CHAPTER

1

Anatomy and Physiology of Normal Sleep

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OUTLINE

INTRODUCTION

The human brain exists in three primary states: wake, sleep with rapid eye movements (REM), and sleep without rapid eye movements (NREM). While sleep clearly subserves an essential role, so much remains unexplained about this physiologic state. Since the discovery of REM by Dement and Kleitman in the 1950s,[1] there has been much interest in the psychiatric and neurologic communities to develop a better understanding of the physiologic underpinnings and neurobehavioral correlates of sleep. Even though each of the states of sleep serve a vital role in the maintained function of all animals, as demonstrated by the physical deterioration and eventual death that some animals experience with sleep deprivation,[2–4] there remain vast

Sleep and Neurologic Disease. http://dx.doi.org/10.1016/B978-0-12-804074-4.00001-7

deficits in the fundamental understanding of sleep's purpose. As Allan Rechtschaffen aptly noted, "If sleep doesn't serve some vital function, it is the biggest mistake evolution ever made."[5]

Sleep is a globally coordinated, but locally propagated phenomenon. Despite incredible progress in scientific understanding of the major brain areas and neurotransmitters involved in sleep and wake, the mechanisms by which transitions between wake, NREM, and REM occur are still somewhat elusive. Even with distinct neuroanatomical regions showing clear changes in their firing patterns or neurotransmitter levels in correlation with different sleep states, the neurophysiologic monitoring of sleep indicates that sleep happens in a progressive fashion, without discrete or complete transitions between stages. In fact, activity-dependent accumulation of tumor necrosis factor alpha (TNFα), a sleep-inducing "somnogen," can promote sleep-like activity in localized cortical neuronal assemblies,[6] and sleep spindles are noted more profusely over the motor strip contralateral to motor learning tasks.[7] This suggests that sleep initiation is a property of local neuronal networks that are dependent upon prior activity specific to that network.

INITIAL DISCOVERIES OF SLEEP CIRCUITRY

As far back as the early 20th century, a basic understanding of the importance of the brain in generating sleep and wake was promoted by the neurologist Baron Constantine von Economo. Based on observations of postmortem central nervous system (CNS) lesions in patients of the encephalitis lethargica epidemic, von Economo found that those patients suffering from excessive sleepiness often had lesions at the junction of the posterior hypothalamus and midbrain, whereas those patients suffering from insomnia had lesions localized more anteriorly in the hypothalamus and the basal forebrain.[8]

However, it was not until 1935 that the first evidence of an arousal circuit was revealed when Bremer noted that transection of the brainstem at the pontomesencephalic junction (as compared to the spinomedullary junction) would produce coma in anesthetized cats.[9] Over a decade later, support for an arousal system originating in the brainstem was furthered by the work of Moruzzi and Magoun, after they demonstrated the ability to induce EEG desynchronization from slow-wave activity by stimulating the rostral pontine reticular formation in anesthetized cats.[10] Hence, the concept of the ascending reticular activating system (ARAS) was born; however, the question as to the nature of the anatomical pathways and neuronal populations that defined the ARAS remained a mystery.

Decades later, evidence of a bipartite arousal system originating from distinct neuronal populations emerged: the first, a cholinergic system, originating in the pedunculopontine (PPT) and laterodorsal (LDT) tegmental nuclei and projecting to the thalamic midline and intralaminar nuclei; the other, a monoaminergic system, bypassing the thalamus to directly activate neurons in the hypothalamus, basal forebrain, and cortex. The cholinergic neurons projecting to the thalamus serve to prevent burst firing of thalamic neurons, thereby allowing for sensory transmission to the cortex.[11] The existence of the thalamo-cortico-thalamic system is supported by the fact that thalamic relay neuronal firing patterns correlate with cortical EEG.[12] However, persistent low-amplitude, mixed-frequency EEG patterns characteristic of arousal and REM sleep can be noted despite lesions of the LDT/PPT or thalamus,[13–15] suggesting that the role of the thalamo-cortical relay is not to serve as a source of cortical arousal, but rather

as a means of providing content *to* the aroused cortex.[16] This can best be illustrated by the transient lapses in conscious processing of external sensory stimuli at sleep onset[17] and the insensate nature of sleepwalking[18]—even resulting in one patient waking to severe frostbite of the feet after a somnambulistic event (Mahowald M. Personal communication, 2015). Conversely, the monoaminergic system bypasses the thalamus, projecting from brainstem nuclei directly to the lateral hypothalamic area (LHA), basal forebrain (BF), and cortex.[19,20] These neuronal populations generally demonstrate diminishing firing rates as the brain progresses from wake to NREM to REM. Conceptualizing the duality of the arousal system might best be illustrated by a comparison between REM sleep (where, despite the absence of monoaminergic tone, the cortex is still able to process sensory stimuli from the thalamocortical network) and delirium (in which a monoaminergically aroused cortex is no longer effectively processing sensory inputs due to cholinergic suppression).[21,22]

Also inherent in von Economo's initial observations was the concept of active promotion of the state of sleep. In the years following his initial observations, confirmation of the importance of more rostral brain structures in facilitating sleep was shown to be preserved across species. Insomnia-inducing lesions were initially reproduced surgically through basal forebrain and preoptic area ablation in rats by Nauta,[23] and subsequently reproduced in felines via the preoptic lesioning experiments performed by McGinty and Sterman.[24]

NEUROANATOMY AND NEUROTRANSMITTERS

Wake-Promoting Neurotransmitter Systems

Acetylcholine (ACh)

The primary locations of cholinergic neurons are in the LDT/PPT and the BF. The LDT is a heterogeneous region, lateral to the periaqueductal gray (PAG), which extends rostrally from the PPT (Fig. 1.1). These brainstem nuclei project primarily to the thalamus (the dorsal path of the bipartite arousal system), lateral hypothalamus, and basal forebrain. However, it is the release of acetylcholine into the thalamus, that is, the primary contributor to the cortical activation during wake and REM sleep.[25,26] The basal forebrain cholinergic population is comprised of the medial septum, magnocellular preoptic nucleus, diagonal band of Broca, and substantia innominanta, which are located in the region surrounding the rostral end of the hypothalamus (Fig. 1.1). Similar to the brainstem nuclei, these cholinergic neurons are primarily active during wakefulness and REM sleep, and cortical acetylcholine levels are noted to be elevated during these two states, while there is negligible release noted during NREM sleep[27] (Table 1.1). In concert with GABAergic inhibition of cortical interneurons, increased levels of cortical and hippocampal acetylcholine have been shown to result in faster EEG activity.[28,29]

Pharmacologic manipulations of the cholinergic system have led to a greater understanding of the biological pathways that contribute to REM. Muscarinic receptor subtypes, located in the pons, mediate the induction of REM sleep, as has been demonstrated in both rats and dogs.[30–32] Injections of cholinergic agents ranging from acetylcholine and nicotine to muscarinic receptor agonists and acetylcholinesterase inhibitors result in desynchronized EEG activity and can precipitate REM.[33–36] Conversely, the duration of REM is reduced and cortical slow-wave activity predominates following administration of muscarinic antagonists such as scopolamine and atropine, predominantly through their actions at the M2 receptor subtype.[37–39]

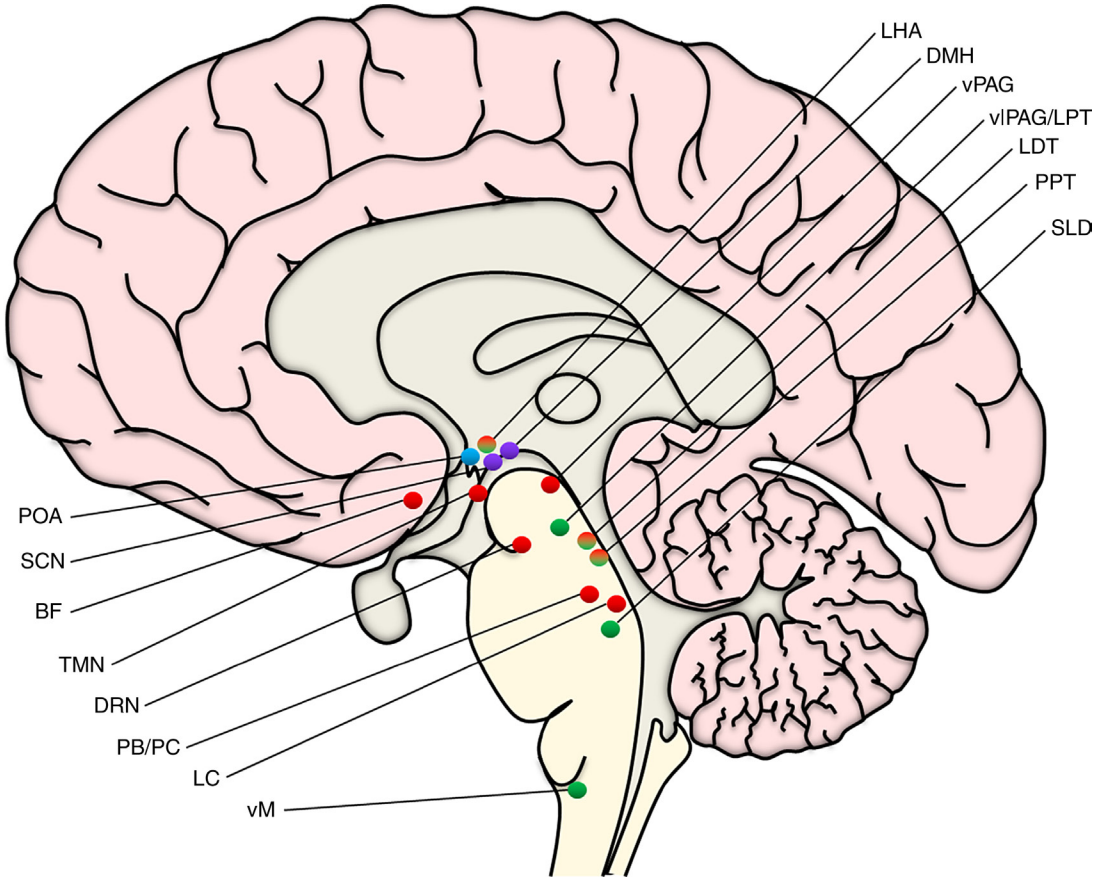

FIGURE 1.1 **General location of the neuroanatomic structures critical to wake/sleep control.** The colors of the marker indicate the predominant role played by the structure: red for arousal, blue for sleep, green for REM, purple for circadian regulation, and multicolored markers indicating multistate activity. Abbreviations: *BF*, basal forebrain; *DMH*, dorsomedial hypothalamic nucleus; *DRN*, dorsal raphe nucleus; *LC*, locus ceruleus; *LDT*, laterodorsal tegmental nucleus; *LHA*, lateral hypothalamic area; *PB/PC*, parabrachial nucleus/preceruleus; *POA*, preoptic area (containing ventrolateral and median preoptic nuclei); *PPT*, pedunculopontine tegmental nucleus; *SCN*, suprachiasmatic nucleus; *SLD*, sublaterodorsal nucleus; *TMN*, tuberomammillary nucleus; *vlPAG/LPT*, ventrolateral periaqueductal gray/lateral pontine tegmentum; *vM*, ventral medulla; *vPAG*, ventral periaqueductal gray.

Norepinephrine (NE)

Of all the noradrenergic brainstem nuclei, the locus ceruleus (LC) has the greatest influence in wake/sleep regulation. As with most of the monoaminergic system, the noradrenergic projections of the LC that promote wakefulness do so along the ventral division of the arousal system, heading from the floor of the fourth ventricle to the forebrain (Fig. 1.1). Firing rates of these neurons and extracellular NE levels are greatest during wake, and progressively drop off in NREM sleep, becoming almost quiescent during REM sleep[40–42] (Table 1.1).

TABLE 1.1 Characterization of the Firing Patterns of the Primary Sleep-Wake Regulatory Systems and Neurotransmitters

System	Primary neurotransmitters	Wake	NREMS	REMS
vPAG, LC, TMN, DRN	Monoamines (MA)	++	+	–
LDT/PPT	Acetylcholine (ACh)	++	–	++
LHA	Hypocretin (Hcrt)	++	–	–
	MCH	–	+	++
POA	GABA and galanin	–	++	++

++, Indicates high activity; +, indicates moderate activity; –, indicates little or no activity; vPAG, ventral periaqueductal gray; LC, locus ceruleus; TMN, tuberomammillary nucleus; DRN, dorsal raphe nucleus; LDT/PPT, laterodorsal tegmental/pedunculopontine tegmental nuclei; LHA, lateral hypothalamic area; POA, preoptic area; MCH, melanin concentrating hormone; GABA, gamma-aminobutyric acid.

The noradrenergic system appears to contribute to multiple aspects of wakefulness through activation of autonomic arousal and selective attention. In fact, LC neuronal firing rates are notably increased during periods of stress and exposure to salient stimuli.[40,42,43] Excessive activity of this system may underlie anxiety-associated insomnia, given the benefits of α1 antagonists such as prazosin in posttraumatic stress disorder (PTSD) patients with nightmares and insomnia.[44] Additionally, antagonists directed at the presynaptic autoinhibition through α2 receptors result in a net increase in adrenergic tone and heightened states of arousal, correlating with increased LC activity.[45] Furthermore, direct noradrenergic α1- and β-receptor stimulation of the medial septal and preoptic area of the basal forebrain promotes both behavioral and EEG measures of wakefulness.[46,47] In contrast, inhibition of the locus ceruleus, either through α2 agonism with clonidine, or α1 and β antagonism with prazosin or timolol, results in an increase in the physiologic and behavioral characteristics of NREM sleep.[48,49]

Dopamine (DA)

Dopaminergic projections are diffuse and thus integral to many neurological functions, such as motor control, learning, reward, and wakefulness. The dopaminergic systems are generally divided into four major pathways: mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular. However, neurons located in the substantia nigra (SN) and ventral tegmentum do not demonstrate firing pattern variability in response to sleep/wake changes, as they do in response to movement and reward.[50–53] More recently, dopaminergic neurons originating in the ventral periaqueductal gray (vPAG), which have reciprocal connections with the sleep-wake circuitry and lie in close approximation to the serotonergic raphe nuclei, have been shown to influence wake activity[54] (Fig. 1.1). Nonetheless, the factors influencing firing in this neuronal population have not been elucidated, although a connection to motivated physical activity as a means of volitional override of sleep onset seems most likely.

The evidence for dopamine's roll in potently promoting wakefulness is best demonstrated through the primary mechanism of stimulant medications. Amphetamines, methylphenidate, and related compounds act to prevent reuptake through dopamine transporter (DAT) blockade, but also disrupt vesicular packaging, thereby promoting dopamine release. However, these

indiscriminant effects result in overactivation of reward pathways and, at higher doses, sympathetic side effects due to the added blockade of the vesicular monoamine transporter (VMAT). A more specific DAT blockade, achieved with agents like modafinil, confirms the central role of dopamine in promoting alertness in the absence of strong reward or autonomic activation.[55–58] The sedating effects of the D2 receptor agonists used in the treatment of Parkinson disease (PD) and restless legs syndrome (RLS) lend further support for the direct influence of dopamine on wakefulness.[59,60] The D2 receptor's short isoform functions as an autoinhibitor, which provides the most likely explanation for the soporific consequence of these medications.[61]

Histamine (His)

The sole source of histamine in the human brain is the tuberomammillary nucleus (TMN). Located at the base of the posterior hypothalamus, adjacent to the paired mammillary bodies, it projects to the basal forebrain and caudally to the brainstem sleep-wake circuitry (Fig. 1.1). Histamine activity, either through direct His administration or through H1 receptor agonism, augments cortical activation and EEG desynchrony.[62,63] As with the other monoamine neurotransmitter systems, the histaminergic neurons fire most readily during wake, with gradual decrements of firing in NREM and even less in REM sleep[64,65] (Table 1.1). While histamine can augment motivated behaviors such as grooming and feeding as well as psychomotor performance, it may also play a critical role in the initiation of arousal in situations mandating vigilance or at the start of the wake period, which has been posited to underlie the "sleep drunkenness" seen in some patients with idiopathic hypersomnia.[66–68]

Perhaps the most notable examples of the histamine system's impact on wakefulness are the side effects of first generation antihistamine allergy medications (e.g., diphenhydramine). The CNS penetration of these histamine antagonists has been shown to produce sleepiness in adults, without clear changes in sleep architecture.[69] Unlike most neurotransmitters in the sleep-wake system, histamine acts not through synaptic transmission but via volume transmission. Targeted histamine receptor subtype 1 manipulations in animals have, however, prompted increases in both NREM and REM sleep.[70] While the exact mechanism of histamine's action remains to be elucidated, optogenetic experiments have confirmed the wake-promoting mechanisms of histamine through multisynaptic, reciprocal connections between the TMN and ventrolateral preoptic nucleus (VLPO).[71] Toward this end, drug development has recently focused on inverse agonists at the recently identified H3 receptor subtype, which is a presynaptic autoinhibitory receptor that may regulate wakefulness not only through regulation of histamine release and biosynthesis but also through inhibiting release of all of the other neurotransmitters essential to sleep and wake.[72,73]

Serotonin (5-HT)

Of the many serotonergic raphe nuclei that line the midline of the brainstem, the dorsal raphe nucleus (DRN) is the main neuronal population responsible for sleep-wake control (Fig. 1.1). As with the other monoaminergic systems, multiple cerebral and brainstem structures implicated in the sleep-wake circuitry receive inputs from the DRN, including the preoptic area, basal forebrain, and hypothalamus. Also, consistent with their wake-promoting behavior, serotonergic neurons tend to fire most frequently during wake, less so during NREM sleep, and have the lowest firing rate during REM sleep[74,75] (Table 1.1).

The abundance of serotonin receptor isoforms and their ubiquity make clarification of the role of serotonin in wakefulness a challenging process. Nonetheless, evidence for serotonin's involvement in sleep comes indirectly from the clinical manifestations of serotonergic medications. Selective serotonin reuptake inhibitors (SSRIs) and other antidepressants with serotonergic activity are known to suppress REM sleep by decreasing REM density and prolonging REM latency.[76] In addition, these medications may also augment REM-sleep behavior disorder (RBD), RLS, and periodic limb movements of sleep (PLMS),[77] and have been used therapeutically to prevent cataplexy, which can be thought of as the intrusion of REM atonia into the waking state.[78] More specific investigations have identified that the 1A, 1B, 2, and 3 receptor subtypes are able to promote wakefulness through their activation.[79–83] Using this novel pathway for drug development, research has recently focused on the development of a 5-HT 2 receptor antagonist as a potential treatment for insomnia.[80,82,84–86]

Hypocretin/Orexin (HCRT)

The relatively recent description of hypocretin (also known as orexin) deficiency in the sleep disorder narcolepsy type I has defined it as a critical moderator in the maintenance of wakefulness.[87–89] A relatively modest number of cells in the lateral hypothalamus are the sole source of hypocretin in the brain (Fig. 1.1). Despite the limited number of hypocretinergic neurons, their sprawling projections reach all major arousal regions, with the greatest number found in the LC and TMN.[90,91] Hypocretin neurons fire during wakefulness, with heightened activity reflecting behaviors such as grooming, feeding, and exploring[92–96] (Table 1.1). The neurons are silent during NREM and REM sleep, and optogenetic activation of the neurons in a sleeping rodent can precipitate an abrupt awakening from sleep.[97,98]

While hypocretin cell loss is the hallmark of narcolepsy type I, other neurological conditions have been associated with lower levels of cerebrospinal fluid (CSF) hypocretin. Parkinson disease, multiple systems atrophy (MSA), myotonic dystrophy type-II, Neiman-Pick, and traumatic brain injury (TBI) have all been associated hypocretin deficiency.[99–103] While the multiple roles of hypocretin are still being elucidated, it is known that it not only serves as a sleep-wake gatekeeper (noting that type I narcoleptics have normal daily sleep amounts, despite the instability in the sleep/wake state),[104] but also likely plays an important role in behavioral regulation. Through influences of somatic humoral (e.g., ghrelin and leptin) and metabolic (glucose) factors on the hypocretin system, and its direct influence on the mesolimbic reward pathways, the association between waking behaviors and the waking state is most evident in the actions of this neurotransmitter.[105–110] Playing upon this unique feature, medications targeting both of the hypocretin receptor isoforms (HCRTR1 and HCRTR2) have been developed to treat insomnia.[111] Such pharmacologic suppression of hypocretin activity has also been noted to decrease drug-seeking behaviors.[105,106,108,109]

Sleep-Promoting Neurotransmitter and Signaling Systems

Gamma-Aminobutyric Acid (GABA)

The active promotion of sleep is reflected in the global increase in inhibitory tone in the sleep-wake system. The primary source of this inhibition resides in the ventrolateral and median preoptic nuclei (VLPO and MnPO, respectively)[112,113] (Fig. 1.1). Lesions in this region result in dramatically reduced and fragmented sleep, similar to the findings of von Economo's

patients with lesions at the junction of the hypothalamus and basal forebrain.[24,114] The start of MnPO neuronal firing immediately preceding NREM sleep suggests that this region may play a role in sleep initiation.[115,116] In contrast, the VLPO neurons are implicated in the maintenance of sleep because they fire most vigorously during NREM sleep, with scant firing during REM, and virtual silence during wakefulness.[116,117] Both the VLPO and MnPO project to the primary arousal system nuclei (LDT/PPT, LC, DR, TMN, and HCRT neurons), where they promote sleep through both GABA and galanin.[112,113] This reciprocal inhibition between the wake- and sleep-promoting systems allows for smooth transitions between states. NREM-active, GABAergic neurons are also located in the basal forebrain and lateral hypothalamus, though their role in sleep facilitation is less clear.[118–120]

GABA has also been noted to play an important role in the production of REM sleep. A cluster of cells ventral to the locus ceruleus, known as the sublaterodorsal nucleus (SLD), plays critical roles in promoting some of the hallmark features of REM sleep.[121] As part of the mechanisms that result in the atonia of REM sleep, direct and indirect pathways from this cell group contribute to the release of GABA on the spinal cord ventral horn cells and glutamate on the ventromedial medulla (vM), respectively.[122] It has also been shown that REM sleep EEG signatures can be promoted through stimulation of the SLD, and REM sleep can be reduced through targeted ablation.[121–126] Toward this end, optic stimulation of vM neurons promotes NREM-to-REM (but not wake-to-REM) transitions and dramatic increases in REM-sleep duration, presumably through GABAergic projections onto inhibitory, REM-suppressing vlPAG neurons.[127] Nonetheless, the role of GABA in REM sleep seems to be more of an indirect, multisynaptic process of disinhibition of REM-active neurons and silencing of REM-inactive neurons, which will be discussed in more detail later.

The circadian regulation of sleep is also heavily influenced by GABA signaling. Differential coupling of the dorsal and ventral cell groups in the SCN via variations in the phasic and tonic firing patterns of GABAergic neurons are critical to aligning the master clock to the season-dependent variations in day length.[128] Additionally, GABAergic signaling from the dorsomedial hypothalamic nucleus (DMH) transmits circadian cues from the SCN to the VLPO in order to allow for environmental regulation of sleep onset.[16]

In the general facilitation of sleep, the primary receptor through which many sedative/hypnotic medications act is the GABA-A receptor subtype.[129,130] This chloride channel has binding sites for a range of sleep-inducing medications: from benzodiazepines, barbiturates, and nonbenzodiazepine receptor agonists (the "Z-drugs") to alcohol to sedatives such as propofol. However, due to the extensive network of GABA receptors and the lack of site specificity of any of these medications, the exact mechanisms by which GABA-A R agonists promote sleep are incompletely characterized. As opposed to the GABA-A ligand-gated ion channel, the GABA-B receptor is a G protein-coupled receptor that is most susceptible to activation by baclofen and gamma-hydroxybutyrate.[131] Similar to GABA-A, however, activation of the GABA-B receptor readily induces somnolence and EEG characteristics of slow wave sleep, although the mechanism remains incompletely understood.[131] Knockout models of the GABA-B receptor have revealed profound disruption of sleep patterns in mice, suggesting a role for this receptor subtype in the circadian organization of sleep.[131] In addition to tolerance and withdrawal, as well as the lack of circuit-specific agonist activity preventing the development of ideal GABA-modulating sleep aids, the dosage ceiling effect imposed by respiratory drive depression and muscle relaxation pose further concerns for the impact on comorbid sleep-disordered breathing.[132]

Acetylcholine (ACh)

A critical constituent of the wake system, acetylcholine also plays a key role in the active promotion of REM sleep. As previously mentioned, subpopulations of the LDT/PPT neuronal group are theorized to be active in both REM sleep and wake, as well as some that are active only during REM sleep[123,133–135] (Table 1.1). Thalamic ACh levels increase during REM sleep, resulting in suppression of spindle activity, while depolarized thalamic neurons are able to transmit single spikes of information to the cortex.[136] Cortical ACh levels also increase, contributing to a suppression of slow-wave activity (SWA) and promoting EEG desynchronization/cortical activation.[27] The combined thalamic transmission and activated cortex suggest that the dream content during REM sleep is the consequence of the cortex's emotional processing of sensory input and may offer particular insight into the violent content of dreams in patients with RBD: they may be dreaming out their acts, rather than acting out their dreams, an interesting theory that has not been firmly established.

Another role for ACh in the promotion of REM is through the facilitation of ponto-geniculo-occipital (PGO) waves. These waves are theorized to be important in the phasic firing patterns induced by the cholinergic subpopulation of the caudal parabrachial body (cPB), thereby facilitating the transition from NREM to REM sleep.[137] While PGO waves have only been inferred in humans through deep brain stimulation and epilepsy monitoring protocols,[137,138] their presence in cats (and, similarly, P-waves in rodents) is a hallmark of the transition to REM sleep.[139] Despite the critical balance between ACh and GABA defining PGO wave/phasic REM-sleep activity, experiments to suppress cholinergic propagation of this phenomenon do not generally result in suppression of REM sleep, suggesting that this is an independent REM sleep-related phenomenon.[140]

Not only does the direct activation of the M2 & M3 receptors in the pontine reticular formation induce REM sleep EEG and behavioral phenomena but the characteristic muscle atonia of REM sleep is also mediated, in part, by acetylcholine.[123,135,136,141] Via projections to the ventromedial medulla (vM), acetylcholine likely aids the SLD neurons in the activation of atonia-producing neurons.[123,141] Nonetheless, the drastic reductions in REM sleep caused by LDT/PPT lesions suggest that this is the primary region responsible for active REM-sleep promotion.[126,142]

Melanin-Concentrating Hormone (MCH)

Melanin-concentrating hormone (MCH) neurons provide a logical juxtaposition to the hypocretin neurons with which they are anatomically associated. GABAergic/MCHergic neurons originating in the hypothalamus parallel the projections of the hypocretin neurons providing an inhibitory activity on all of the same targets in the brainstem arousal nuclei.[143–147] MCH agonists effectively increase REM sleep quantity, while antagonists decrease it.[147,148] Furthermore, based on their firing activity being maximal in REM sleep and absent during wakefulness (Table 1.1), MCH neurons are presumed to serve a role opposite to hypocretin neurons.[118] However, MCH neurons demonstrate a moderate level of firing during NREM sleep and they have been noted to result in decreases in both REM and NREM in knockout models,[149] suggesting that there is still much to learn about the contribution of MCH neurons to sleep state regulation.

Somnogens

Early investigations into the "substance" of sleep began over a century ago. Applying Koch's postulates, Ishimori (1909), followed independently by Legendre and Pieron (1913),

BOX 1.1

SLEEP REGULATORY SUBSTANCE CRITERIA.[153]

1. Should promote sleep (or inhibit it, if a waking substance)
2. If the SRS is inhibited, the expected state should decrease
3. Levels in the brain (or receptor sensitivity or abundance) should vary with sleep propensity
4. The SRS should act on sleep regulatory circuits
5. Changes are proportionate with pathologies that are associated with sleep/sleepiness or wake/wakefulness

induced sleep in normal dogs through transfusion of cerebrospinal fluid from sleep-deprived dogs.[150,151] Sixty years later, Pappenheimer and others recovered muramyl peptide (Factor S) from goats; however, this was later revealed to be a bacterial contaminant (though it still may have been soporific through induction of interleukin-1β).[152] Since these initial discoveries, much effort has been invested in discovering these nonneurotransmitter somnogens as a means of understanding the pathogenesis of sleep/wake disorders as well as for the development of more targeted therapeutics. Criteria for sleep-regulatory substances (SRSs) have been proposed (Box 1.1),[153] and a limited number of substances qualify for the promotion of NREM sleep (growth hormone-releasing hormone, adenosine, interleukin-1β, tumor necrosis factor alpha, prostaglandin D_2, and nitric oxide), REM sleep (vasoactive intestinal peptide, and prolactin), and wake (corticotrophin-releasing hormone, and ghrelin). Only a few of the well studied, sleep-promoting SRSs will be discussed here.

ADENOSINE/ADENOSINE TRIPHOSPHATE (ATP)

Perhaps the most well known SRS is adenosine. First proposed in 1984 by Radulovacki and coworkers, adenosine remains the best example of an SRS underlying the homeostatic sleep drive.[154] Adenosine follows the expected pattern of a somnogen: increasing as a consequence of high metabolic activity and prolonged wakefulness and falling with recovery sleep.[154–157] The primary receptors for adenosine are in the purine P1 receptor family: the inhibitory A1 receptor, which is ubiquitous throughout the brain; and the excitatory A2a receptor, which is primarily located in the meninges underlying the VLPO. While the role of adenosine as the primary regulator of the homeostatic drive seems most apparent from the efficacy of caffeine, an adenosine receptor antagonist,[156,158–161] A1R and A2aR knockouts do not result in impaired sleep homeostasis.[16] Furthermore, the critical role in adenosine signaling played by support cells, such as astroglia, is underscored by the fact that the expected increases in sleep and delta power following sleep deprivation can be reduced by astrocytic manipulations.[156,157,162]

The mechanisms of purinergic sleep regulation are elaborate. The abundance of ATP in vesicles that are coreleased with the majority of neurotransmitters (GABA, ACh, NE, and glutamate) predominantly bind to the P2 family of purine receptors, located on both the postsynaptic membrane and local glia. At the same time, ectonucleotidases convert ATP in the

synaptic cleft into adenosine. Glial-based, ATP-induced release of TNFα, interleukin-1β (IL-1β), brain-derived neurotrophic factor (BDNF), and additional ATP results in NFκB-mediated transcription of adenosine 1 receptors (A1R) and glutamate AMPA receptors (AMPAR) in the postsynaptic membrane, thereby scaling the sensitivity of the postsynaptic neurons to the prior use of the synapse.[153] This augmented receptor sensitivity to adenosine as a consequence of the degree of neuronal activity is most supportive of the theory that sleep is a locally initiated phenomenon. This effect is demonstrated in the cellular network activity of cortical columns independently oscillating between sleep-like and wake-like states,[163] and is suggested electrophysiologically by augmented slow-wave activity in the hemisphere contralateral to motor learning tasks.[164,165] Further support for the homeostatic regulation of adenosine is noted in the conversion of adenosine to ATP with sufficient energy availability.[155] Thus, it is likely that it is the balance of adenosine and ATP rather than either metabolite individually that truly modulates purinergic sleep regulation.

The soporific activity of adenosine is not just a central nervous system-mediated process. In 1972, ATP was first proposed to serve a peripheral nonadrenergic/noncholinergic autonomic afferent role.[166] More recent studies have revealed the ability of peripheral intramuscular injection of combinations of metabolites (protons, lactate, and ATP) to induce global fatigue and even a sense of pain and muscle ache.[167] Thus, distortion of the concerted peripheral and central purinergic signaling of adenosine/ATP may be involved in the pathogenesis of systemic exercise intolerance disease (SEID, formerly known as chronic fatigue syndrome/myalgic encephalitis), although this has not been substantiated.

CYTOKINES

The most notable cytokines playing a role in sleep homeostasis are IL-1β and TNFα. Their role in the purinergic homeostat has already been discussed; however, they also have an independent role in the regulation of sleep. IL-1β and TNFα show characteristics of a physiologically normal sleep-regulatory substance: levels of IL-1β and TNFα increase with prolonged wakefulness, reach a maximum around sleep onset, and decline with sleep.[168–171] Additionally, NREM activity is notably increased through physiologic manipulations that increase IL-1β and TNFα, such as high-fat diets or increases in ambient temperature. Furthermore, direct application of IL-1β and TNFα (as well as other cytokines such as linoleic acid and prostaglandin D_2) to the surface of the cortex increases c-Fos activation in the VLPO and enhances delta EEG power during NREM sleep, pointing to activation of sleep-regulatory circuitry.[153] Furthermore, the NREM rebound that characteristically follows sleep deprivation can be blocked through IL-1β and TNFα antagonists, gene knockout animal models, and interfering antibodies.[168] Nonetheless, it is the pathologic manifestations of increased NREM and decreased REM sleep that result from cytokine production in the setting of infection (specifically mediated by lipopolysaccharide and muramyl peptide) that suggest a role for sleep in the recovery process.[172] However, this sleep-wake alteration may come at the cost of inducing the twilight state of delirium (typified by the characteristic encephalopathic slow-wave activity on EEG) in those individuals most susceptible.

PROSTAGLANDIN D_2 (PGD2)

As mention earlier, the application of prostaglandin D_2 results in increased c-Fos expression in the VLPO as well as enhanced EEG delta power, as a result of direct cortical application,

highlighting the activation of sleep-regulatory circuits.[153] In fact, the normal production of PGD2 demonstrates the expected diurnal variation—with a maximum during the sleep period[173]—and increases with sleep deprivation.[174] Production of PGD2 is predominantly noted in the basal meninges,[175] and preoptic injections of PGD2 have been shown to activate the VLPO (increasing both NREM and REM sleep), possibly mediated by adenosine's A2aR activity.[176–180] Like most prostaglandins, PGD2 is a byproduct of cyclooxygenase action on lipid membrane fatty acid esters. The soporific role of inflammation may be mediated in part by PGD2, since patients with African sleeping sickness have been noted to have elevated cerebrospinal PGD2 levels.[181]

SLEEP-WAKE CIRCUITRY

In attempting to understand the interactions between the many neurotransmitter systems that exist to promote wakefulness, consider the following: if each of the aforementioned arousal systems can independently promote a state of arousal, then why are there so many? A possibility would be that there needs to be biologically assured redundancy in the system so that a dysfunction in any one system does not impair it entirely (Fig. 1.2). This thought is teleologically intuitive, making the rostral midbrain/posterior hypothalamus one of the only regions that can produce coma from a single lesion. However, an additional interpretation would be that each arousal system contributes a different aspect of arousal and input to the maintenance of wakefulness and the activities/behaviors necessitated therein. Attention is enhanced by norepinephrine (NE) and histamine (His) in the setting of novel or stressful stimuli, while DA seems to be associated with reward-motivated behaviors, based on its connections to the limbic system. Hypocretin's wake-to-sleep gating activity points to a critical role in maintaining wakefulness, particularly in the context of goal-oriented behaviors and locomotion. Nevertheless, the ultimate result of the arousal systems' individual effects is excitement of the thalamus and cortex.

The cortical excitation caused by monoamines and AChincreases the neuronal sensitivity to incoming sensory stimuli,[182,183] and it is through interactions between these subcortical systems and the thalamus and cortex that consciousness and associated EEG activity originate. The desynchronization of the EEG during wake and REM sleep indicates the cortical receptivity to the thalamic transmission of sensory and limbic signals. ACh is also the primary regulator of the thalamic depolarization that clears the way for information passing through the thalamus.[136] During NREM sleep, when cholinergic tone is lowest, the thalamic neurons are hyperpolarized, changing the reciprocal communication with the cortex. With GABAergic activity predominating among cortical projection neurons and the thalamic reticular nucleus, the hallmark slow-wave activity and spindles of NREM sleep can predominate.[184,185] However, despite the loss of consciousness imparted by thalamic lesions (as in the overwhelming majority of patients in a persistent vegetative state),[186] the persistence of the organization of wakefulness and NREM/REM sleep highlights that the thalamus is not a critical constituent of the brain's sleep circuitry.[187–190]

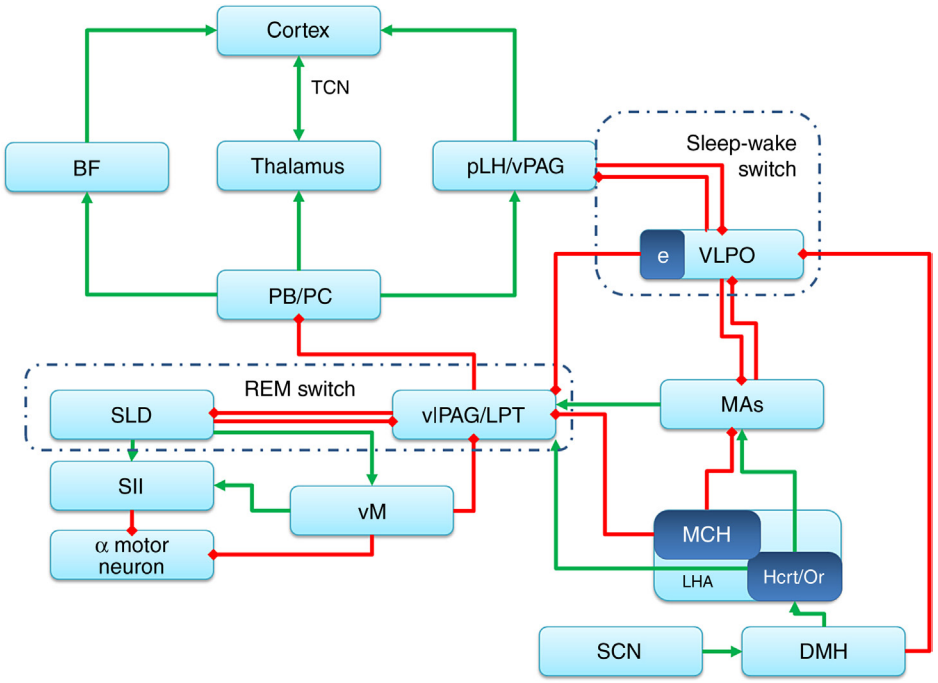

FIGURE 1.2 **Essential components of the sleep-wake circuitry.** Not all connections between areas are indicated, but the fundamental network connectivity is highlighted and separated out in order to show different components of the circuitry in relation to the sleep-wake and REM flip-flop switches, rather than anatomic relationships. Excitatory connections are in green, and inhibitory connections in red. The VLPO plays a major regulatory role in sleep-wake activity via projections to the pLH/vPAG, but also influences REM switching at the vlPAG/LPT. The incorporation of the PB/PC glutamatergic activity into the model emphasizes the critical role this region plays in sleep-wake behavior (via pLH/vPAG), conscious processing (via thalamus), and cortical arousal (via BF). Abbreviations: *BF*, basal forebrain; *DMH*, dorsomedial hypothalamic nucleus, *(e)VLPO*, (extended) ventrolateral preoptic nucleus; *Hcrt/Or*, hypocretin/orexin; *LHA*, lateral hypothalamic area; *MAs*, monoaminergic systems (locus ceruleus, tuberomammillary nucleus, dorsal raphe nucleus, and ventral periaqueductal gray); *MCH*, melanin-concentrating hormone; *TCN*, thalamocortical network; *PB/PC*, parabrachial nucleus/preceruleus; *SCN*, suprachiasmatic nucleus; *SII*, spinal inhibitory interneurons; *SLD*, sublaterodorsal nucleus; *vlPAG/LPT*, ventrolateral periaqueductal gray/lateral pontine tegmentum; *vM*, ventral medulla; *pLH /vPAG*, posterior lateral hypothalamus/ventral periaqeuductal gray.

Sustaining Wakefulness

As mentioned previously, there appear to be two main branches to the ascending arousal system: the dorsal pathway leading from the LDT/PPT to the thalamus, promoting sensory transmission through to the cortex, and the ventral pathway, which projects from the monoaminergic (MA) brainstem nuclei to the LHA, BF, and cortex (Fig. 1.3). This latter branch of the arousal system has firing patterns that are greatest during wakefulness, diminished during NREM sleep, and all but silent during REM sleep. It is through the mutually inhibitory connections to the preoptic area that the primary flip-flop switch controlling wake and sleep theoretically operates[19,20] (Fig. 1.2). The VLPO has primary inhibitory tone that is balanced through reciprocal, counter-inhibitory connections from the TMN, DRN, vPAG, LC, and LHA.

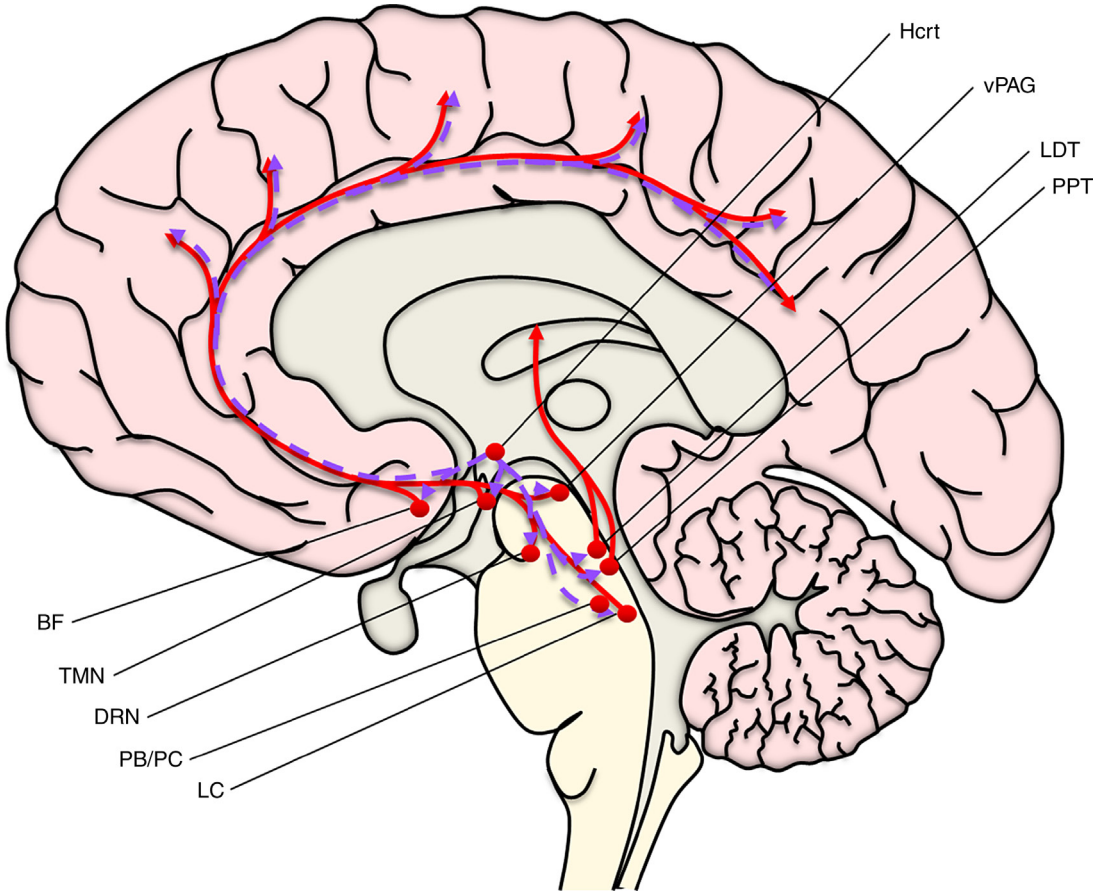

FIGURE 1.3 **The arousal-promoting pathways.** The dorsal, cholinergic pathway is demonstrated to originate in the LDT/PPT and proceed up to the thalamus. The ventral flow of the monoaminergic systems is also illustrated in red. The purple, *dashed lines* indicate projections of the hypocretin system feeding into the monoaminergic system, as well as the BF and cortex. Abbreviations: *BF*, basal forebrain; *DRN*, dorsal raphe nucleus; *Hcrt*, hypocretin; *LC*, locus ceruleus; *LDT*, laterodorsal tegmental nucleus; *PB/PC*, parabrachial nucleus/preceruleus; *PPT*, pedunculopontine tegmental nucleus; *TMN*, tuberomammillary nucleus; *vPAG*, ventral periaqueductal gray.

One of the critical nodes of this wake-promoting circuitry is the LHA, the seat of hypocretin neurons. Hypocretin neurons are wake-active and promote arousal via TMN, LC, DRN, and cortical projections;[191] however, hypocretin neurons do not project directly to the VLPO (which consequently lacks hypocretin receptors), suggesting that they serve more of a wake-state-stabilizing role external to the primary sleep-wake circuit. As evidence of this, hypocretinergic neuronal loss, as in type I narcolepsy, results in frequent state transitions with an overall normal sleep duration.[104] Similarly, lesions to the closely associated MCH neurons, which are noted to be predominantly REM-active, do not result in changes in the amount of wakefulness.[192] Nonetheless, the LHA's reciprocal connections to the monoaminergic system, as well as its basal forebrain and cortical projections, highlight the important role that this

region plays in maintaining wakefulness, as noted by the fact that lesions to the LHA region generally result in hypersomnia.[23,104,147,191,193,194]

The BF is composed of the nucleus basalis of Meynert, the magnocellular preoptic nucleus in the substantia innominata, the medial septal nucleus, and the nucleus of the diagonal band of Broca. The BF receives inputs from the MA system as well as the LHA, and appears to serve as a waystation for cortical arousal signals. Support for this hypothesis is provided by the fact that the BF has predominantly cholinergic outputs, as well as the fact that cortical EEG activation is time-locked to burst firing in stimulated BF neurons.[195,196]

A more recently discovered wake-promoting glutamatergic neuronal group, which originates in the parabrachial nucleus (PB), parallels MA system projections. In comparison to the relatively minor decrements to wakefulness noted from lesions to any of the monoaminergic pathways, disruption of this glutamatergic system results in nearly 40% increases in total sleep time,[122] suggesting a more central role in the maintenance of wakefulness. It may be through the primary connections to the posterior lateral hypothalamus (pLH), BF, and thalamus that the primary wake-promoting effects are realized.[122]

Turning Off the Arousal System

It is the balance of activity from both sleep-promoting and wake-promoting regions that constitute the flip-flop switch necessary to transition into sleep (Fig. 1.2). The first indication that sleep was an active process were the insomniac patients with basal forebrain/anterior hypothalamic area lesions who were documented by von Economo.[8] Subsequent studies recapitulated these findings and eventually suggested that this sleep-promoting region is located around the sleep-active GABAergic and galaninergic cell populations in the preoptic area.[8,23,24,197]

The VLPO plays a critical role in regulating sleep-wake behaviors (Fig. 1.4). As mentioned earlier, the mutual inhibition between the VLPO and the monoaminergic and hypothalamic components of the arousal system contribute to the sleep-wake flip-flop switch. Consistent with this belief is the finding that lesions to the VLPO produce profound insomnia and sleep fragmentation.[114] While the firing patterns of the VLPO neurons are greatest throughout sleeping states (most notably during NREM), it is the median preoptic nucleus (MnPO) that may actually flip the switch, since firing rates of this neuronal population precede transitions to NREM sleep.[115,116]

Transitioning to REM

REM sleep is characterized by autonomic instability, skeletal muscle atonia, and the desynchronized cortical EEG patterns that resulted in the descriptions of this state as "active" or "paradoxical" sleep. Building upon the feline transectioning studies performed by Jouvet and a growing body of neuropharmacologic evidence, a flip-flop switch of "reciprocal interaction" was first proposed as the mechanism by which the brainstem regulates the ultradian cycling into REM sleep.[198] Although initially purported to rely upon MA and cholinergic stimulation, similar to that which subserves the bipartite arousal circuitry, subsequent experiments on REM sleep, demonstrating noncholinergic neurons active in the primary REM circuitry (e.g., SLD) and minimal changes in REM sleep as a consequence of selective lesions in either

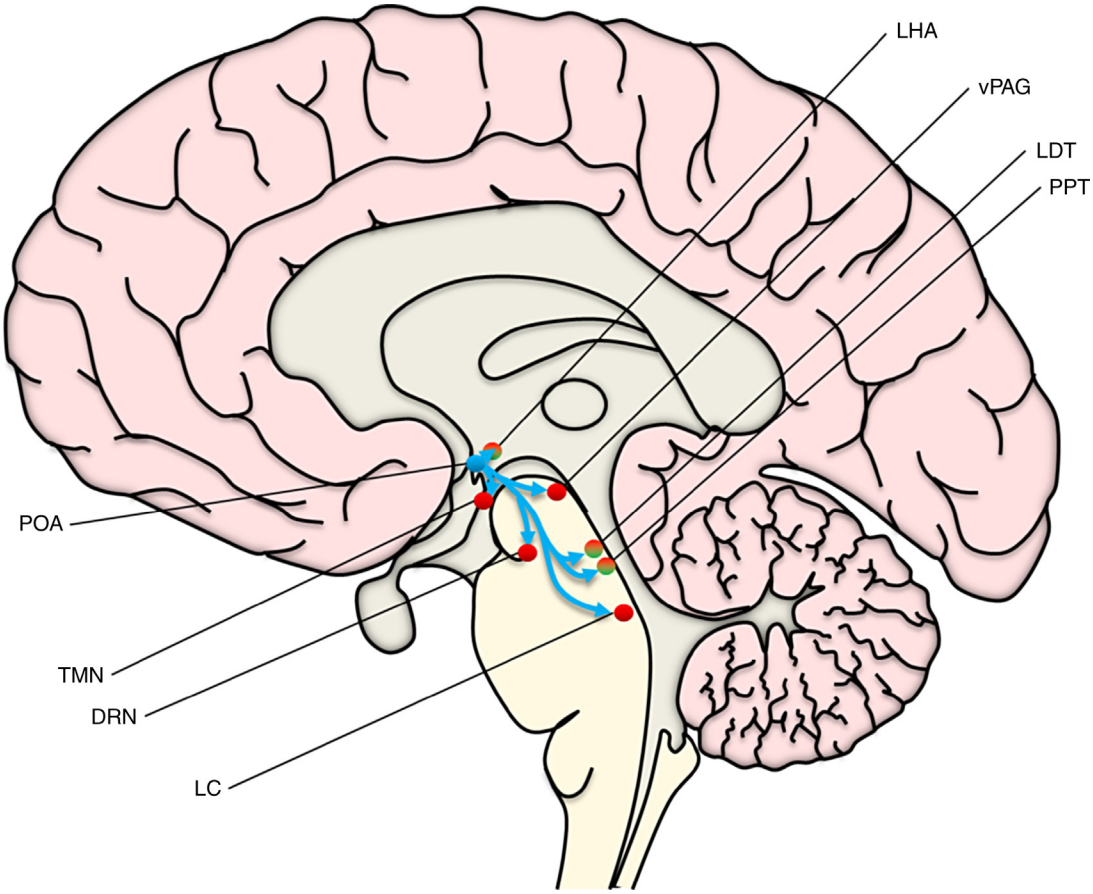

FIGURE 1.4 **The primary pathways subserving sleep promotion originating in the POA (in the ventrolateral and median preoptic nuclei).** The colors of the marker indicate the predominant role played by the structure: red for arousal, blue for sleep, green for REM, and multicolored markers indicating multistate activity. Abbreviations: *DRN*, dorsal raphe nucleus; *LC*, locus ceruleus; *LDT*, laterodorsal tegmental nucleus; *LHA*, lateral hypothalamic area; *POA*, preoptic area (containing ventrolateral and median preoptic nuclei); *PPT*, pedunculopontine tegmental nucleus; *TMN*, tuberomammillary nucleus; *vPAG*, ventral periaqueductal gray.

cholinergic or monoaminergic brainstem nuclei, suggested that the MA and cholinergic systems are neither necessary nor sufficient for the production of REM sleep.[123,199,200]

Again, the VLPO serves a primary role in the promotion of both primary states of sleep, however it is through extended VLPO (eVLPO) projections to the ventrolateral periaqueductal (vlPAG) and the lateral pontine tegmentum (LPT) that it is involved in REM sleep promotion.[122] Through a double-inhibitory mechanism, the VLPO feeds into the REM-promoting flip-flop switch (Fig. 1.2): (1) REM-active, GABAergic neurons in the eVLPO project to and inactivate (2) the REM-inactive, GABAergic neurons in the vlPAG and LPT, which, in turn, have reciprocally inhibitory connections with (3) REM-active GABAergic and glutamatergic neurons in the SLD (Fig. 1.5). In this model, the vlPAG and LPT serve as a waystation for REM

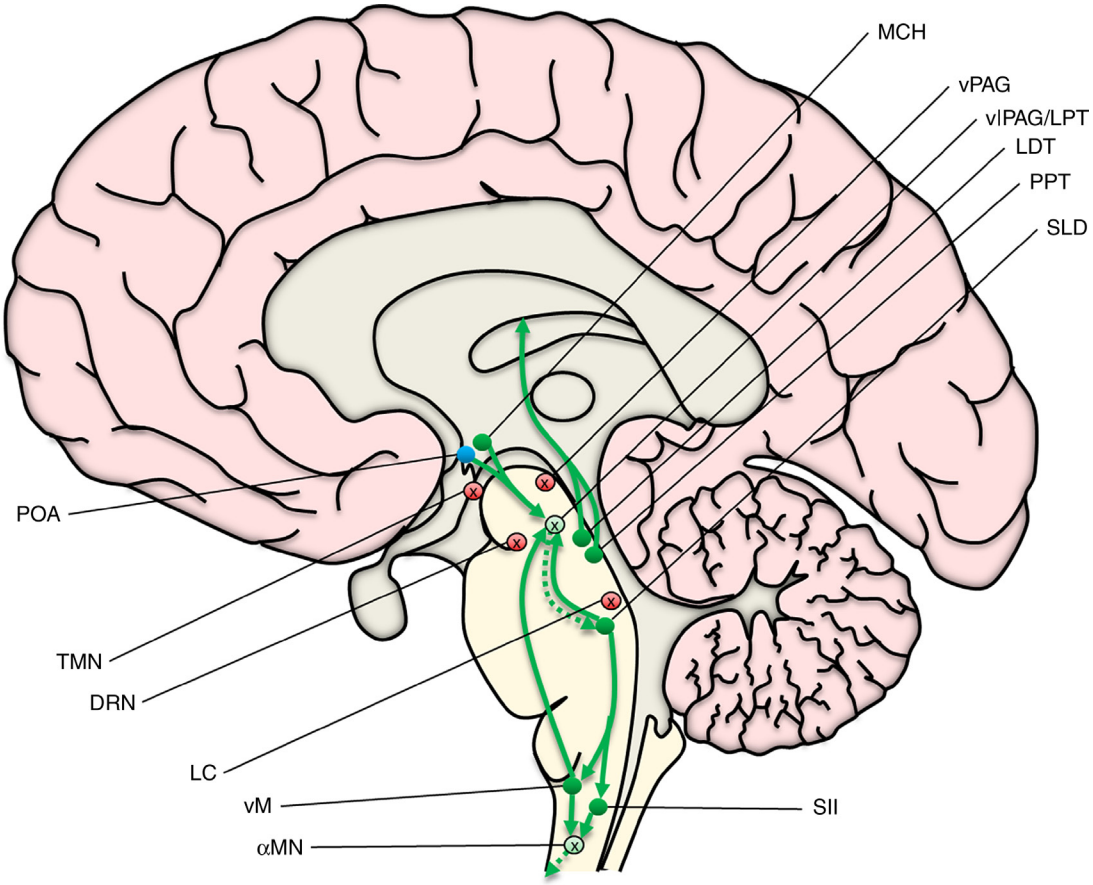

FIGURE 1.5 **The current characterization of the REM sleep architecture.** The colors of the marker indicate the predominant role played by the structure: red for arousal, blue for sleep, and green for REM. The *solid arrows* indicate REM-active limbs of the sleep-wake circuitry. Faded markers with an "X" and dashed pathways indicate REM-inactive neuronal populations and projections, respectively. Abbreviations: *αMN*, alpha motor neuron; DRN, dorsal raphe nucleus; *LC*, locus ceruleus; *LDT*, laterodorsal tegmental nucleus; *MCH*, melanin-concentrating hormone; *POA*, preoptic area (containing ventrolateral and median preoptic nuclei); *PPT*, pedunculopontine tegmental nucleus; *SII*, spinal inhibitory interneuron; *SLD*, sublaterodorsal nucleus; *TMN*, tuberomammillary nucleus; *vlPAG/LPT*, ventrolateral periaqueductal gray/lateral pontine tegmentum; *vM*, ventral medulla; *vPAG*, ventral periaqueductal gray.

regulation. The REM-inactive (i.e., REM-suppressing, when active) GABAergics in this region are also stimulated by monoaminergic and hypocretinergic inputs, while MCH and vM neurons provide an inhibitory (REM-promoting) input mediated primarily through GABA.[92,147,201–203]

With the withdrawal of the vlPAG/LPT inhibitory tone, REM phenomena can predominate. The uninhibited PB and preceruleus (PC) together promote activation of the cortical and hippocampal EEG by way of glutamatergic projections onto corticopetal cholinergic and GABAergic pathways in the BF and medial septum.[16] Furthermore, the atonia of REM is principally controlled by the SLD, lying at the other end of the REM flip-flop switch[122] (Fig. 1.2).

The SLD's GABAergic projections back onto the vlPAG/LPT are essential in the transition to and maintenance of REM. The potent REM promotion of the SLD glutamatergic outputs activating vM GABAergic suppression of the vlPAG/LPT, further emphasizes the role of the SLD in REM sleep. However, it is important to note that the SLD-vM, multisynaptic REM promotion is a phenomenon that is only observed as an NREM-to-REM transition, rather than a wake-to-REM transition,[127] suggesting that the vM's inhibitory activity on the vlPAG/LPT is not sufficient for REM induction and, therefore, is not a primary constituent of the flip-flop switch. Furthermore, glutamatergic outputs of the SLD are essential to both direct and indirect induction of atonia. The pathway mediated by SLD-activated vM cell groups as well as direct synapses on spinal inhibitory interneurons use GABA and glycine to prevent the corporeal manifestations of the central pattern generators and myoclonic activity through the production of atonia during REM sleep.[122] The central role of these pontine and medullary glutamatergic neurons in the generation of REM-sleep atonia is consistent with Braak's hypothesized spread of α-synuclein,[204] confirming that the loss of REM atonia in REM-sleep behavior disorder is a biomarker of synucleinopathies, predating disease onset by more than a decade.[205]

CIRCADIAN AND HOMEOSTATIC REGULATION OF SLEEP

The interaction between a circadian alerting signal (process C) and a homeostatic soporific signal (process S) was first proposed by Borbély and Tobler in 1982, and was dubbed the two-process model of sleep regulation.[206] Forced desynchronization experiments performed by Dijk and Czeisler and subsequent studies in the field have sought to confirm that the circadian signal is alerting in humans.[207–209] However, the circadian signal not only regulates the level of wakefulness throughout the day, it also serves as the body's primary time keeper, aligning all physiologic functions through a network of multisynaptic systems.[210,211] While the master clock, housed in the SCN, is active during the *light* cycle, the VLPO is always active during the *sleep* cycle, regardless of circadian phenotype (e.g., diurnal vs. nocturnal). Thus, it is theorized that the complex connectivity linking the SCN to the main sleep-wake and autoregulatory behavioral activities of the hypothalamus allows for adaptation of rest-activity cycles to the needs of an organism through an integration of environmental influences—such as temperature, feeding, social cues—with the primary zeitgeber (time giver) of light. The influence of the circadian system on sleep is discussed in detail in the next chapter.

CONCLUSIONS

Sleep is an elaborate and complex process. The redundancy and multinodal nature of the neurocircuitry allows sleep to be sculpted to suit the needs of the organism. While strategically placed lesions in only a few of the key neuroanatomical areas are sufficient to cause substantial changes in sleep-wake duration, all of the areas contribute essential modulating effects on the coordination of sleep. The variety of neurotransmitters, neuropeptides, and neuromodulators that feed into the pair of flip-flop switches allow for the integration of external cues in the adaptation of sleep to meet the needs of the organism. Behavioral entrainment

is possible through a number of the monoamines as well as hypocretin. The somnogen-based homeostatic system, which ensures that the drive for recovery is scaled to the degree of use, may also serve to promote learning by means of Hebbian plasticity. Finally, environmental alignment is possible through the coupling of the externally activated SCN and the internally active VLPO. We have only just begun to understand the many roles that sleep serves: from energy renewal, to waste removal and damage repair, to information organization and learning consolidation. While sleep's complexity and multisystem redundancies highlight the importance of this physiologic function, it is through damage to the architecture underlying this globally coordinated process that the clinical impact of neurologic diseases can be understood, and the pathophysiology of the diseases themselves explored.

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