REVIEW ARTICLE

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Neurobiology and Neuroprotective Benefits of Sleep

By Logan Schneider, MD

ABSTRACT

PURPOSE OF REVIEW: This article outlines the neurocircuitry underlying sleep-wake and circadian physiology with a focus on the fundamental roles that sleep and circadian health play in optimal neurologic function.

RECENT FINDINGS: The foundation of sleep and wake promotion is laid primarily by the "fast-acting" neurotransmitters: γ-aminobutyric acid (GABA) for sleep and glutamate for wake. External to these primary systems are a host of modulatory systems that are characterized by two flip-flop switches of mutually inhibitory neurotransmitter systems that facilitate transitions between wake and sleep as well as non–rapid eye movement (non-REM) and REM sleep. Additional mechanisms are in place to help coordinate the sleep-wake states with environmental, metabolic, and behavioral demands. The complexity of the evolutionarily preserved sleep-wake and circadian systems, the proportion of the day dedicated to the natural sleeping period, as well as the neurocognitive dysfunction and neurodegeneration caused by deficient sleep highlight the importance of defining, assessing, and optimizing the sleep health of our patients and ourselves.

SUMMARY: Exciting discoveries continue to elucidate the underlying mechanisms of sleep and wake state coordination, reinforcing fundamental healthy practices and paving the way for new interventions that preserve and promote optimal neurologic health.

CITE AS:
CONTINUUM (MINNEAP MINN) 2020;26(4, SLEEP NEUROLOGY): 848–870.

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RELATIONSHIP DISCLOSURE:
Dr Schneider has served as an editorial board member for *Practical Neurology* and *Sleep and Breathing* and has received personal compensation for serving on the speakers' bureau for Harmony Biosciences, LLC, and Jazz Pharmaceuticals, Inc, and as a sleep health consultant for Alphabet Inc. Dr Schneider has received research/grant support as a VISN 21 research fellow from the US Department of Veteran Affairs Mental Illness Research, Education and Clinical Centers.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Schneider reports no disclosure.

INTRODUCTION

"If sleep doesn't serve some vital function, it is the biggest mistake evolution ever made."
—Allan Rechtschaffen[1]

Once thought to be a relatively passive state of inactivity, over the past few decades sleep's elaborately orchestrated processes have begun to be revealed as a period of abundant brain activity that is essential to neurologic and general health. Two main brain states of sleep exist: sleep with and without rapid eye movement (REM). Each of these neurocognitive states is fundamental to proper neurologic function, such that selective deprivation of either major sleep stage results in a strong homeostatic rebound of that stage.[2] This emphasizes why sufficient sleep

duration is essential to allowing the dynamic stages of sleep to play out fully (FIGURE 1-1). To coordinate transitions between the three primary states of wake, non-REM sleep, and REM sleep, a highly conserved neurocircuitry has evolved to allow for repeated, smooth transitions between states via mutually antagonistic flip-flop sleep switches that modulate an architecture of "fast-acting" excitatory (primarily glutamate) and inhibitory (primarily γ-aminobutyric acid [GABA]) neurotransmitter systems.

Sleep has been posited to be the price we pay for our brain's plasticity and ability to learn.[3] This homeostatic plasticity theory finds support in the nature of the perceptual disengagement that sleep affords to allow for "offline" processing, the usage-dependent accumulation of somnogens (eg, adenosine), and the sleep-dependent clearance of byproducts of synaptic turnover, such as amyloid-β (Aβ). As such, it appears that we sleep not only to remember but also to forget. From this standpoint, sleep clearly has a role in the preservation of neurologic and physical health. A growing body of evidence is beginning to demonstrate that impairments in sleep quantity and quality—from circadian misalignments, to high day-to-day variability in sleep schedule, to disorders that disrupt sleep—may adversely affect neurologic function. Toward this end, an emphasis on looking at sleep health as a preventive measure in the effort to stave off neurologic decline is growing in evidence-based support and clinical awareness.

The foci of this article are twofold: (1) outline the underlying mechanisms of sleep-wake and circadian physiology and (2) explore the current state of knowledge relating sleep to neurologic health.

THE BASIS OF SLEEP

Sleep, by its nature, is an inherently bottom-up process, and thus, it lends itself to such a description: beginning with neurotransmitter systems, then the self-regulatory circuitry, and finally the interaction between the external environment and the sleep apparatus. This article begins with a description of

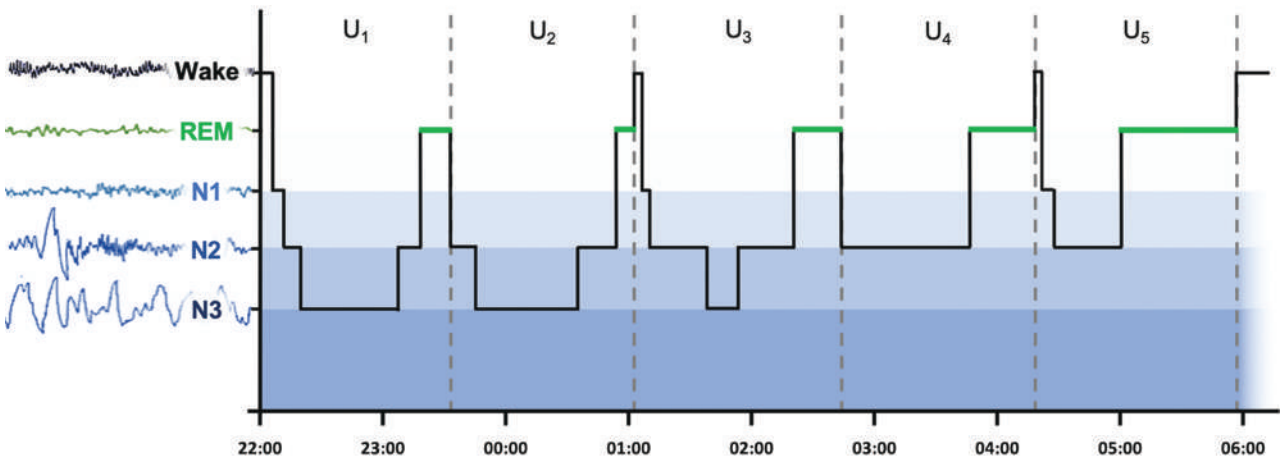

FIGURE 1-1

Schematic of normal sleep architecture across the sleep period. Notice the progressive decrease in N3 (slow-wave) sleep and concomitant increase in the duration of rapid eye movement (REM) sleep bouts as the night progresses over the expected 90- to 120-minute cycles through various sleep stages (ultradian cycles [U_i]), 4 to 6 times a night.

each of the major neurotransmitter systems (their neurophysiology and neurobiology) as they relate to wakefulness and the two main sleep states (non-REM and REM).

Wake-Promoting Neurotransmitters

Two major pathways contribute to the awake, alert, and oriented patient. The ventral partition is constituted by multiple monoaminergic pathways that project from various diencephalic and brainstem regions rostrally via the basal forebrain, promoting cortical arousal (FIGURE 1-2,[4] red pathway). The primary neurotransmitters involved are norepinephrine, arising predominantly from the locus coeruleus; serotonin (5-hydroxytryptamine), localized in the dorsal raphe nucleus; histamine, derived from the tuberomammillary nucleus; and the dopaminergic neurons located in the ventral periaqueductal gray (FIGURE 1-2, nuclear groups in red). These neuronal populations generally exhibit their highest activity during wakefulness, gradually diminish in firing during non-REM sleep, and remain relatively quiescent during REM sleep.

It is not entirely clear why there are so many neurotransmitter systems involved in the promotion of wakefulness. The fact that the elimination of the

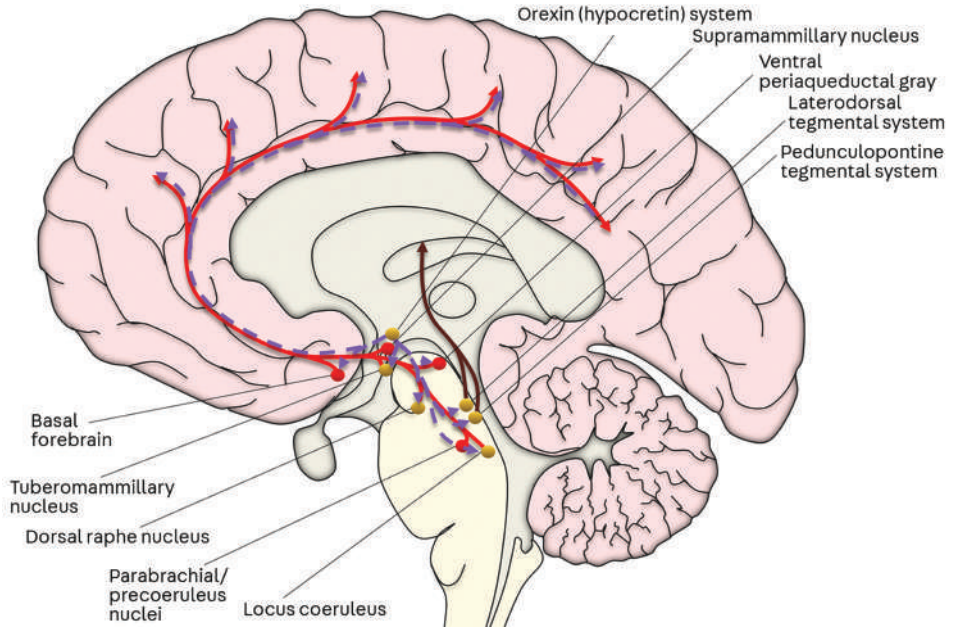

FIGURE 1-2

The neuronal populations primarily responsible for wakefulness. The core systems using "fast-acting" neurotransmitters are highlighted in *red*: the glutamatergic parabrachial/precoeruleus and supramammillary nuclei, as well as the γ-aminobutyric acid–mediated (GABA-ergic) and cholinergic projections of the basal forebrain. Given the relatively prominent decreases in wakefulness (~20%) noted with disruption of the dopaminergic ventral periaqueductal gray, this monoaminergic region is also highlighted in *red*. The modulatory monoaminergic (noradrenergic locus coeruleus, histaminergic tuberomammillary nucleus, serotonergic dorsal raphe nucleus) and cholinergic (laterodorsal tegmental and pedunculopontine tegmental) systems are highlighted in *yellow* with a dorsal pathway feeding into the thalamus indicated in *brown*. The orexin (hypocretin) system that stabilizes the wake state is also highlighted in *yellow*, given its modulatory role, with primary projections indicated in a *dashed purple* line.

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function of any single monoaminergic system is not able to substantially reduce wakefulness, yet so many of the monoaminergic systems can potently promote wakefulness, might point to an intentional redundancy to avoid impairment of such a critical function. However, in light of the discovery that "fast-acting" neurotransmitter systems (such as glutamate, which achieves its effects on target cells within milliseconds through the activation of ligand-gated ion channels) can substantially diminish wakefulness when impaired, an alternative theory suggests that each of the monoaminergic arousal systems tends to promote activities/behaviors that necessarily occur during the waking period, ultimately providing input to the maintenance of wakefulness via distinct pathways. As such, dopamine tends to be associated with motivational/reward-based behaviors (noting connections to the limbic system). Histaminergic and noradrenergic signaling tend to enhance attention in the setting of stressful or novel stimuli. In contrast, serotoninergic neurons tend to also be activated by stress but are noted to produce a state of quiet wakefulness through suppression of non-REM and REM sleep. Regardless of the means by which these systems modulate the waking state, their excitatory effects on the cortex and thalamus appear to be predicated upon the "fast-acting" neurotransmitter glutamate. Observations of the effects these systems have on wakefulness can be examined through the medications whose actions increase or decrease their levels (**TABLE 1-1**). A number of antihypertensive medications suppressing sympathetic activity via α_2 agonism as well as α_1 or β antagonism can result in behavioral and physiologic manifestations of sleepiness. Conversely, amphetamines and amphetaminelike compounds (eg, methylphenidate), which have sympathomimetic effects as a result of not only reuptake inhibition but also release of dopamine (and norepinephrine at higher doses), tend to be potent stimulant medications. Along this line, even medications that only prevent reuptake, such as modafinil (dopamine), the recently US Food and Drug Administration (FDA)-approved solriamfetol (dopamine/norepinephrine), and even bupropion (dopamine/norepinephrine), effectively promote wakefulness but with lower abuse potential. While activation of one isoform of the dopamine receptor DA_1 tends to result in alertness, agonists of the DA_2 receptor frequently result in drowsiness and, occasionally, sleep attacks because of the inhibitory nature of this receptor subtype. The sedating and slow-wave–promoting effects of histamine suppression have been known for decades as a result of mostly off-label use of first-generation antihistamines and psychotropic medications with relative histamine receptor selectivity at lower doses (eg, doxepin, mirtazapine, trazodone). However, because of sleep neurocircuitry revelations derived from narcolepsy, new pharmacologic therapies have been developed, such as histamine (H_3) inverse agonists (acting on presynaptic H_3 autoreceptors), which potently promote wakefulness and even suppress REM sleep phenomena; the latter effect is likely mediated through H_3 heteroreceptors among other monoaminergic pathways. While the multiple isoforms and relative ubiquity of serotonin receptors make it difficult to pinpoint the sleep-wake effects of serotonergic drugs, the vast number of psychiatric medications that result in increased activation of serotonin receptors (eg, selective serotonin reuptake inhibitors, atypical antipsychotics) are generally noted to result in suppression of REM sleep.

However, as mentioned above, none of the monoaminergic systems appear to be necessary for the maintenance of wakefulness to a significant degree. This has led to a recent line of research suggesting that the monoamine systems provide

KEY POINTS

- All stages of sleep are essential, are actively promoted, and will homeostatically rebound if selectively deprived.
- Sleep is dynamic, cycling through stages every 90 to 120 minutes, but also changing from slow-wave predominant to REM predominant over the course of the night.
- Sleep health is not just defined by the duration of sleep but also by schedule regularity, alignment with circadian biorhythms, and continuity/stability.
- Monoamines (dopamine, norepinephrine, serotonin, and histamine) are modulatory neurotransmitters that promote wakefulness.
- The "fast-acting" neurotransmitter, glutamate, is the backbone of the wake-promoting neurocircuitry. The parabrachial/precoeruleus and supramammillary nuclei are the primary wake-promoting glutamatergic centers.

behavioral modulation of a more potent glutamatergic wake-promoting system housed in the parabrachial nucleus (FIGURE 1-2).[5] A subpopulation of neurons in the parabrachial nucleus appears to be responsive to noxious stimuli (eg, stomach stretch) and may underly the arousal response to respiratory blood gas imbalances.[5] Similar to the parabrachial nucleus, glutamatergic systems have also been found in the supramammillary area, with projections demonstrated throughout the basal forebrain and cortex.[5] However, the glutamatergic populations present in the basal forebrain do not appear to play a fundamental role in the wake-promoting activity of this node of the ventral arousal pathways. Instead, the GABA-ergic parvalbumin neurons—along with "back-up" cholinergic populations—seem to mediate the wakefulness facilitated by this brain region as demonstrated by characteristic behavioral and EEG changes induced by selective optogenetic stimulation.[5]

Diverging from the monoaminergic pathways is the dorsally oriented acetylcholine system. The sources of the main sleep-wake relevant cholinergic

TABLE 1-1 **Commonly Encountered Neurologic Medication Classes That Affect Sleep, Wake, and Circadian Systems**

Medication	Proposed Mechanism of Influence
Classes impairing wake	
α_1 Antagonists (eg, prazosin)	Noradrenergic signaling inhibition
α_2 Agonists (eg, dexmedetomidine)	Presynaptic, noradrenergic signaling inhibition
Anticholinergics	Acetylcholine signaling inhibition
Anticonvulsants	Various mechanisms focused on suppressing neuronal excitatory activity (eg, increased γ-aminobutyric acid [GABA] tone)
Antihistamines (particularly first generation)	Histamine signaling inhibition
Antiparkinsonian agents (eg, dopamine agonists)	DA_2 inhibitory receptor activation
Barbiturates and benzodiazepines	GABA signaling
Narcotics	Central κ-opioid agonism
Psychiatric medications: antidepressants (certain monoamine oxidase inhibitors [MAOIs], certain tricyclic antidepressants [TCAs], selective serotonin reuptake inhibitors [SSRIs]) and most antipsychotics	Various mechanisms including serotonin (5-hydroxytryptamine) autoinhibition, anticholinergic activity, and antihistaminergic activity
Skeletal muscle relaxants and antispasmodics (eg, baclofen)	Various central nervous system targets including, $GABA_B$, $5HT_2$, and α_2
Classes impairing sleep	
Antiparkinsonian agents (eg, levodopa, amantadine)	Increased dopaminergic signaling
Cholinesterase inhibitors	Augmentation of acetylcholinergic tone
Catechol-*O*-methyltransferase inhibitors	Decreased monoamine degradation

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neuronal populations are the laterodorsal tegmental and pedunculopontine tegmental nuclei.[4] In contrast to the monoamines, cholinergic neurons show their lowest activity during non-REM sleep and are most active during both wake and REM sleep, likely explaining the common occurrence of post–REM sleep awakenings with most nocturnal ultradian cycles (approximately 90- to 120-minute cycles through sleep stages). It is through the action of these neuronal populations that the cortical desynchronization of conscious processing in wake and REM sleep is likely produced, a phenomenon that is reflected by low-voltage, mixed-frequency activity on EEG.[4] In fact, it is the thalamic depolarization promoted by the laterodorsal tegmental/pedunculopontine tegmental projections that allows for the passage of sensory information to the cortex for processing, as illustrated in **CASE 1-1**. As noted previously, nuclei in the basal forebrain appear to be waystations for signals from monoaminergic systems, as well as the lateral hypothalamic area. Additionally, sending projections to the cortex from a variety of cholinergic populations in the magnocellular preoptic

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Medication	Proposed Mechanism of Influence
Corticosteroids	$GABA_A$ inhibition
Dalfampridine	Potassium channel blockade resulting in neuronal excitability
Narcotics	Central μ-opioid agonism
Nicotinic receptor agonists	Augmented acetylcholinergic tone
Psychiatric medications (SSRIs, serotonin/norepinephrine reuptake inhibitors [SNRIs], certain TCAs, dopamine/norepinephrine reuptake inhibitor [DNRI])	Various mechanisms including increased monoamine (eg, dopamine) activity
Stimulants (amphetamine salts and amphetaminoids)	Dopamine and norepinephrine release and reuptake inhibition
Classes impairing circadian rhythms	
Beta-blockers (eg, propranolol)	Blockade of transduced light cues from the suprachiasmatic nucleus
Classes with other effects on sleep	
Antiparkinsonian agents (eg, levodopa, dopamine agonists)	Restless legs syndrome augmentation, unclear mechanism
Barbiturates and benzodiazepines	Inhibition of medullary respiratory centers
Cholinesterase inhibitors	Odd dreams from cholinergic cortical activation
Narcotics	Chemostatic respiratory suppression of medullary centers and parabrachial nuclei
Serotonergic medications	Inhibition of REM-active atonia-inducing neurons likely implicated in REM sleep behavior disorder, restless legs syndrome, periodic limb movements

nucleus, the substantia innominata, the medial septal nucleus, the nucleus of the Broca diagonal band, and the nucleus basalis of Meynert, the firing patterns of waking cortical EEG are time-locked to the firing of neurons in these regions, suggesting a central role for acetylcholine in the cortical desynchronization of consciousness.

The relatively recent revelation that orexin (hypocretin) underlies the sleep-wake state instability of narcolepsy type 1 has led to the understanding of yet another system important in maintaining wakefulness. The wake-to-sleep gating activity of orexin (hypocretin) seems to promote wakefulness in the context of locomotion and goal-oriented behaviors, such as grooming and feeding. Despite a relatively limited number of orexinergic (hypocretinergic) neurons (~70,000 to 90,000) located exclusively in the lateral hypothalamus,

CASE 1-1

An 80-year-old woman with Alzheimer dementia was admitted 3 days ago for treatment of a community-acquired pneumonia. Despite stability of her metabolic panel and resolution of her leukocytosis with a regimen of IV ceftriaxone and clarithromycin, she became agitated and combative throughout much of the night and day following the addition of a "sleep aid" to her regimen. In her hospital room, she was in four-point restraints in her bed, the curtains were drawn allowing the room to be dark, quiet, and calming, and there was a bedside sitter to prevent the patient from harming herself or others. The patient was disoriented and drowsy, reportedly from being up all night yelling and spitting at the nurses, and became quite agitated with stimulation, preventing meaningful cognitive examination. The remainder of the neurologic examination was nonfocal.

COMMENT

This patient is demonstrating classic characteristics of delirium. In addition to being at a higher risk of a delirium due to her underlying dementia and advanced age, the patient has other acute risk factors, including the environment change and an infection. However, a number of sleep-wake–related dysfunctions also appear to be playing a role. First and foremost is the common culprit of a likely anticholinergic or γ-aminobutyric acid–mediated (GABA-ergic) medication in the patient's regimen. Anticholinergic medications, in particular, suppress the efficacy of conscious processing while the persistence of monoaminergic tone results in an "awake and alert" (but not "oriented") patient who exists in a dreamlike state.

In addition to eliminating offending agents, a mainstay of treatment is regularization of this patient's sleep-wake schedule. Her circadian system can be reestablished by setting a diurnal schedule of activity, sufficient bright-light exposure throughout the day, and regular interaction/reorientation. Additionally, a quiet, dark, undisturbed sleep environment at night should be ensured, and a small dose of 0.3 mg to 0.5 mg of melatonin 2 hours before the desired bedtime could be added. By reinforcing the intrinsic sleep-wake architecture, the proper circadian neurotransmitter rhythmicity can help prevent sundowning.

these neurons have extensive projections throughout the arousal circuitry (FIGURE 1-2, purple pathway). Their potent wake-promoting effects likely result from the relatively dense innervation of the noradrenergic locus coeruleus and histaminergic tuberomammillary nucleus. However, given that patients with narcolepsy type 1 have normal 24-hour sleep durations, despite the nearly complete loss of orexinergic (hypocretinergic) neurons through autoimmune destruction (FIGURE 1-3[6]), the evidence suggests that orexin (hypocretin) is not essential for wakefulness; it appears that it is more important for maintaining a given sleep-wake state, allowing for consolidated bouts of wake and sleep.[7]

Sleep-Promoting Neurotransmitters

Based on the common mechanism of action underlying most sedative/hypnotic medications from barbiturates to benzodiazepines to "Z-drugs" (benzodiazepine receptor agonists that are highly selective for the $GABA_A$ receptor's α_1 subunit, such as zolpidem, zaleplon, and zopiclone), the most obvious neurotransmitter candidate that facilitates sleep is GABA. The main sources of sleep-promoting GABA-ergic activity are the ventrolateral and median preoptic areas (FIGURE 1-4).[4] In concert with the inhibitory neurotransmitter galanin, these groups of neurons project to all of the modulatory arousal systems previously discussed. These neurons are most active in their inhibitory activity during non-REM sleep, with slightly diminished activity during REM sleep, and relative quiescence during wake. Given the relation to the recent discovery of the potently stimulatory, glutamatergic parabrachial nucleus, GABA-ergic neurons in the parafacial zone (so named because of the ventrolateral orientation to the

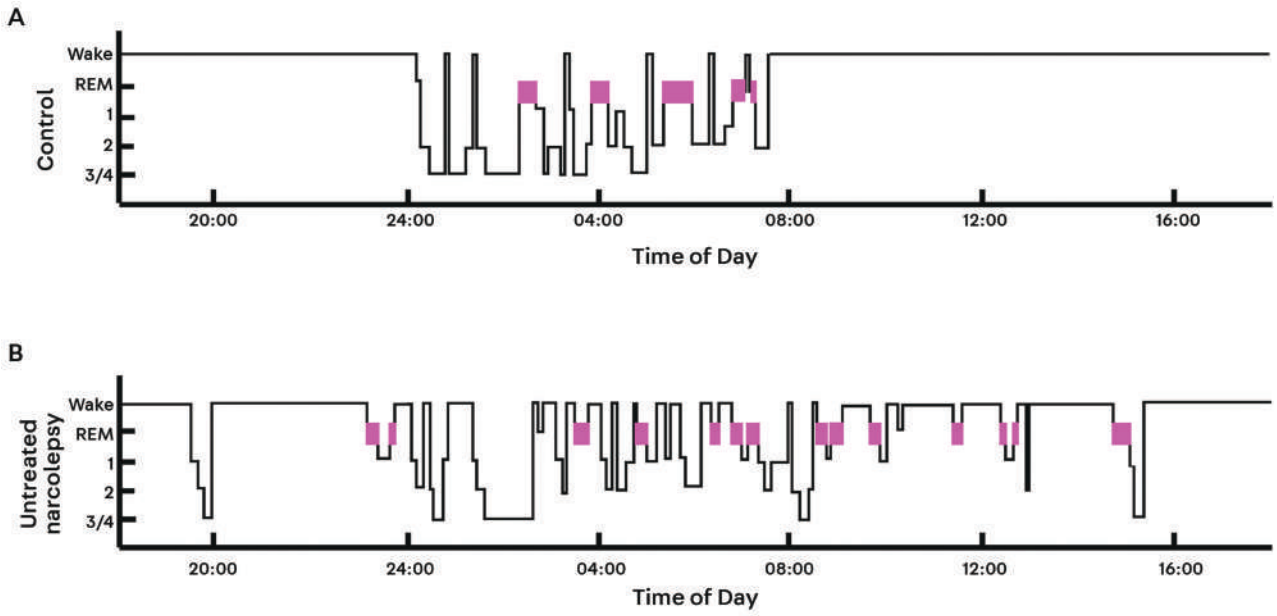

FIGURE 1-3

Comparison of 24-hour hypnograms between a healthy individual (*A*) and an individual with untreated narcolepsy (*B*). Because of sleep-state instability causing nocturnal fragmentation and daytime sleep intrusions, the normal quantities of sleep and wake are abnormally distributed across the 24-hour day in those with narcolepsy.

REM = rapid eye movement.

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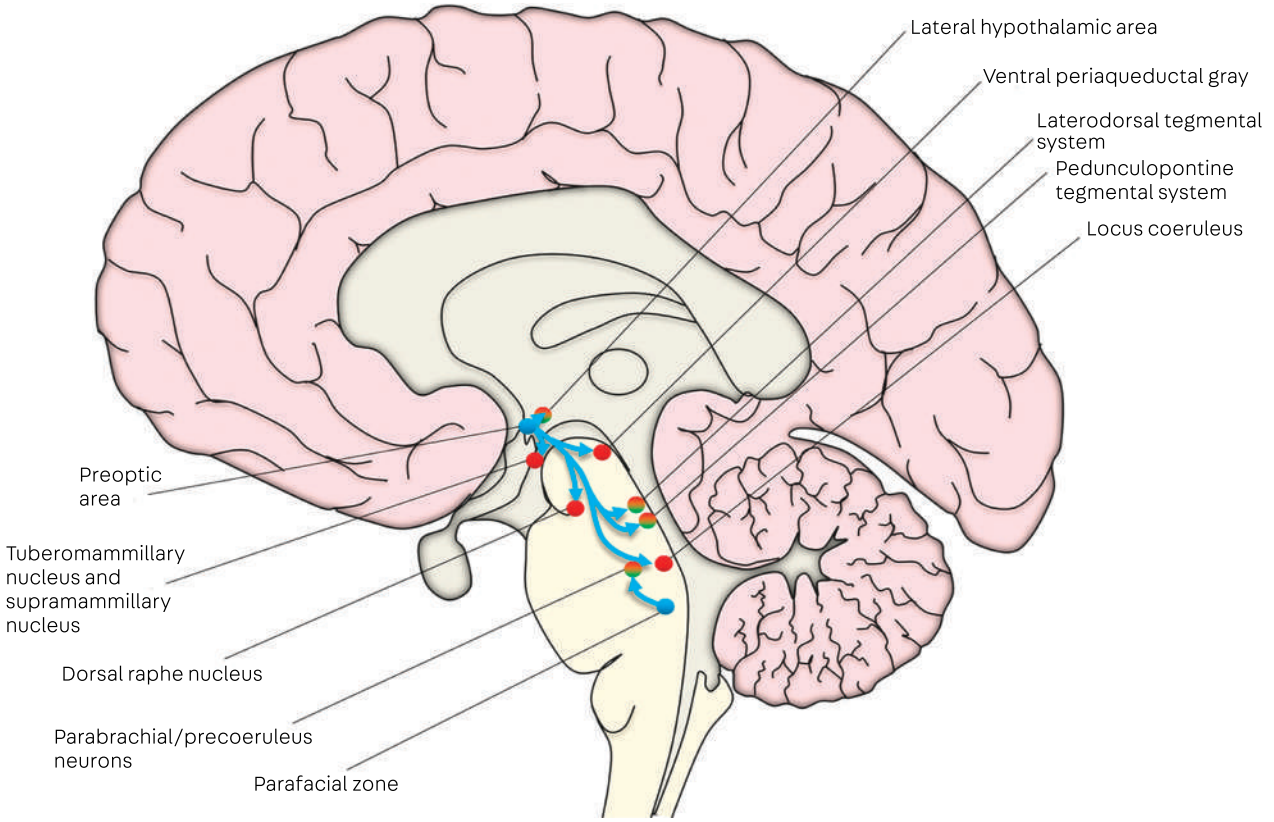

FIGURE 1-4

Primary neurotransmitter systems involved in the promotion of sleep. The γ-aminobutyric acid–mediated (GABA-ergic)/galaninergic preoptic area populations of the ventrolateral preoptic and median preoptic nuclei suppress the activity of the main wake-promoting systems, including the potently wake-promoting monoamine systems, as well as the orexin (hypocretin) system and glutamatergic supramammillary nucleus. The parafacial zone GABA-ergic projections directly inhibit the parabrachial/precoeruleus neurons, as well. Regions predominantly active during wake (noradrenergic locus coeruleus, histaminergic tuberomammillary nucleus, serotonergic dorsal raphe nucleus, and dopaminergic ventral periaqueductal gray) are highlighted in *red*, and regions with activity in both wake and rapid eye movement (REM) sleep (cholinergic laterodorsal tegmental/pedunculopontine tegmental, glutamatergic, and the melanin-concentrating hormone-secreting cells in the lateral hypothalamic area) are colored *red* and *green*.

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seventh cranial nerve) have such profound sleep-inducing and sleep-maintaining effects that traditional stimulants, such as modafinil and caffeine, have no effect on parafacial zone activation.[8] Comparatively, GABA-ergic neurons in the sublaterodorsal nucleus appear to be the primary facilitators of transitioning from non-REM to REM sleep through inhibition of the mutually antagonistic ventrolateral periaqueductal gray (FIGURE 1-5).[4]

Complementing the GABA-induced state of sleep, acetylcholine activity is required for the physiologic change from non-REM to REM sleep. Similar to wake, the neuronal populations originating in the laterodorsal tegmentum/pedunculopontine tegmentum are required for thalamocortical modulation by depolarizing thalamic neurons and converting the "off-line" cortical ensemble synchronous firing into a state of active processing (the theoretical underpinning

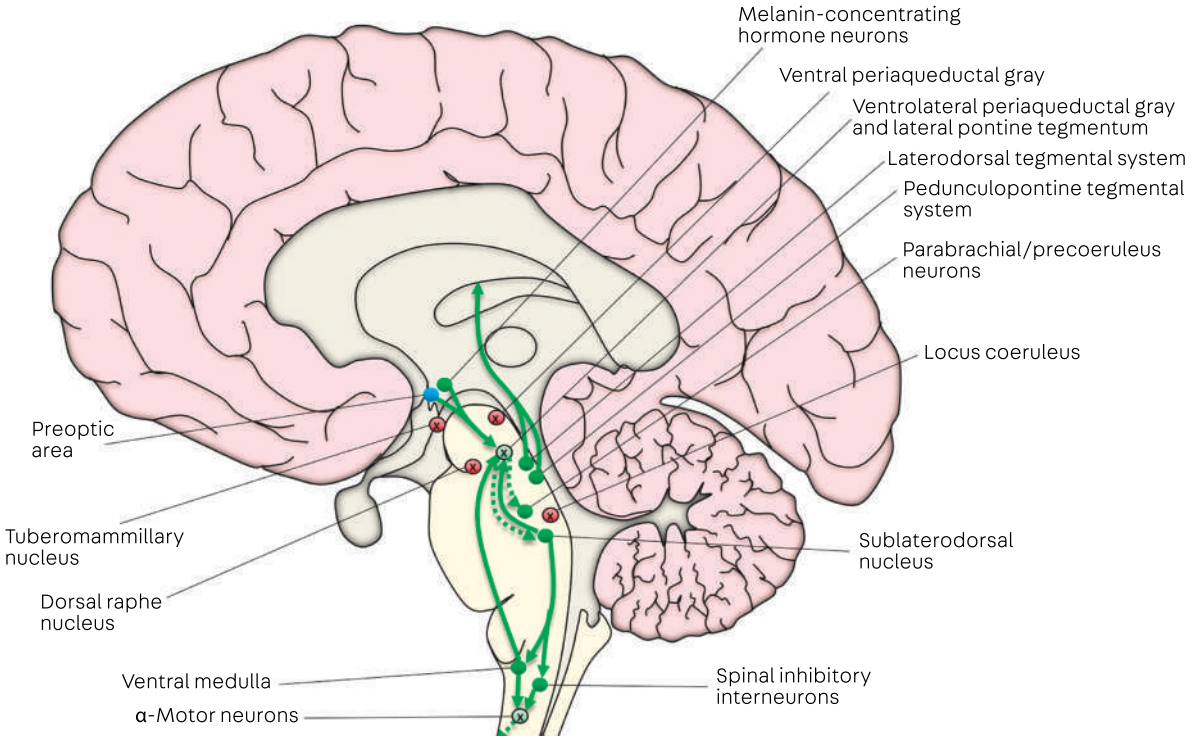

FIGURE 1-5

The rapid eye movement (REM)-active (*solid lines* and *circles*) and REM-inactive (*dashed lines* and *pale, crossed circles*) neurocircuitry. Accompanying the γ-aminobutyric acid (GABA)-induced maintenance of sleep facilitated by the preoptic area, the melanin-concentrating hormone neurons suppress the ventrolateral periaqueductal gray neurons, promoting sublaterodorsal nucleus dominance in the non-REM to REM switch. Direct glutamatergic projections from the sublaterodorsal activate GABA-ergic centers in the ventral medulla to supplement the REM-promoting inhibition of the ventrolateral periaqueductal gray; these glutamatergic projections also activate the glycinergic spinal inhibitory interneurons that, along with caudally projecting ventral medulla neurons, promote REM atonia through suppression of α-motor neurons. The reactivation of cholinergic laterodorsal tegmental/pedunculopontine tegmental and uninhibited glutamatergic parabrachial/precoeruleus neurons contribute to cortical desynchrony.

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of dream mentation). Acetylcholine may also serve a supportive but nonessential role in the facilitation of REM atonia through sublaterodorsal projections to the ventral medulla, which feeds GABA-ergic inhibitory tone back to the ventrolateral periaqueductal gray rostrally and down to the spinal α-motor neurons caudally.[4]

A final, less well-understood, neuronal population is the melanin-concentrating hormone cellular fraction of the lateral hypothalamus that has a nearly one-to-one association with orexin (hypocretin) neurons. Their firing activity—greatest in REM sleep, moderate in non-REM sleep, and virtually absent in wake—and concomitant GABA-ergic staining suggest that they are synapsing upon similar targets as orexin (hypocretin) neurons but may play an opposite role: one of sleep facilitation.[4] Toward this end, manipulations of melanin-concentrating hormone activity demonstrate significant REM-promoting activity through facilitation of non-REM to REM transitions and REM sleep prolongation.[9] A study in 2019 suggested that ambient temperature may play a significant role in

KEY POINTS

- The basal forebrain (using γ-aminobutyric acid [GABA] and acetylcholine) and ventral periaqueductal gray (using dopamine) also strongly promote wake.
- A dorsal flow of acetylcholine pathways from the laterodorsal tegmental and pedunculopontine tegmental nuclei to the thalamus promotes cortical processing reflected by a desynchronized EEG.
- Orexin (hypocretin) neurons in the lateral hypothalamus are critical to stabilization of the wake state and are virtually absent in individuals with narcolepsy type 1 due to immune-mediated destruction.
- GABA is the primary neurotransmitter system involved in active sleep promotion. The main sources of GABA activity are the preoptic area and parafacial zone.
- The acetylcholine system becomes active again during REM sleep, allowing for information to transit through the thalamus for cortical processing.
- Melanin-concentrating hormone neurons in the lateral hypothalamus facilitate non-REM to REM transitions and promote REM sleep in the context of optimal environmental conditions.

the activity of these neurons, such that warmer temperatures appear to facilitate melanin-concentrating hormone neuronal promotion of REM sleep, given that REM sleep is a thermogenically disadvantaged state (due to skeletal muscle paralysis).[10]

Flip-Flop Switches Regulate "Fast-Acting" Neurotransmission

As mentioned above, the backbone of the sleep-wake system has recently been hypothesized to rely upon neurons that can package and release the "fast-acting" neurotransmitters: glutamate and GABA.[5] Based on the fact that relatively minor sleep duration differences are noted with manipulation of the monoaminergic and cholinergic systems, whereas profound changes in wakefulness have been noted with changes to the glutamatergic and GABA-ergic neuronal populations, the monoaminergic and cholinergic neurotransmitters appear to play more of a modulatory role. Fundamentally, the most prominent impairments of consciousness are seen with lesions of rostrally projecting glutamatergic parabrachial nucleus neurons and cortically projecting GABA-ergic/cholinergic basal forebrain neurons.[5] Similar but less profound impairments of wakefulness—on the order of 20% reductions—are noted with lesions to the glutamatergic supramammillary nucleus and the dopaminergic ventral periaqueductal gray.[5]

External to this primary architecture is the complex framework that facilitates transitions between states of wake, non-REM sleep, and REM sleep (FIGURE 1-6). The first of a pair of flip-flop switches is the wake-sleep switch, which is coordinated through a balancing of mutual inhibition between the GABA tone from the preoptic area and the stimulation of the monoaminergic systems. External to this flip-flop switch is the orexin (hypocretin) system, which projects primarily to the monoaminergic nuclei—tuberomammillary nucleus, locus coeruleus, ventral periaqueductal gray, dorsal raphe nucleus—as well as the basal forebrain and cortex.[4] While the orexin (hypocretin) neurons receive inhibitory input from the ventrolateral preoptic area, they do not appear to synapse on neurons in this region, suggesting that their role is primarily one of stabilization of the wake state. Conversely, another group of GABA-ergic neurons in the lateral hypothalamus also appear to promote wake through suppression of thalamic and preoptic area sleep centers.[5]

The transition from wake to sleep leverages the median preoptic area neurons and ventrolateral preoptic area neurons at different times. It appears that the switch is flipped by activity increases in median preoptic area GABA-ergic neurons preceding transitions into non-REM sleep.[4] Thereafter, sustained increases in ventrolateral preoptic area GABA-ergic and galaninergic firing suggest that this subset of preoptic area neurons play a role in the maintenance of sleep.[4]

While maintaining sleep, a subpopulation of the ventrolateral preoptic area—the extended ventrolateral preoptic area—aids in the transition to REM sleep by inhibitory projections onto the ventrolateral periaqueductal gray and lateral pontine tegmentum.[4] By favoring a REM-promoting imbalance of the mutual antagonism between the ventrolateral periaqueductal gray/lateral pontine tegmentum and sublaterodorsal nucleus, the flip-flop switch is able to smoothly transition as the REM-active neurons of the sublaterodorsal nucleus begin to predominate in activity. The suppressed ventrolateral periaqueductal gray/lateral pontine tegmentum activity also withdraws inhibition of the

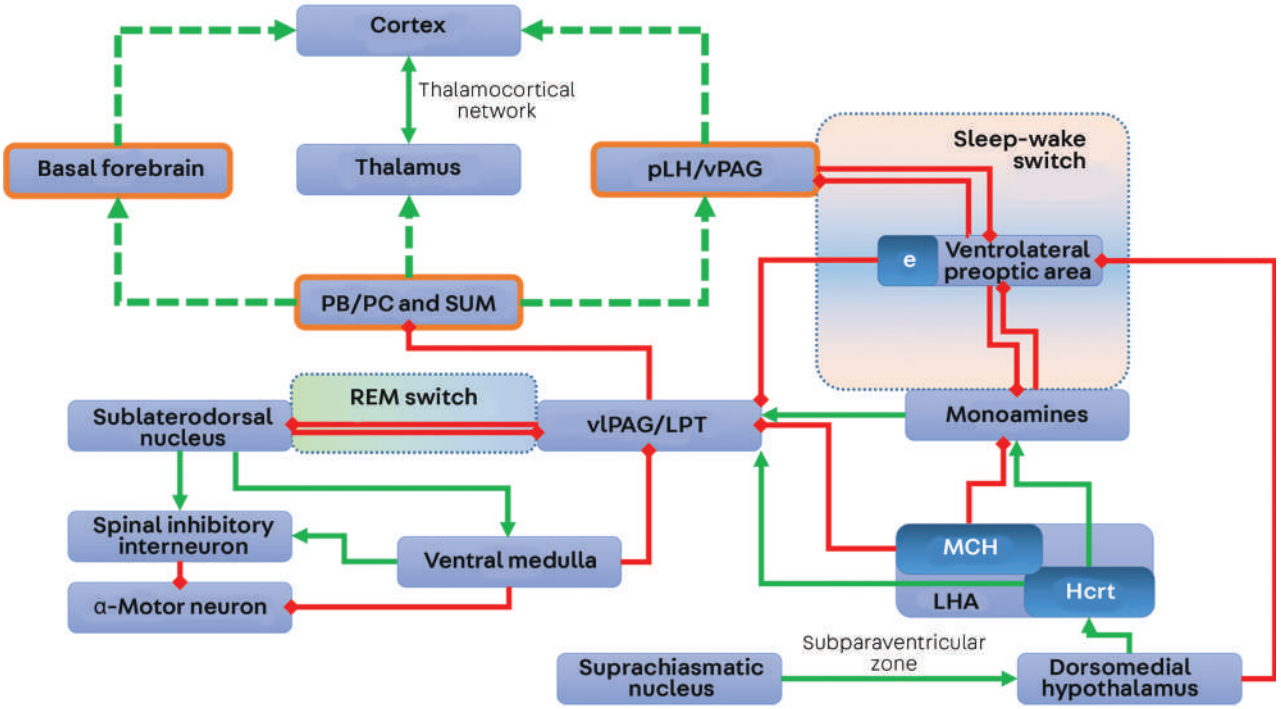

FIGURE 1-6

Schematic of some of the primary pathways involved in sleep and wake promotion: *green* and *red lines* indicate excitatory and inhibitory pathways, respectively. The primary excitatory regions (*orange outlines*) and pathways of the arousal system (*dashed lines)* are indicated. Additionally, the modulatory flip-flop switches are highlighted demonstrating the mutual inhibition primarily between the preoptic area and monoamines as well as between the sublaterodorsal nucleus and the ventrolateral periaqueductal gray/lateral pontine tegmentum (vlPAG/LPT). External to these systems are the state-stabilizing hormones in the lateral hypothalamic area (LHA) and the environmentally/organismally adaptive inputs integrated through the dorsomedial hypothalamus.

e = extended ventrolateral preoptic area; Hcrt = orexin (hypocretin); MCH = melanin-concentrating hormone; PB/PC and SUM = parabrachial/precoeruleus and supramamillary nuclei; pLH/vPAG = posterior lateral hypothalamus/ventral periaqueductal gray; REM = rapid eye movement; vM = ventral medulla.

glutamatergic parabrachial nucleus neurons, facilitating cortical and hippocampal EEG activation. Supplementing either side of this flip-flop switch are the monoaminergic and orexinergic (hypocretinergic) inputs that augment the activity of the REM-inactive (ie, REM-suppressing when active) neurons, in addition to the GABA-ergic collateral pathways from the melanin-concentrating hormone neurons and ventral medulla that promote REM sleep through inhibiting the REM-inactive neurons. From the sublaterodorsal nucleus, a series of glutamatergic excitatory pathways course caudally, feeding into the ventral medulla and spinal inhibitory interneurons to produce the characteristic atonia of REM sleep.

Two-Process Model

The aforementioned sleep-wake circuitry is the product of millions of years of evolution, with myriad species manifesting at least some form of quiet (non-REM) and active/paradoxical (REM) sleep. As such, mechanisms have evolved to adapt the coordination of sleep and wake to the needs of individual

organisms. The most notable hypothesis regarding sleep-modulating systems was put forth by Borbély[11] in 1982: the two-process model (FIGURE 1-7). In this model, a homeostatic drive (Process S) to sleep depends on duration of wakefulness and level of physical and cognitive activity. Additionally, an externally entrainable system (Process C) functions to integrate environmental and organismal cues into approximately 24-hour—circadian, "about a day"—biorhythms that orient alertness to the times most suited for waking activities (eg, feeding).

As a result of experiments demonstrating the interorganism transmissibility (via CSF transfusions) of sleepiness at the beginning of the 20th century, efforts to discover the "substance" of sleep have been ongoing, revealing a host of biological substances from hormones to neuropeptides to simple signaling molecules. Formalized criteria have been proposed regarding what can constitute such state-regulating substances (TABLE 1-2[12]), of which a number have been discovered in relation to the promotion of wakefulness (corticotrophin-releasing hormone and ghrelin), non-REM sleep (growth hormone–releasing hormone, adenosine, interleukin 1β, tumor necrosis factor α, prostaglandin D_2, and nitric oxide), and REM sleep (vasoactive intestinal peptide and prolactin). The most studied of these various substances is adenosine. Adenosine appears to play important roles in sleep promotion via the local induction of sleep through action on inhibitory purine receptor A_1 isoforms located ubiquitously throughout the brain and top-down transmission of the homeostatic drive to the sleep-promoting ventrolateral preoptic area by means of excitatory A_{2a} purine receptors that are located in the adjacent meninges.[4] Moderated by astroglial signaling, postsynaptic A_1 receptor sensitivity is increased in the face of increased synaptic ATP, which is coreleased from vesicles along with most neurotransmitters and is converted to adenosine by synaptic ectonucleotidases.[4]

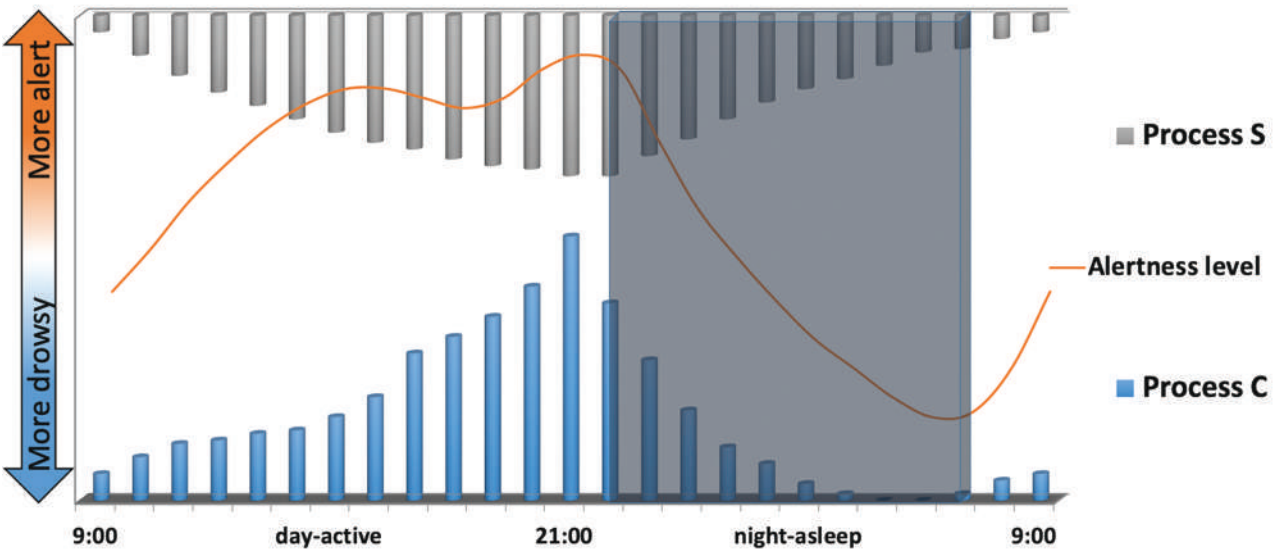

FIGURE 1-7
Two-process model of sleep. A linearly accumulating and dissipating homeostatic (Process S) drive to sleep counteracted by a circadian alerting signal that has approximately 24-hour biorhythmicity (Process C).

This points to a mechanism by which locally promoted sleep scales in proportion to the degree of neuronal activity.

As noted above, somnogens like adenosine are the most likely neurobiological agents underlying the homeostatic Process S. The build-up of these state-regulating substances parallels behavioral signs of sleepiness and delta power in the EEG.[13] Cortical application of some of the state-regulating substances (eg, interleukin 1β, tumor necrosis factor α, and prostaglandin D_2) can induce local slow-wave activity and heightened c-Fos expression (a marker of neuronal activity) in the ventrolateral preoptic area, pointing to a top-down homeostatic instigation of sleep.[12] To balance this, the circadian system is hypothesized to increase wakefulness at the end of the day, when the accumulated homeostatic drive to sleep is greatest.[14] Given that sleep homeostatic drive is derived from multiple brain regions, the specific interaction with circadian circuitry has been hard to pinpoint, although the ventrolateral preoptic area seems to be a logical nexus of activity. Toward this end, experiments in *Drosophila* point to a role for circadian cells in mediating the ability of sleep-promoting brain regions (such as the adenosine-activated ventrolateral preoptic area) to drive sleep, particularly at the day-night transition when the load of somnogens is reaching a zenith.[15]

Retinohypothalamic neurons transduce photic stimuli via the blue-light-sensitive (~479-nm wavelength) melanopsin photopigment.[16] This light signal is mediated by G proteins, which serve to synchronize the transcription of a complex positive and negative feedback gene architecture (eg, *CLOCK:BMAL1/ARNTL*, *PER:CRY*), thereby dictating the rhythm of the endogenously cycling master clock (ie, the suprachiasmatic nucleus).[17] The suprachiasmatic nucleus signal traverses the subparaventricular zone as it heads to the dorsomedial hypothalamic nucleus, where it then connects to the primary sleep-wake circuitry, providing glutamatergic projections to the orexin (hypocretin) system of the lateral hypothalamic area and GABA-ergic inhibition to the ventrolateral preoptic area.[18] The connectivity of the dorsomedial hypothalamic nucleus in concert with the finding that subparaventricular zone/dorsomedial hypothalamic nucleus-lesioning studies result in disruption of multiple dimensions of biorhythmicity further supports the notion that Process C is an alerting signal and is generally inhibitory to the active promotion of sleep.[11]

Proposed State-Regulating Substance Criteria[a] **TABLE 1-2**

- Should primarily promote indicated state (ie, sleep, non–rapid eye movement [REM], or REM)
- State decreases should occur with inhibition of the state-regulating substance activity
- State propensity should correlate with state-regulating substance levels in the brain (or receptor sensitivity or abundance)
- The state-regulating substance should act on sleep regulatory circuits
- Changes are proportionate with pathologies that are associated with sleep/sleepiness or wake/wakefulness

[a] Data from Krueger JM, et al.[12]

Additionally, the circadian regulation of biorhythms is facilitated through the release of hormones in anticipation of the desired activity state. The paraventricular hypothalamic nucleus is tonically inhibited by light-activated suprachiasmatic nucleus GABA-ergic projections. The pathway then proceeds via a second-order neuron down to the intermediolateral cell column of the spinal cord and on to the superior cervical ganglion. The postganglionic sympathetic release of norepinephrine activates β-adrenergic receptors in the pineal gland, which results in the production of melatonin. Thus, the disinhibition of the paraventricular hypothalamic nucleus, facilitated by crepuscular (twilight) light levels, results in sleep-anticipatory melatonin level increases (ie, the dim-light melatonin onset) about 2 hours before habitual bedtime in humans. Negative feedback mechanisms of melatonin onto the suprachiasmatic nucleus—more so by melatonin receptor subtype MT1 than MT2—indicate that melatonin-receptor signaling is required for entrainment of biorhythms.[19] Similar to melatonin secretion, the wake-anticipatory release of corticosteroids is moderated by the paraventricular hypothalamic nucleus. Primarily through dorsomedial hypothalamic nucleus intermediaries, polysynaptic suprachiasmatic nucleus outputs prompt the release of corticotropin-releasing hormone from the parvocellular division of the paraventricular hypothalamic nucleus. This results in increases in cortisol approximately 2 to 3 hours before habitual wake time (coinciding with the nadir in core body temperature and the apex in melatonin levels), signaling the activation of the hypothalamic-pituitary-adrenal axis, thereby readying the organism for the myriad stressors of the active phase.

THE FUNCTIONS OF SLEEP

In the face of epidemic levels of insufficient sleep and a general decline in nightly sleep durations over the last century, many groups have provided guidelines on the amount of sleep recommended across the lifespan (FIGURE 1-8[20–22]). Using a chronic sleep-restriction protocol, Van Dongen and colleagues[23] demonstrated not only that at least 8 hours of sleep per night is needed to prevent decrements in vigilance but also that individuals quickly—within 3 days—lose awareness of the accumulating impairments imposed by chronic sleep restriction. While a significant amount of emphasis is placed on achieving optimal sleep duration, this likely distracts from aspects of sleep that underly its fundamental functions in brain and body health. The changes in macroarchitecture over the course of a night's sleep suggest that sleep is not measured just by quantity but also by quality. However, aside from the absence of sleep disorders, a definition of sleep and circadian health, as it pertains to the optimization of neurologic function, is likely a multidimensional construct that has yet to be elucidated.

Toward this end, as a final exploration of sleep in this article, we turn to the question of the functions of sleep. Most of the implicated functions of sleep are based on observational studies and lack the ability to establish causality. However, a vast body of research has grown out of these associations in connection with better neurophysiologic measurement of the impact of sleep and sleep deprivation. The most extensive exploration of the effects of sleep deprivation, performed by Rechtschaffen and colleagues,[24] emphasizes the global dysfunction of total, non-REM, and paradoxical (REM) sleep disruption/deprivation in rats: weight loss, decreased food intake and increased

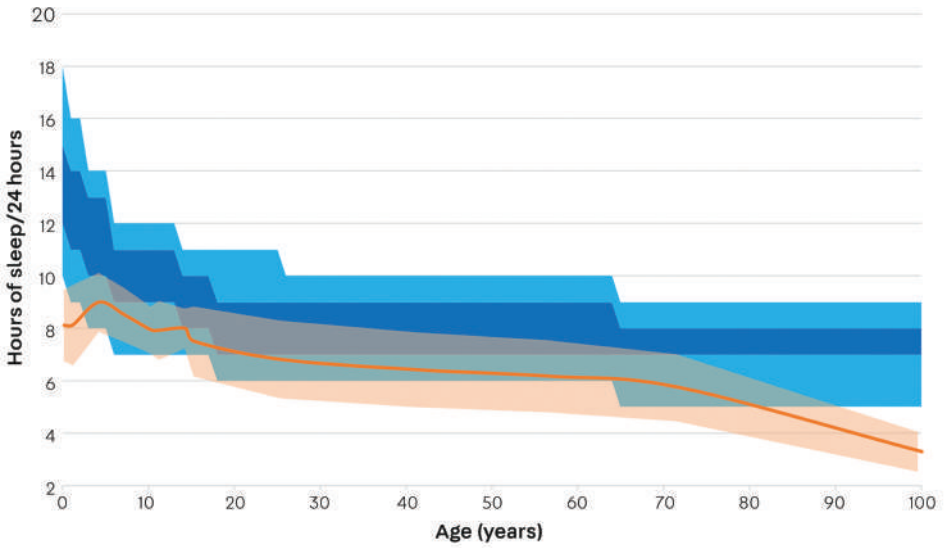

FIGURE 1-8

Comparison of National Sleep Foundation sleep opportunity recommendations[20] (*dark blue*: recommended; *light blue*: may be appropriate) to actual nocturnal sleep duration (represented as mean ± standard error of the mean by the *orange line and area*) derived from 209 pediatric sleep studies, divided by developmental stage,[21] and a meta-analysis of 5273 polysomnograms in healthy adults[22] over the lifespan. Note that the deviation from sleep duration recommendations for those younger than the age of 5 is a reflection of the fact that the nocturnal polysomnographic sleep durations do not include daytime naps.

energy expenditure, poikilothermia, disheveled fur and skin lesions, adrenergic activation and lowered thyroxine, and eventual death.[24] One seemingly obvious basis of sleep is for recovery through the clearance of the toxic consequences of neuronal activity (FIGURE 1-9[25]).[26] Given the potential excitotoxicity of persistent glutamatergic signaling, mediated by reactive oxygen species, and the reductions in normal levels of reducing agents (eg, glutathione and superoxide dismutase) in sleep-deprived animals, a role for sleep in recovery seems apparent. Furthermore, common proteins associated with neurodegenerative processes—Aβ, tau, and α-synuclein—accumulate as a consequence of neuronal activity. As such, the finding that clearance of potentially neurotoxic substances (such as Aβ and tau) is hindered by sleep deprivation has implications for human neurodegenerative disease pathogenesis.[27] Conversely, orexin (hypocretin) antagonists have been found to dramatically improve the sleep of patients with Alzheimer disease (AD) and to decrease Aβ plaque formation in mice, supporting a potential connection between increased orexin (hypocretin) levels and Aβ in patients who have mild cognitive impairment and AD.[25,28] Despite this being a reasonable association and hypothesis, the normal prevalence of AD in patients who have orexin (hypocretin)–deficient narcolepsy would suggest that orexin (hypocretin) suppression alone is not sufficient to ameliorate neurodegeneration associated with sleep deficiency. With the recent description of the brain's extensive paravascular glymphatic system, facilitating clearance of such metabolic byproducts most effectively in slow-wave sleep, the connection between sleep and neural/glial health is beginning to crystalize.[29] These mechanisms are not just modulated by state of sleep but are also influenced by circadian regulation of central and peripheral proteasome function, redox

KEY POINTS

- There are two flip-flop switches modulating wake-sleep and non-REM to REM transitions through balances of mutual inhibition: the former is primarily composed of the preoptic area and the monoaminergic system, and the latter is primarily composed of the ventrolateral periaqueductal gray and the sublaterodorsal nucleus.
- External to the intrinsic sleep-wake circuitry are processes—homeostatic and circadian—that adapt sleep to the needs of the organism.
- A number of state-regulating substances have been identified, the most well-known of which is the sleep-promoting molecule adenosine, which strongly correlates with sleepiness and delta power in the EEG.
- An approximately 24-hour (circadian) alerting signal promotes wakefulness during the day but dips in the latter half of the night to maintain sleep.
- Light-transducing retinohypothalamic signals are integrated with other time-giving signals in the dorsomedial hypothalamus to align central biorhythms to behavioral and environmental inputs.
- Blue light (like that from phone, computer, and television screens) suppresses the sleep-related hormone, melatonin, which begins to elevate 2 hours before habitual bedtime and peaks 2 to 3 hours before habitual wake time.

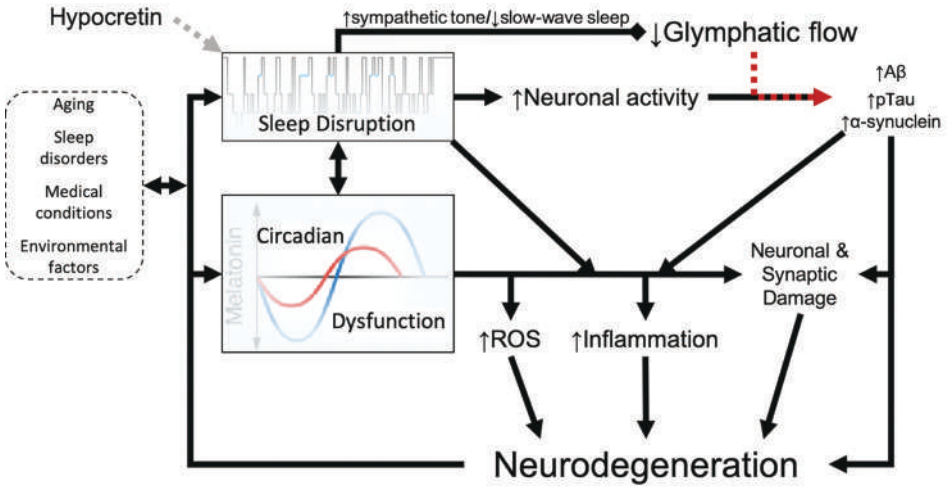

FIGURE 1-9

Model demonstrating the contribution of sleep and circadian function to the neurodegenerative process. Through diminished, fragmented, and misaligned sleep, increases in neuronal activity consequently increase toxic protein production—amyloid β (Aβ), hyperphosphorylated tau (pTau), and α-synuclein—and accumulation as a result of decreased sleep-mediated glymphatic clearance. Additionally, increased inflammation as well as excitotoxic reactive oxygen species (ROS) production and dysregulated antioxidant activity compound the neuronal and synaptic damage that leads to neurodegeneration, promoting further sleep-wake and circadian impairment. While sleep and circadian degradation is related to the natural aging process, a number of external influences can exacerbate the problem. The wake-stabilizing hormone, orexin (hypocretin), has been noted to be elevated in individuals with Alzheimer disease–related cognitive decline and sleep deficiency, but its role in the pathogenesis of the disease is not fully understood.

Modified with permission from Musiek ES and Holtzman DM, Science.[25] © 2016 American Association for the Advancement of Science.

activity and antioxidants (such as glutathione), glucose and lipid metabolism, immune system function, hormone secretion, and even gut microbiome oscillations.[25] Toward this end, dysregulation of these biorhythms through acute "jet lag" in animal models results in diminished hippocampal neurogenesis and impaired learning and memory, while in humans chronic circadian misalignment (as in intercontinental flight attendants) is associated with hippocampal atrophy.[25]

Additionally, energy conservation has been proposed as one of the primary functions of sleep. Reductions in energy expenditure are logically attributable to circadian influence, thermoregulation, and reduced muscle activity, but the metabolic rate reduces by only about 15% during sleep (given that the basal metabolic rate contributes to about 80% of energy expenditure), suggesting that sleep may not be so much about reduced energy expenditure but more about optimal allocation of energy expenditure to different brain/body functions across different sleep/wake states.[30] As such, in the context of sleep deprivation, energy expenditure paradoxically increases at the expense of efficiency.[24] This process is purported to be mediated through changes in hormonal secretion patterns, sympathetic stimulation, and inflammation. One cohesive explanation for such diverse and systemic metabolic consequences of sleep deprivation relies on the economics of supply and demand in a body whose paramount metabolic player is the brain.[31] As a consequence of the derangement of the neuron-glia metabolic

coupling caused by the stress of sleep deprivation, a metabolic "brain pull" is established to meet the increased neuroenergetic demands of the brain at the expense of the body. Through a combination of redistributed brain metabolic resources causing poor decision making (eg, through hypometabolism in prefrontal cortices) and hunger hormone imbalance (ie, increased ghrelin/decreased leptin), ample energy intake from the local environment is ensured when sleep is impaired. Concomitantly, to ensure the maintenance of sufficient energy supply, insulin resistance and glycogenolysis/gluconeogenesis are facilitated through the hypothalamic-pituitary-adrenal axis and sympathetic activation.

With the repletion of energy stores permitted by the energetically favorable sleep state, the body's energy balance can be restored, favoring one of the original hypotheses for sleep function: tissue recovery. The immune system is a prime example of how the resilience of the body is intimately connected to sleep. In particular, a large number of studies have implicated sleep and the immune system in a bidirectional relationship. The activation of astrocytes and the inflammatory response of microglia both demonstrate pronounced circadian variation.[25] Additionally, cytokines increase both centrally and peripherally with sustained wakefulness, the former behavior characterizing cytokines as state-regulating substances that can be potentiated in the context of antigenic challenge with hosts suffering increased susceptibility to infection in the setting of sleep deprivation.[32] Furthermore, leukocyte levels (as opposed to erythrocytes) have been noted to proportionally increase in relation to longer sleep times in mammals.[33] Finally, establishing immune memory may be dependent on quality sleep, as people with impaired sleep demonstrated nearly twofold reductions on antibody titers in response to vaccination.[34]

The neurocognitive consequences of sleep deprivation suggest a role for sleep in ensuring proper neural function and network stability. Even though the individually variable effects of acute and chronic sleep restriction/deprivation suggest a genetic susceptibility, the general accumulation of impairments over the course of sleep deprivation is most evident in tasks requiring processing speed, executive function, and working memory.[23,35] The deficits in these higher-order cognitive domains correlate with dysfunction in prefrontal cortex, anterior cingulate, posterior parietal systems, and thalamus, with functional neuroimaging studies (ie, functional MRI [fMRI] and positron emission tomography [PET]) suggesting that the wake-state instability may be the result of the impingement of sleep-promoting activity, as exemplified in **CASE 1-2**. Despite this, complex tasks are able to recruit larger networks to maintain performance levels, whereas vigilant attention remains impaired due to a lack of broader network activation.[35] Decreased metabolism locally (in the aforementioned systems) but not globally, as well as changes in receptor binding (eg, increases in A_1 receptors in orbitofrontal cortex and decreases in thalamic DA_2/DA_3 binding), suggest that accumulating homeostatic sleep drive contributes to eventually irrepressible input to the sleep-promoting circuitry (ie, ventrolateral preoptic area) and promotes wake-sleep transitions locally. It is this phenomenon that informs the very nature of sleep's role in memory creation as well.

As noted earlier, mechanisms such as the adenosine/ATP balance allow for targeting the most used circuits for stabilization, thereby preserving learned memories. This makes intuitive sense in the context of Hebbian learning,

KEY POINTS

- Allowing for the recommended age-appropriate sleep opportunity every night is essential to ensure optimal daytime neurocognitive function.
- Chronic (partial) sleep deprivation of non-REM or REM sleep can result in dysfunction of multiple organ systems, ultimately resulting in death; both non-REM and REM sleep are essential.
- Increased production and decreased clearance of toxic proteins—Aβ, tau, and α-synuclein—are a fundamental dimension of the neurodegenerative consequences of sleep/circadian deficiency.
- Sufficient sleep is necessary to ensure that the brain and body properly allocate and restore energy stores.
- Central neuroinflammation and peripheral immune-compromise are consequences of insufficient sleep.
- Cytokines (eg, tumor necrosis factor α and interleukin 1β) are state-regulating substances that promote sleep in the setting of infection/inflammation.
- Vigilance and attention are neurocognitive functions most vulnerable to impairment from acute and chronic sleep deprivation, likely as a consequence of microsleeps impinging into wakefulness.

CASE 1-2

Following a busy 28-hour call shift that included 10 overnight consults and admissions, a junior resident was attempting to present the overnight admissions to the team on morning rounds. Despite referencing his notes, the resident had difficulty recalling the details of the cases and mixed up patient histories and examinations. When the attending physician attempted to teach during the discussion of the cases, the resident frequently yawned and was noted to briefly fall asleep in his chair. After rounds, the senior resident had to keep prodding the junior resident to get his notes written and head home, but the junior resident was taking longer than usual because he kept rechecking the same imaging and laboratory studies to add them to the notes. The junior resident also kept complaining about how cold the workroom was, despite wearing a hooded sweatshirt, and uncharacteristically ate nearly one-half of the doughnuts that the attending physician brought for the team.

COMMENT

This junior resident is manifesting many of the hallmarks of acute sleep deprivation: memory problems, overt sleepiness, concentration difficulties, poikilothermia, and impaired judgment. These issues were likely compounded by the chronic insufficient sleep that may be encountered in residency training. The neurocognitive domain that is most impaired following acute sleep deprivation is alertness.[36] A number of symptoms can manifest as a result of acute sleep deprivation, including brief (3- to 10-second) periods of sleep that impinge into wakefulness (microsleeps). While highly engaging tasks may help individuals maintain consciousness, low-stimulation activities, including passive didactics, note writing, and the monotony of driving, increase the likelihood of lapses into sleep, and thus, anyone in this state of sleep deprivation should not drive. In fact, after 24 hours of sustained wakefulness, cognitive psychomotor performance is equivalent to a blood alcohol concentration of 0.1% (above the legal limit for driving in most states).[37]

In addition to acute neurocognitive impairments, sleep is fundamental to the ability to encode memories.[38] We sleep not only to remember but also to forget. Ensuring sufficient duration of sleep and appropriate timing in relation to learning is the only way to effectively eliminate extraneous data and consolidate important information. The junior resident's difficulty with organizing the details of the multiple cases while on rounds likely reflects the consequences of the lack of time allocated for sleep-dependent memory processes. Not only does this likely impede effective learning in the training environment—dispelling the classic "quantity over quality" dogma of residency training—but it may also underlie learner dissatisfaction and burnout.[39]

whereby sleep can promote the recalibration of synaptic strength and cellular homeostasis.[40] Such a need for synaptic regulation to reinforce memory traces in the plastic brain has been confirmed on a cellular level, as well as through connectivity analyses in functional neuroimaging and electrophysiologic studies. As such, animal studies have begun to elucidate the role of specific sleep states in the learning process. Originally presumed to serve a role only in synaptic downscaling through cortical disengagement, slow-wave sleep appears to serve both a memory-consolidating and a memory-diminishing role.[38] Exploration of the phase and firing rates of neurons during slow-wave sleep has suggested that subthreshold synaptic inputs during slow-wave up states may result in synaptic weakening, whereas inputs sufficient to elicit postsynaptic spiking during slow-wave down states might lead to synapse strengthening. This is congruent with the observation that disruption of slow-wave sleep can impair memory consolidation, in addition to the fact that slow-wave sleep augmentation through closed-loop auditory or transcranial direct-current stimulation can improve motor recovery in patients with stroke and declarative memory in cognitively unimpaired individuals as well as those with mild cognitive impairment. Another characteristic non-REM electrographic phenomenon, the spindle, has been repeatedly demonstrated to be important in sleep-related memory consolidation. In addition to a topographic relationship to learning, such that spindle density is increased in regions of preceding task acquisition, the phase relationship to the slow-wave up state, which tends to degrade in late life, seems to be important.[41] Comparatively, REM sleep has been linked to perceptual learning, creative problem solving, and emotional memory consolidation, the last of which has been correlated to the hallmark prefrontal theta activity.[38] These theta waves appear to be instigated by parvalbumin-expressing hippocampal fast-spiking interneurons and have a phase relationship with pontine-geniculate-occipital waves. Similar to non-REM, the coordination of the phase and timing of these various electrographic phenomena lead to dendritic remodeling. In sum, the evolving knowledge of sleep-dependent memory consolidation and downscaling both being present in all primary sleep states suggests that wake-firing–based spiking activity drives sleep-related neuronal firing phase relationships, allowing for spike-timing–dependent plasticity among neurons in resonance as well as renormalization of neuronal firing activity, more generally.

The role of sleep's promotion and reflection of healthy network activity is also evidenced by the seemingly critical role it plays in mood regulation. Supportive of this perspective is the finding that individuals report higher levels of postsleep happiness when they have had sufficient opportunity to experience enough of the problem-solving sleep state—REM sleep.[42] Despite difficulties in studying such causation definitively, accumulated evidence from neuroimaging studies and dream reporting after laboratory-initiated awakenings, spontaneous recall in the home, and through psychotherapeutic recounting, suggests that dreaming may serve the primary mechanism by which this process plays out.[43] Around the time of REM's discovery, Freudian psychoanalysts were the proponents of the belief that dreams provided a forum for the expression of primitive, unacceptable drives. However, research exploring the functional connectivity during REM sleep suggests that the brain is primed for emotional processing of associative memories due to the preferential activation of limbic/paralimbic structures over those areas necessary for decision making and memory (eg, dorsolateral prefrontal cortex and hippocampus). With the transition to a cholinergic-predominant tone,

KEY POINTS

- **Sleep is essential not only for reinforcing and associating important learning but also for eliminating extraneous and intrusive engrams.**
- **The complex problem solving and emotionally charged content of REM/dream sleep is suggested to be essential for mood regulation.**

concomitant hippocampal-neocortical communication suppression impairs episodic memory processing, and dorsolateral prefrontal cortex activity is replaced by amygdala-driven activation of the anterior cingulate and medial prefrontal cortices, thereby facilitating emotional memory processing. The consequences of REM perturbation are most evident in the short latency to the first REM period, increased REM density in the early night, and REM fragmentation seen in a variety of negative-emotion, psychological states, from major depression and bereavement to posttraumatic stress disorder. Furthermore, the ability to recollect positive (and neutral) stimuli has been noted to correlate with hippocampal and medial prefrontal cortical activation, but the deterioration of recollection to predominantly negative content (facilitated by amygdala activity) is noted in the setting of sleep deprivation.[44] In fact, studies have demonstrated that individuals exposed to traumatic imagery had fewer and less distressing intrusive trauma memories when allowed to sleep after exposure, highlighting the therapeutic potential of sleep in and of itself.[45]

CONCLUSION

The exciting developments in the knowledge base of the sleep-wake and circadian circuitry are highlighting the critical role that sleep plays in the neurologic and physical well-being of an organism. Empowered with a clearer picture of the systems that regulate sleep, targeted behavioral, physiologic, and pharmacologic interventions are beginning to show promise. More importantly, however, is the recognition that neglecting sleep is detrimental to both patient and provider. With the evolution of the understanding of the multifaceted nature of sleep health, not only insufficient quantity but also insufficient quality of sleep must be addressed to improve the neurologic health and function of patients and those who treat them.

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