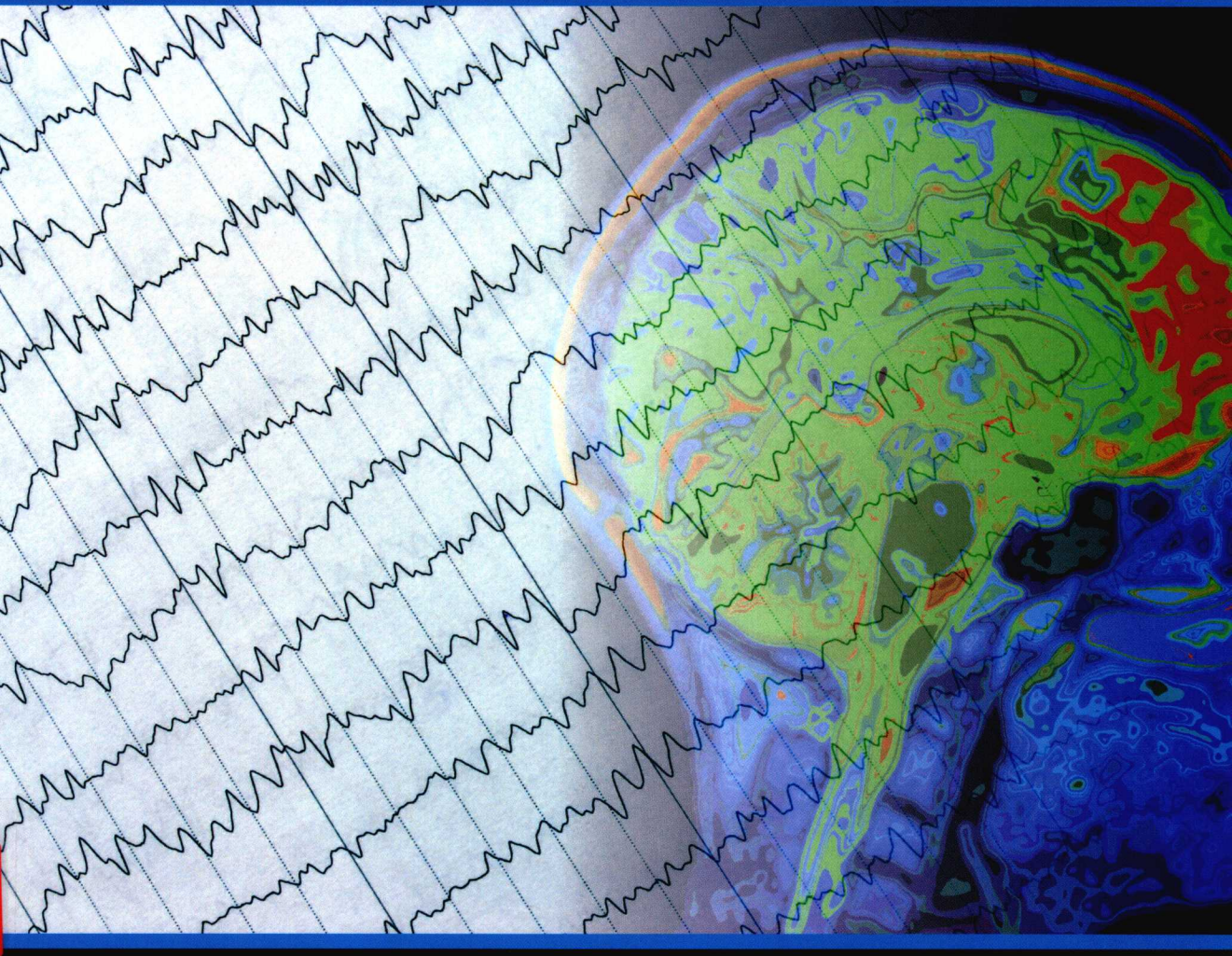
SLEEP AND NEUROLOGIC DISEASE



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SLEEP AND NEUROLOGIC DISEASE

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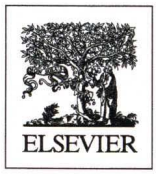

ACADEMIC PRESS
An imprint of Elsevier
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Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-804074-4

Publisher: Mara Conner
Acquisition Editor: Melanie Tucker
Sr. Editorial Project Manager: Kristi Anderson
Production Project Manager: Karen East and Kirsty Halterman
Designer: Matthew Limbert

Typeset by Thomson Digital

SLEEP AND NEUROLOGIC DISEASE

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Foreword

This is a very exciting time for the field of sleep neurology. Through knowledge gained in sleep neuroanatomy and neurophysiology, the vast and complex network of systems that regulate our states of being is just starting to be unraveled. As new discoveries challenge empirically established conventions, no field of the neurosciences is more primed for transformation than the field of sleep medicine. Sleep disorders offer a lens through which we can better understand the impact of healthy sleep on neurological function. This neurologic "black box" of sleep is just starting to be deciphered, revealing new insights into our understanding of neurological diseases.

Since the initial descriptions of rapid eye movements (REM) and their correlation with dream mentation just over half a century ago, explorations into the functions of various sleep states have rapidly expanded. Since this time, we have come to realize that monitoring of sleep physiology can provide key insights into neurologic dysfunction. Whether it's the loss of REM atonia that heralds the rostral spread of α-synuclein in neurodegenerative disease, the role of sleep and memory consolidation, or the association of sleep disruption, and fatigue in many of the central nervous system disorders that result in network inefficiency (e.g., multiple sclerosis, stroke, etc.), there are many things that sleep can teach us about neurological function.

Moreover, when the functional reserve of the brain deteriorates, sleep's powerful influence on health becomes even more apparent, as is most evident when sleep/wake disruptions in our elderly inpatient populations induce delirium. With stroke incidence peaking in the early morning hours and certain seizure subtypes occurring predominantly at night, the role of our body's internal clock becomes readily apparent. There are countless examples of how addressing the quality and quantity of sleep can impact the lives of our patients, such as the morning headaches that are precipitated by a number of sleep-related factors, white matter disease burden correlating with obstructive sleep apnea, and impaired amyloid clearance during states of sleep deprivation and the implications this may have for those with cognitive impairment.

And, don't forget that sleep disorders are neurologic diseases! Once housed squarely in the realm of psychiatry, narcolepsy type 1 is now known to be related to a loss of hypocretin neurons in the hypothalamus, correlating well with symptoms experienced by Ma-2-associated encephalitis and NMO patients who bear hypothalamic pathology. Additionally, the sensory integration issues related to restless legs syndrome are starting to be elucidated as we search to explain the efficacy, but inevitable augmentation, of dopamine agonist medications. Even sleep apnea, the bread and butter of all sleep specialists, is under a variety of elaborate neurologic control mechanisms, an association which becomes readily apparent when we look at how prevalent sleep apnea is in the acute stroke period.

There is still so much to learn, and the explanations for why we sleep are speculative at best. Each state of being (from wake to NREM to REM) serves different functions,

and it is time to return our focus to the brain as we move forward in further developing our understanding of sleep. We must incorporate more than just respiratory analysis from our polysomnograms and implement more sophisticated analyses for disease characterization, thus striving for greater granularity. With a more nuanced understanding, sleep has the potential to provide the neurologic community with more robust treatment options and even opportunities for preventive medicine. Most importantly, now that we recognize the impact that poor sleep can have on neurologic disease, simply being aware of this association is of the utmost importance for better treatment, and thus better quality of life, for all of our patients.

Logan Schneider

Preface

A few years ago I was invited to speak at our department's grand rounds on a topic of my choice. I knew immediately that I wanted to present something on the subject of sleep and neurology, but on what specifically? Neurology had always been my first interest, as it is for most neurologists, but once I began my clinical rotations in medical school I quickly became interested in the field of sleep medicine. Sleep seemed to serve such important neurological functions, vital even; and yet the physiology was incompletely understood, the treatments were limited, and the discipline seemed to generate more questions than answers.

Despite the fact that we now have a greater understanding of some of these concepts, sleep still remains a topic that we understand on a relatively superficial level. How much sleep do we need? Why do we dream? Why do we *sleep*? These are questions that my patients ask me almost daily, and they remain questions that I struggle to answer, for the most part because we still do not know the answers. While frustrating in some regards, this is also part of the excitement. Of all the neurological subspecialties, sleep medicine to me possesses the greatest potential for future growth, both at the basic science level and in the clinic.

I began to think about some of these issues when I was preparing my presentation, and instead of focusing on one area of sleep and neurologic disease, as I had initially decided to, I chose to highlight several: stroke, epilepsy, headache, neuromuscular disease, neurodegenerative disease...the list quickly grew and I easily ran out of time and space, and ended up cutting a great deal. I realized at this point that there was so much to cover on this topic that a 45-min talk could, at best, only scratch the surface. The subject could easily span an entire textbook. Hence the genesis of *Sleep and Neurologic Disease*.

Our goal in the creation of this book was to provide a resource for practicing neurologists and sleep medicine physicians. In my experience, I have yet to encounter a patient in the neurology clinic who does not also have some problem with their sleep. This may be an overstatement in some regards, and partly reflective of a greater problem in our society, but it is undeniable that nearly all neurological diseases can and do result in distinct patterns of sleep disruption. Conversely, many sleep disorders also impact neurological disease. While we still have more questions than answers, our objectives are to strengthen the dialogue between sleep physicians and neurologists, to realize that sleep medicine is more than just treatment of sleep apnea, and that sleep is truly a neurological function. Patients that do not sleep well manifest clear signs and symptoms of neurological impairment.

I am indebted to the prior generation of sleep physicians and sleep scientists who helped to establish sleep as not only a viable but a necessary field of medicine, and am privileged to count some of them as colleagues. I am indebted to all of the authors of this text, who put in the time and effort to help promote this very important field. We hope that it can offer something for your practice, even in some small way, that you can use and take back to your patients. We can all attest to the power of a good night's sleep, and being able to provide this to our patients can be a very powerful thing.

Mitchell G. Miglis

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CHAPTER

1

Anatomy and Physiology of Normal Sleep

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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]

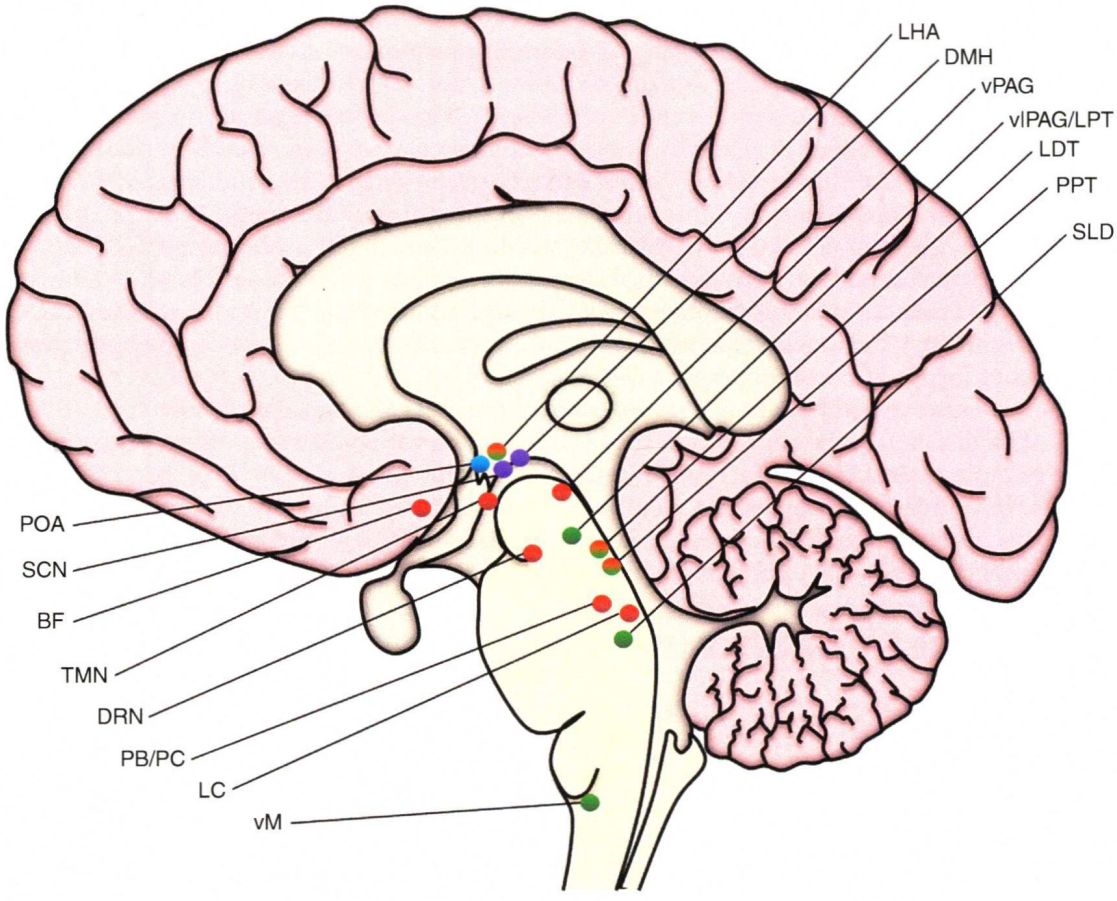

FIGURE 1.1 **General location of the neuroanatomic structures critical to wake/sleep control.** The colors of the marker indicate the predominant role played by the structure: red for arousal, blue for sleep, green for REM, purple for circadian regulation, and multicolored markers indicating multistate 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).