterior hypothalamus.

As this review will show, these neurologists were correct in their deductions. **Case 1-1** describes a modern-day patient who presented with hypersomnolence that resolved into narcolepsy due to a brain lesion similar to those described above.

THE ASCENDING AROUSAL SYSTEM

In the 1930s, Frédéric Bremer showed that if he transected the brainstem of a cat between the inferior and superior colliculi, the animal would fall into an

Case 1-1

An 18-year-old male college freshman who had been an outstanding student suddenly began to have trouble with his grades. On examination, he had short stature and delayed puberty. A craniopharyngioma was found on an MRI scan of the brain and was surgically removed. Postoperatively, he fell into a coma and was found to have bilateral infarction of most of the hypothalamus that extended laterally into the basal forebrain and amygdala and caudally into the midbrain (**Figure 1-1**). He was treated for panhypopituitarism and eventually awoke, but over the next year he slept for more than 12 hours each day. He eventually returned to about 10 hours of sleep per night with a 1- to 2-hour nap each afternoon, but he still experienced several episodes of excessive sleepiness each day that resolved with a short nap. When told a joke, he had occasional episodes of weakness that sometimes resulted in his falling to the ground without injury. He had vivid visual hallucinations when drowsy and brief episodes of paralysis as he fell asleep or emerged from sleep. EEG did not show evidence of a seizure disorder, but a polysomnogram showed a sleep latency of 1.0 minute, with REM sleep latency of 1.5 minutes and 15 spontaneous awakenings during the night without evidence of sleep apnea. A multiple sleep latency test showed that he fell asleep in less

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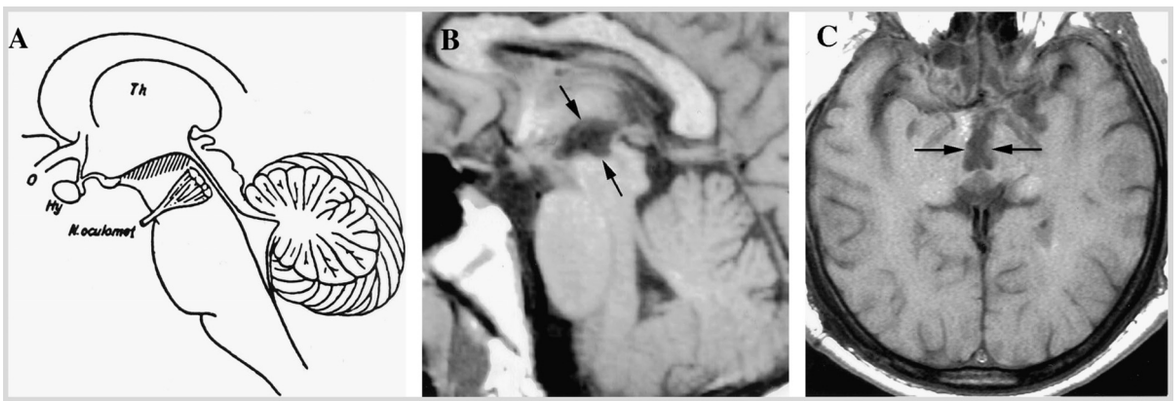

FIGURE 1-1 *A*, A drawing from von Economo's original article illustrating a lesion at the junction of the midbrain and the diencephalon that he found to be the cause of excess sleepiness in patients with encephalitis lethargica. This compares closely with the lesion found in this patient, who had an infarct involving the mesodiencephalic junction following removal of a craniopharyngioma. In both the sagittal (*B*) and axial (*C*) MRI scans, the lesion in this patient extends more rostrally than the lesion illustrated by von Economo, into the region occupied by the orexin neurons in the posterior lateral hypothalamus. The patient experienced initial excess sleepiness for about 1 year, followed by continuing narcolepsy.

than 30 seconds on average at all times of the day, and he entered REM sleep with a latency of 3.5 minutes on all four nap attempts. He was HLA-DQB1*0602 negative, but measurement of CSF orexin levels showed them to be about half that of normal controls.

Comment. This young man had the upper brainstem lesion that von Economo proposed as a cause of prolonged somnolence, as well as subsequent narcolepsy from involvement of the orexin neurons in the posterior hypothalamus.[3]

irreversible coma. Later studies showed no loss of wakefulness if the transection was placed in the midpons or lower. This work established the origin in the rostral pons and caudal midbrain of the ascending pathway that keeps the forebrain awake. Although investigators at the time attributed this arousal influence to the reticular formation, later studies showed that the pathway originates from neurons in discrete cell groups and is associated with specific neurotransmitters. This arousal system takes two main ascending pathways[2,4] (**Figure 1-2**). One pathway, which comes mainly from cholinergic neurons in the pedunculopontine and laterodorsal tegmental nuclei, primarily innervates the thalamus, particularly the relay nuclei (such as the ventroposterior complex or mediodorsal nucleus) and the reticular nucleus. The latter is important because the reticular nucleus consists of gamma-aminobutyric acid–mediated (GABA-ergic) neurons that project back into the thalamus and inhibit it. The arousal system inhibits the reticular nucleus, thus opening the way for thalamocortical transmission. The second pathway mainly contains monoaminergic neurons and includes the noradrenergic locus coeruleus, serotoninergic dorsal and median raphe nuclei, glutamatergic parabrachial nucleus, dopaminergic periaqueductal gray matter, and histaminergic tuberomammillary

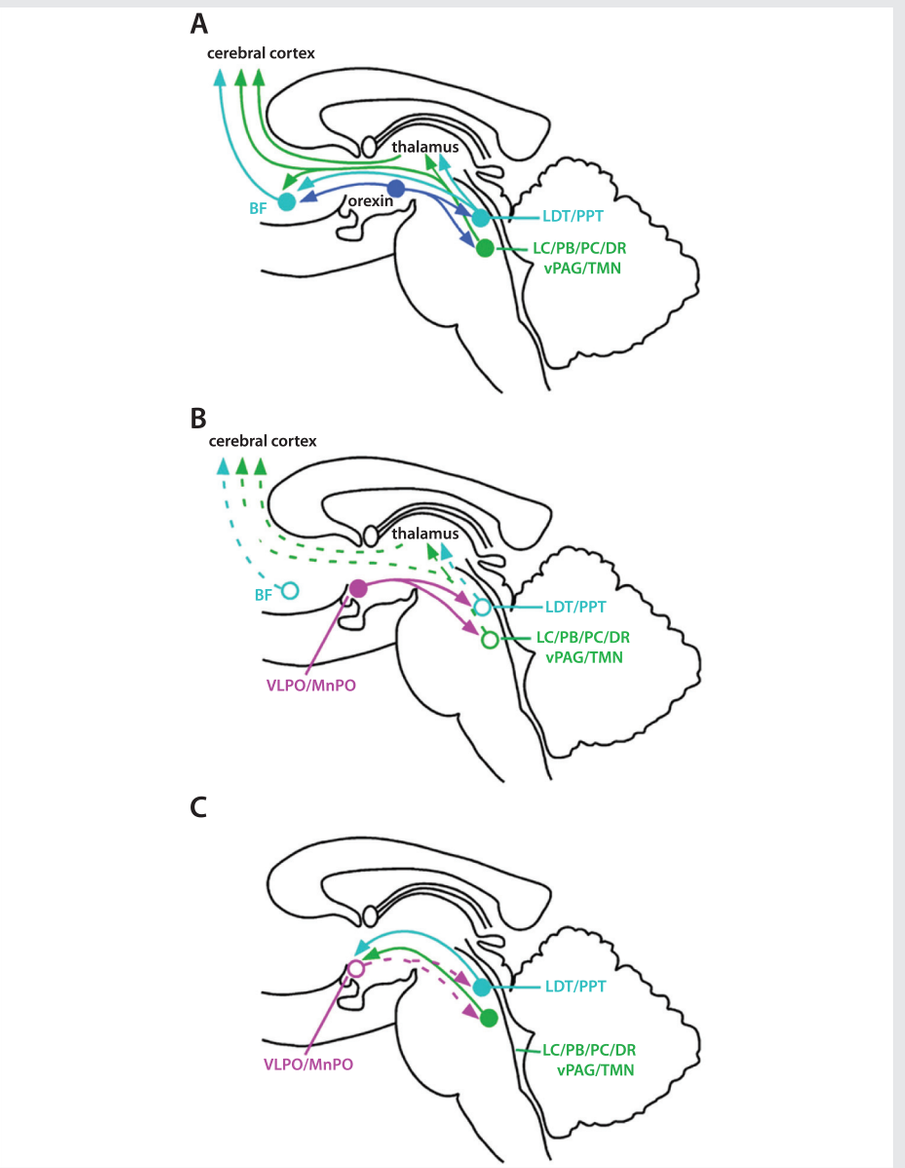

FIGURE 1-2 A series of schematic drawings of the arousal system (*A*), the sleep-promoting system (*B*), and their mutually inhibitory interactions (*C*). *A*, The monoaminergic arousal system (*green*) includes neurons in the noradrenergic locus coeruleus (LC), glutamatergic parabrachial nucleus (PB) and precoeruleus area (PC), serotoninergic dorsal raphe (DR), dopaminergic ventral periaqueductal gray matter (vPAG), and histaminergic tuberomammillary nucleus (TMN). Their ascending axons run through the hypothalamus, where they contact lateral hypothalamic orexin neurons (*blue*) and basal forebrain (BF) cholinergic, and GABA-ergic neurons (*light blue*). All of these systems directly innervate the cerebral cortex and contribute to its arousal. The cholinergic pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT) (*light blue*) innervate the thalamus and promote the arrival of sensory information (*green*) to the cerebral cortex. *B*, The GABA-ergic ventrolateral preoptic nuclei (VLPO) and median preoptic nuclei (MnPO) (*magenta*) innervate the components of the arousal system and actively inhibit them during sleep. *C*, The arousal systems also innervate the preoptic sleep-promoting cell groups and inhibit them. This sets up the conditions for a flip-flop switch that ensures rapid and complete transitions.

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nucleus. Neurons in each of these sites send axons through the lateral hypothalamus to the basal forebrain and cerebral cortex. In addition, peptidergic (ie, orexin, or hypocretin) and glutamatergic neurons in the lateral hypothalamus and cholinergic and GABA-ergic neurons in the basal forebrain that project to the cerebral cortex contribute to the pathway. All of these pathways serve to activate the cerebral cortex so that it can efficiently process sensory input.

THE SLEEP-INDUCING SYSTEM

The neurons in the ascending arousal system are inhibited during sleep by GABA-ergic input. A major source of this input is from neurons in the ventrolateral preoptic nucleus (**Figure 1-2**). Ventrolateral preoptic neurons contain both GABA and galanin, an inhibitory neuropeptide, and innervate most of the components of the arousal system.[2,4] The ventrolateral preoptic neurons are mainly active during sleep, and damage to these neurons dramatically reduces the amount of sleep that an animal achieves, similar to von Economo's patients who had lesions in this area.[5,6] Other neurons in the median preoptic nucleus also fire during sleep and innervate many of the same targets.[7,8] The median preoptic neurons are also GABA-ergic but do not contain galanin. During sleep deprivation in animals, the median preoptic neurons show activation, but the ventrolateral preoptic neurons are not activated until the animal actually falls asleep.[7] Thus, the median preoptic neurons are thought to respond to signals, such as buildup of extracellular adenosine, that indicate the accumulated need to sleep, and may in part work by activating ventrolateral preoptic neurons. Other hypothalamic neurons, which contain the peptide melanin-concentrating hormone as well as GABA, also are most active during sleep.[9] In addition, an ascending sleep-promoting influence has been traced to the lower pons or medulla, and recent work suggests that it may originate in GABA-ergic neurons in the caudolateral pontine reticular formation.[10]

THE FLIP-FLOP SWITCH MODEL OF SLEEP-WAKE REGULATION

The GABA-ergic neurons in the ventrolateral preoptic nucleus are also innervated by neurons in many of the arousal systems, and the effects of that innervation are also inhibitory. When two pathways inhibit each other, they produce the conditions for what electrical engineers call a ''flip-flop switch.'' In this type of switching system, when one side gains control, it turns off the other side, thus stabilizing its own firing.[2,4] Such switches are designed into electronic circuitry to produce two stable states with rapid transitions between them. Sleep is normally driven by physiologic systems that accumulate sleep need (a homeostatic input) and vary by time of day (a circadian input). These inputs change very slowly over a period of hours. If there were no flip-flop switch in the sleep-wake system, the person might drift slowly between wake and sleep states over the course of the day. Instead, the transitions into and out of sleep take place over just seconds to minutes (**Figure 1-3**).[4,11] Most people spend 98% or more of their day in one state or the other and less than 2% in transition. This seems to occur because of the mutual antagonism between sleep-promoting and wake-promoting systems in the brain.

SLEEP ITSELF CONTAINS DIFFERENT STATES

As a normal person falls asleep, the EEG slows from the typical awake state (desynchronized, with some alpha rhythm, particularly posteriorly) to the

KEY POINTS

- The ascending arousal system begins in the upper pons and contains two branches, one to the thalamus and the other through the hypothalamus and basal forebrain, both of which activate the cerebral cortex.
- Sleep-promoting neurons in the preoptic area, posterior lateral hypothalamus, and possibly the lower brainstem inhibit the neurons in the arousal areas during sleep.
- The mutual inhibition between the wake-promoting and sleep-promoting circuits produces a flip-flop switch, which ensures rapid and complete transitions between sleep and wakefulness.

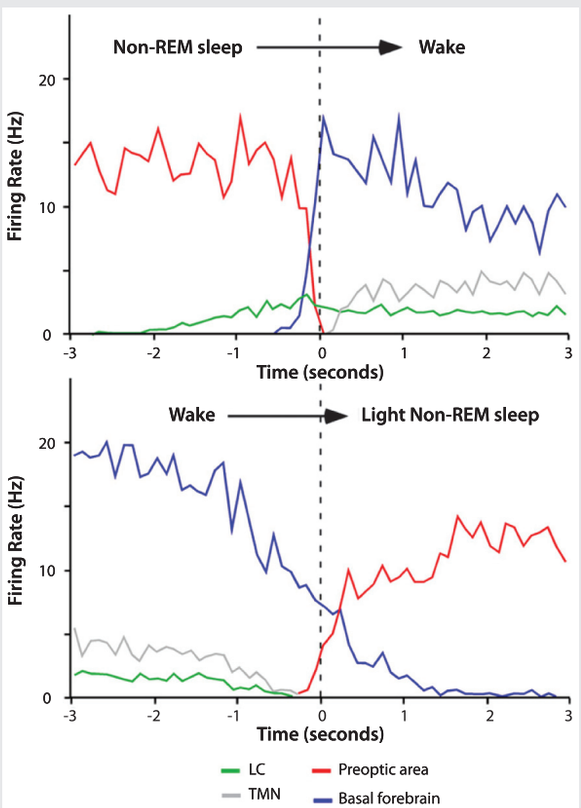

FIGURE 1-3 A pair of graphs comparing the firing of neurons in the noradrenergic locus coeruleus (LC) (*green*) and histaminergic tuberomammillary neurons (TMN) (*gray*) with basal forebrain wake-promoting (*blue*) and preoptic sleep-promoting (*red*) neurons across the time of transition between wakefulness and light non-REM sleep. Firing of the LC leads and the TMN follows the transition from sleep to wake, but a sharp change in the firing of the preoptic sleep-promoting neurons and the basal forebrain wake-promoting neurons occurs in the half second before the transition, suggesting that they may cause the transition. Conversely, a sharp increase in the firing of preoptic sleep-promoting neurons begins just before the onset of sleep.

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KEY POINT

- Sleep is divided into REM sleep, characterized by a fast EEG and muscle atonia, and non-REM sleep, during which the EEG is slow and high voltage, and muscle tone is present but low.

theta range (4 Hz to 7 Hz). As sleep deepens, the EEG rhythm slows further, and occasional very slow (delta) waves appear (K complexes). Sleep spindles, which are waxing and waning periods of alpha-frequency EEG, begin to occur. As the person enters the deeper stages of sleep (stages N2 and N3), the slower frequencies predominate, with greater amounts of delta activity. After about 45 minutes, the EEG begins to increase in frequency again as the person passes from deep slow-wave to lighter stages of sleep. As the EEG reaches the theta range, an abrupt transition to a desynchronized EEG that is more similar to the waking state may occur. The person does not awaken during such a transition or become more arousable, despite the desynchronized EEG. At the same time, a change in EMG from a state of low but constant muscle tone to virtual absence of muscle tone (atonia) occurs. The person's eyes may move, thus giving this stage the descriptive name "rapid eye movement," or REM, sleep. People more frequently report dreaming during awakenings from REM versus non-REM (NREM) sleep, and the dreams tend to be longer and involve more social interaction.

INSOMNIA IS CAUSED BY HYPERAROUSAL

Insomnia, the inability to get enough sleep to function normally despite adequate opportunity, is the most common sleep complaint.[12,13] Insomnia may be primary (ie, not associated with another disorder), but it is also seen in many other disorders, ranging from pain to depression. Insomnia may also be intermittent, which is usually associated with various stressors, or it may be chronic. PET studies of the brains of patients who have chronic insomnia show that there is abnormal activation not only of the components of the arousal system, including the hypothalamus and upper brainstem, but also their targets, especially the medial prefrontal cortex and the amygdala. EEG studies show that subjects with insomnia often have nearly normal amounts of sleep, as measured by traditional scoring methods (which identify NREM sleep by slow activity and REM sleep by EMG atonia and a fast EEG). However, analysis of higher frequencies in the EEG, such as

the gamma (greater than 30 Hz) range, shows that the brains of subjects with insomnia have excess gamma activity.[12,14] As gamma activity is associated with waking cortical activity, the EEG in insomnia actually shows components of wake and sleep at the same time, that is, constituting a different state from either traditional sleep or wakefulness. This disparity may account for why, after a night in the sleep laboratory, the clinician thinks that the patient was asleep for most of the night whereas the patient reports that she was awake for most of the night. This ''sleep state misperception'' is not on the part of the patient, but rather the clinician, who is using traditional sleep scoring methods that do not measure the high-frequency cortical arousal.

REM SLEEP IS DRIVEN BY NEURONS IN THE PONS

Recent studies have shown that neurons in the upper pons generate the state of REM sleep.[15,16] These neurons are located in the region just ventral to the locus coeruleus in cats, mice, and probably humans, and just ventral to the laterodorsal tegmental nucleus in rats, and are variously called the subcoeruleus area or the sublaterodorsal nucleus by different authors (**Figure 1-4**). Lesions in this area may cause intermittent loss of some of the features of REM sleep. For example, neurons in the lower part of the sublaterodorsal area are glutamatergic, and they cause the loss of muscle tone (atonia) during REM sleep, which prevents the acting out of dreams. Lesions of this region cause intermittent loss of atonia during REM sleep, leading to a condition called REM sleep behavior disorder, in which dreams are acted out (**Case 1-2**).[15,17] People with REM sleep behavior disorder call out, thrash around, and fight off attackers. Some individuals get out of bed and may hurt themselves by falling over furniture, walking into walls, or even falling out of windows. Studies over the past decade have found that most people with idiopathic REM sleep behavior disorder go on to develop a synucleinopathy, most commonly Parkinson disease or Lewy body dementia, although some develop multiple system atrophy.[19,20] Surprisingly, the mean time from diagnosis of REM sleep behavior disorder to diagnosis of the synucleinopathy is about 12 years, with over 80% developing a synucleinopathy within 20 years. Conversely, about 30% of patients with Parkinson disease or Lewy body dementia have clear evidence of REM sleep behavior disorder in the sleep laboratory. However, the loss of REM atonia is intermittent and there may be relatively little REM sleep during the first night in the laboratory. In addition, reports of calling out, thrashing about in bed, or getting out of bed are common when the patient with Parkinson disease has a bed partner, but many such patients sleep alone. Thus, the prevalence of REM sleep behavior disorder in patients with Parkinson disease may be underestimated. Pathologic examination of the brains of patients with synucleinopathies frequently shows damage to the subcoeruleus region.[21] However, it remains to be established whether this is the cause of the sleep disorder.

Other characteristics of REM sleep, such as the rapid eye movements and EEG desynchronization, also appear to be driven by neurons in the sublaterodorsal region, but each of these phenomena may be controlled by different populations of neurons.[4,15] Thus, it is possible for the phenomena normally associated with REM sleep to become fragmented and for patients to show only some of the typical characteristics. This issue will be addressed below when considering narcolepsy.

KEY POINTS

- Primary insomnia is associated with a state of coactivation of both arousal- and sleep-promoting systems, resulting in a different state in which the EEG simultaneously shows both the slowing of non-REM sleep and the fast frequencies associated with active wakefulness.
- REM sleep behavior disorder is due to a failure of atonia circuitry during REM sleep, allowing the patient to act out dreams, which often are violent.

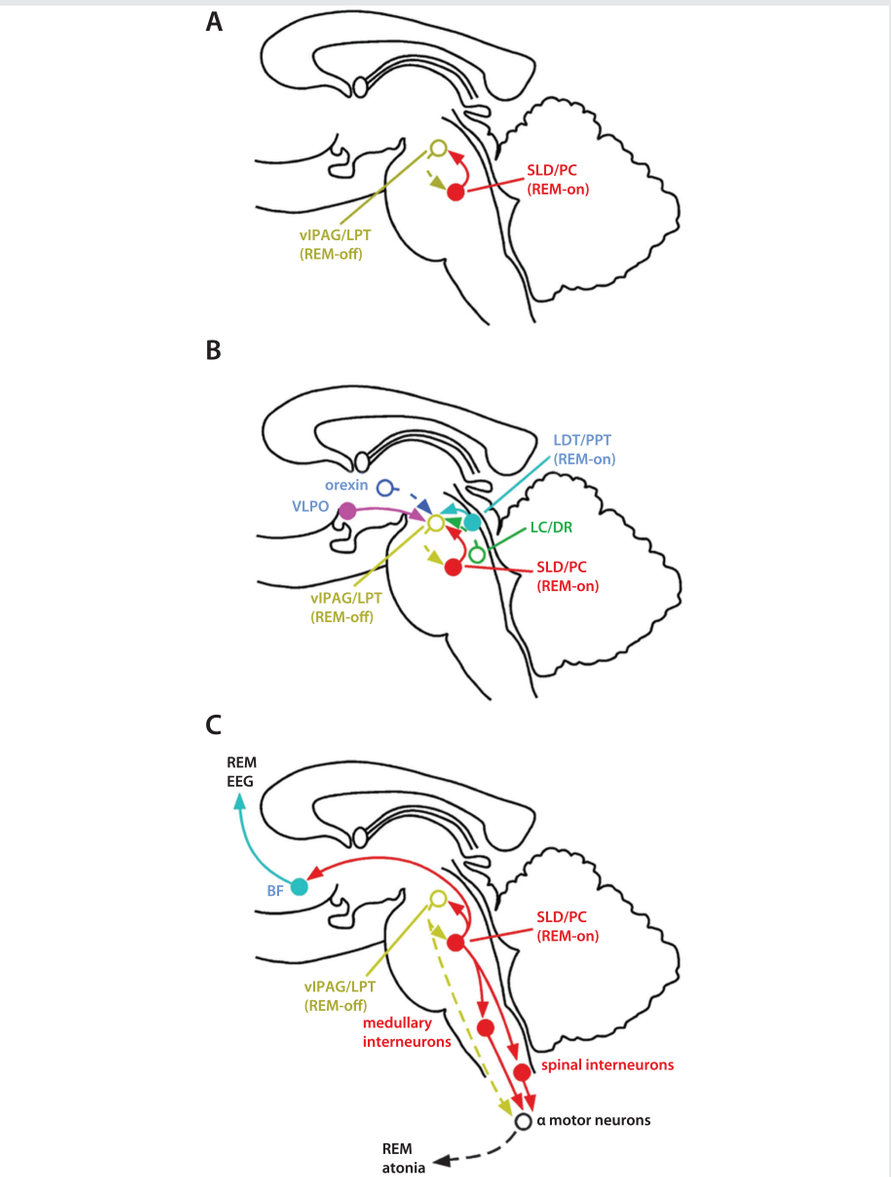

FIGURE 1-4 A series of schematic drawings to illustrate the circuitry thought to be involved in switching into and out of REM sleep. *A*, Neurons in the sublaterodorsal nucleus (SLD) and adjacent precoeruleus region (PC) (*red*) fire during REM sleep and are thought to be the generator for REM sleep. The SLD/PC neurons are inhibited by neurons in the ventrolateral periaqueductal gray matter (vlPAG) and adjacent lateral pontine tegmentum (LPT) (*gold*), and inhibit them, as well. This mutually inhibitory relationship is thought to set up another flip-flop switch, for regulating the transitions into and out of REM sleep. *B*, The REM-off area is regulated by excitatory inputs from the orexin neurons and the monoaminergic locus coeruleus (LC) and dorsal raphe (DR), which prevent REM sleep, and by inhibitory inputs from the ventrolateral preoptic nucleus (VLPO) and cholinergic laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT), which promote REM sleep. *C*, During REM sleep, the REM generator neurons in the SLD/PC send ascending projections to the hypothalamus and basal forebrain that promote a dreaming state and descending projections to the brainstem that cause rapid eye movements and muscle atonia. The atonia is produced by inputs from the SLD to medullary and spinal inhibitory interneurons, which hyperpolarize the alpha motor neurons.

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Case 1-2

A 61-year-old man was seen for evaluation of a right-hand tremor, slowness of movement, and abnormal gait. On examination, he had a soft voice, decreased blinking, and decreased facial expression. He had increased tone and a pill-rolling tremor of the right hand, and he wrote with small letters. The patient walked with a stooped posture, reduced arm swing, and had short steps. A diagnosis of idiopathic Parkinson disease was made, and the patient was started on levodopa, which improved his symptoms.

The patient was a widower who lived alone. He noted that on several occasions he had awakened on the floor with a bruise on his shin, which he had apparently injured when falling across the bedside table. During a sleep laboratory evaluation, he had two brief episodes during REM sleep in which he called out while fighting violently against an imagined intruder. He awakened during one particularly active episode and, when questioned, indicated that he dreamed he took off his shoe and hit the intruder over the head with it. Review of the videotape showed him pantomiming the attack.

He was treated initially with 1 mg clonazepam at bedtime, which reduced the frequency of attacks but did not eliminate them. Melatonin, up to 9 mg at bedtime, did not further alter the frequency. He eventually had to place his mattress on the floor and remove all the furniture from the room. He placed a strap across his body during sleep that prevented him from getting out of bed without waking up.

Comment. Many patients with Parkinson disease or Lewy body dementia have REM sleep behavior disorder. In some cases, the sleep disorder precedes onset of the movement disorder by 10 years or more.[17,18] However, unless the patient gets out of bed during the attacks, the diagnosis often depends upon the report of a partner who sleeps in the same room. Up to 90% of patients diagnosed with idiopathic REM sleep behavior disorder are male, with a peak onset in the seventh and eighth decades of life. Whether this represents a sex difference or an ascertainment bias is not known.

KEY POINT

- REM generator neurons in the upper pons are tonically inhibited by REM-off neurons in the lower midbrain, which gate the entry into REM sleep.

The sublaterodorsal neurons that control REM sleep are normally under GABA-ergic inhibition from nearby interneurons located just rostrally, in the ventrolateral periaqueductal gray matter and in the adjacent part of the lateral pontine tegmentum.[15,22] When these interneurons are firing, they prevent REM sleep (ie, they are REM-off neurons). The REM-off neurons receive input from the ventrolateral preoptic nucleus and the lateral hypothalamus (both orexin and melanin-concentrating hormone neurons), as well as the local cholinergic neurons (which fire during REM sleep) and monoaminergic systems (such as the locus coeruleus and raphe, which cease firing during REM sleep). All of these influences normally regulate REM sleep. In addition, GABA-ergic neurons in the sublaterodorsal nucleus project back to the ventrolateral periaqueductal gray matter and may inhibit the REM-off neurons during REM sleep. This relationship produces the conditions for another flip-flop switch, controlling REM sleep, which may account for the relatively rapid and complete transitions between NREM and REM sleep, which occur over seconds to a few minutes.[4]

KEY POINT

- Orexin neurons in the posterior lateral hypothalamus stabilize the sleep-wake and the REM switches.

OREXIN NEURONS STABILIZE THE SLEEP AND REM SWITCHES

The orexin neurons, which reside in the posterior lateral hypothalamus, contact neurons at multiple levels of the sleep-wake regulatory system.[23,24] There are two orexin receptors, both of which are excitatory, so the effect of this peptide is to activate its targets. These targets include the ascending monoaminergic systems, the basal forebrain cholinergic system, and the REM-off neurons. Orexin neurons typically fire most vigorously during an aroused wake state in which a person is actively exploring the environment (eg, while walking).[25,26] This relationship makes it very difficult to fall asleep while standing or moving about, which of course protects against falls, and is used by sleep-deprived shift workers to remain awake, especially during night work. Because the orexin neurons target the monoaminergic arousal and REM-off neurons, the brain is stabilized in the normal waking state and transition to REM sleep from a waking state is almost impossible for an intact person (**Figure 1-5**).[4]

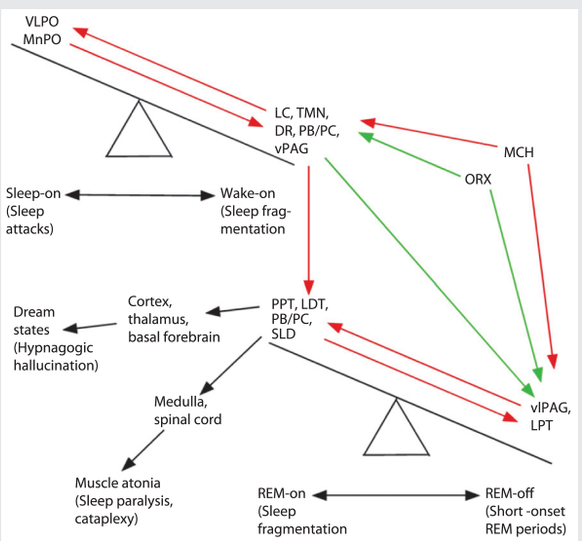

FIGURE 1-5 The two flip-flop switches controlling wake-sleep transitions (*upper left*) and REM-non-REM transitions (*lower right*) form a cascade. During wakefulness, the activity of the monoaminergic cell groups (locus coeruleus [LC], tuberomammillary neurons [TMN], dorsal raphe [DR], parabrachial nucleus/precoeruleus area [PB/PC], and ventral periaqueductal gray matter [vPAG]) inhibit both the preoptic sleep-promoting neurons (ventrolateral preoptic nuclei [VLPO] and median preoptic nuclei [MnPO]) and pontine REM-promoting neurons (pedunculopontine tegmental nuclei [PPT], laterodorsal tegmental nuclei [LDT], PB/PC, sublaterodorsal nucleus [SLD]). This prevents a waking person from directly entering REM sleep. The strength of the monoaminergic system in stabilizing both switches is reinforced by the orexin (ORX) neurons, which are excitatory and fire during wakefulness, and the melanin-concentrating (MCH) neurons that inhibit the monoamine systems and the REM-off cell groups (ventrolateral periaqueductal gray matter [vlPAG], lateral pontine tegmentum [LPT]), and fire primarily during sleep and fastest during REM sleep. In the absence of the ORX neurons in patients with narcolepsy, both switches are destabilized. The instability of the wake-sleep switch produces excess sleepiness during the wake period and excess waking during the sleep period. The instability of the REM switch causes rapid, and in some cases, direct entry into REM from the waking state, as well as fragments of REM sleep, such as muscle atonia (cataplexy) and dreaming (hypnagogic hallucinations), to occur while awake. *Red lines* represent inhibitory pathways and *green lines* show excitatory pathways.

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The effects of loss of the orexin neurons are consistent with these observations.[27] A person who has lost orexin neurons is sleepy during the day and falls asleep easily during lulls in stimulation. Because less tone is present in the REM-off system, people may fall into REM sleep very shortly after sleep onset, and experience fragments of REM sleep while awake. For example, REM atonia may occur during wakefulness. When this occurs in the border zone between sleep and wake, it is called sleep paralysis. Sleep paralysis can occur in normal people, especially if they have been sleep deprived. Some may also have REM-type dreams during the border zone between wake and sleep. When this phenomenon occurs while falling asleep, such dreams are called hypnagogic hallucinations; if they occur while awakening, they are called hypnopompic hallucinations. Such hallucinations are rare in normal people unless they have been sleep deprived, but are very similar to peduncular hallucinosis, which occurs

in patients who have lesions of the midbrain that presumably affect the REM control circuitry. REM atonia may also occur abruptly while awake, often when a person is active and experiencing laughter or joy. These attacks are called cataplexy. Cataplexy does not occur in normal subjects but is a cardinal feature of narcolepsy (**Case 1-3**). Patients with narcolepsy often report sleep paralysis

Case 1-3

A 20-year-old male college student was referred to the neurologist from the student health center for excessive daytime sleepiness. He had been well, sleeping from midnight or 1:00 AM until 7:00 AM or 8:00 AM during most nights of the week and longer on weekends, until about 2 months earlier. At that time, he had a nonspecific flulike illness. One to 2 weeks later, he began to have difficulty staying awake during the day and maintaining sleep during the night. In classes he often felt overcome with sleepiness during a lecture, and napped for 15 to 20 minutes, after which he felt refreshed. One evening while sitting in a chair reading, he realized that he could not move. He tried to get up to ask for help but was unable to move for about 5 minutes before the ability to move returned. On another occasion, while with friends at a pizza parlor, he slumped uncontrollably to the floor while laughing at a joke and was unable to move for 1 to 2 minutes.

He noted that he had gained a few pounds, although his appetite had not increased; however, he admitted to engaging in less exercise and athletics. The general medical and neurologic examinations were normal. An overnight sleep study showed that he had frequent awakenings. A multiple sleep latency test performed the next day showed that he fell asleep in less than 5 minutes on each of five attempts and had short-onset REM periods in three of these.

Genetic testing for HLA-DQB1*0602 was positive. Spinal fluid orexin levels were only 10% of normal.

A diagnosis of narcolepsy was made, and the patient was treated with venlafaxine, a combined norepinephrine and serotonin reuptake inhibitor, in the morning because venlafaxine increases the monoaminergic tone in the brainstem and blocks entry into REM sleep. He also required treatment with modafinil during the day to prevent excessive sleepiness.

Two months later he continued to experience episodes of cataplexy and was started on sodium oxybate (gamma-hydroxybutyrate) at bedtime and again when awakening at 3:00 AM. This drug causes profound and consolidated delta sleep, and the patient found that he was less sleepy the next day and had no further attacks of cataplexy.

Comment. The peak age of onset of narcolepsy is in the teens and twenties, and most patients have had symptoms for several weeks or months before they seek attention.[27] This patient had sleep attacks, sleep paralysis, and attacks of cataplexy. The increased fragmentation of sleep is also a common finding in narcolepsy. It may seem paradoxical, but most patients with narcolepsy with cataplexy both fall asleep too much during wakefulness and wake up too much during sleep.[2,4] This relationship can be explained by the flip-flop switch model of sleep-wake regulation. Similarly, the entry directly from wakefulness into fragments of REM sleep (eg, atonia) is thought to be due to loss of orexin's stabilization of the non-REM flip-flop switch.[4]

Patients with narcolepsy often have a small reduction in appetite but a larger reduction in activity levels, which can result in modest weight gain.

The onset of narcolepsy with cataplexy usually occurs during the second or third decade of life and is associated with loss of the orexin neurons and low orexin levels in the CSF. While in some cases (such as the ones described by von Economo or in the patient described previously in **Case 1-1**) this is due to a lesion involving the posterior lateral hypothalamus, in most patients there is no apparent structural damage. It is believed that the loss of orexin neurons during adolescence or early adulthood is most likely due to an autoantibody that occurs in many populations, mainly in individuals with the HLA-DQB1*0602 genotype, and evidence exists for an increase in frequency following influenza epidemics.[28] Narcolepsy without cataplexy also occurs, but it is not associated with low CSF orexin levels in most patients, in whom the cause remains unknown.

KEY POINT

- The loss of orexin neurons produces narcolepsy, which is characterized by state instability: falling asleep too often when awake, waking up too often when asleep, and falling into partial REM states such as atonia (cataplexy) or dreaming (hypnagogic or hypnopompic hallucinations).

and hypnagogic or hypnopompic hallucinations as well, even when not sleep deprived. Surprisingly, narcoleptic patients not only fall asleep too often during the day, but they also wake up too often at night. It is difficult to understand this predisposition if one considers the orexin neurons to be solely wake-promoting. On the other hand, if one recognizes that the role of orexin is to stabilize the wake-sleep flip-flop switch in the waking state, then loss of consolidated wakefulness will inevitably diminish accumulation of homeostatic sleep drive during the day and thus cause excess transitions of the flip-flop switch from sleep into wakefulness during the night as well. This property of flip-flop switches—that anything that weakens them will cause increased transitions in both states—can be derived mathematically from their properties. This model also predicts that if sleep can be consolidated (eg, by giving a drug such as sodium oxybate), then daytime waking of narcoleptic patients will be more consolidated as well, with fewer transitions to sleep or cataplexy.

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