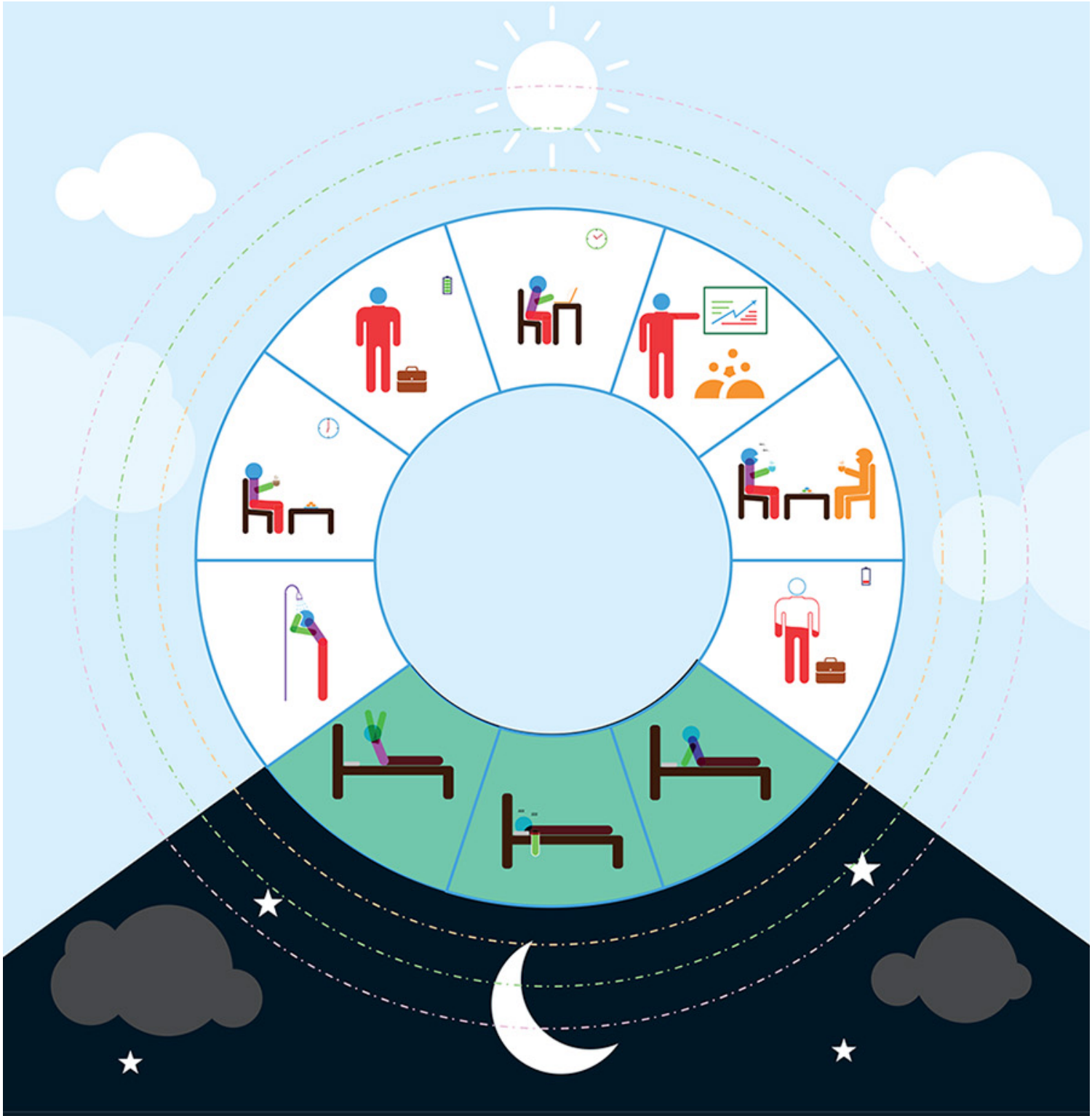

The Behavioral, Molecular, Pharmacological, and Clinical Basis of the Sleep–Wake Cycle

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CHAPTER

4

Neurochemistry and Pharmacology of Sleep

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ABBREVIATIONS

2-AG	2-archidonylglycerol
AEA	anandamide
BF	basal forebrain
CB1	cannabinoid receptor 1
CNS	central nervous system

DAT	dopamine active transporter
DORA	dual orexin receptor antagonist
DR	dorsal raphe nucleus
DREADD	designer receptors exclusively activated by designer drugs
EDS	excessive daytime sleepiness
EEG	electroencephalogram
IL-1	interleukin-1
LC	locus coeruleus
LDT	latero-dorsal tegmental nuclei
MCH	melanin-concentrating hormone
NO	nitric oxide
NPO	nucleus pontis oralis
NREM	nonrapid eye movement
POA	preoptic area
PPT	peduncle-pontine tegmental nuclei
RBD	REM sleep behavioral disorder
REM	rapid eye movement
SCN	suprachiasmatic nucleus
TNF	tumor necrosis factor
vlPAG	ventrolateral periaqueductal gray
VLPO	ventrolateral region of the preoptic area
VTA	ventral tegmental area
W	wakefulness

4.1 INTRODUCTION

Knowledge of the neurochemical basis of sleep provides the clinician with the foundations to understand sleep pathology and pharmacological strategies for its treatment. Sleep pathologies are characterized by the lack of quantity or necessary quality of sleep (insomnia), or by sleep excess (hypersomnia). There are also syndromes characterized by the presence of abnormal behaviors during sleep (parasomnias) as well as circadian maladjustments. In addition, sleep related breathing and movement disorders are other types of sleep pathologies.[1] Finally, the modern way of living also challenges the physiological sleep needs, and has engendered an epidemic of chronic partial sleep deprivation.

In many of these conditions, a neurochemical imbalance has been demonstrated, and the pharmacological treatment strategy is to recover the neurochemical equilibrium. In this work, we review the state of the art of the neurochemical basis of sleep and wakefulness. With this foundation in mind, we also discuss the neurobiological basis of the current pharmacological approaches to treat paradigmatic sleep disturbances.

4.2 SLEEP AND WAKEFULNESS

In humans (and mammals in general), three behavioral states can be distinguished: wakefulness (W), nonrapid eye movement (NREM) sleep (also called slow wave sleep), and rapid eye movement (REM) sleep.

These behavioral states can be recognized by means of polysomnography, which consists of the simultaneous recording of various physiological parameters such as electroencephalogram (EEG), electromyogram, and electrooculogram.

Consciousness (awareness) is the cognitive counterpart of W. The EEG recording of W is marked by the presence of high frequency and low voltage oscillations (cortical activation). In the falling asleep process, adults enter into NREM sleep. In humans, three NREM sleep phases are recognized: N1, N2, and N3, according to the depth of the state. N1 is the transitional stage from W, while N2 is characterized by the presence of sleep spindles and K-complexes. The presence of low frequency (0.5–4 Hz, delta oscillations) of high amplitude waves characterizes the EEG during N3.[2] Although dreams can occur during light NREM sleep, oneiric activity is scarce during N3.[3–5]

REM sleep (also called stage R), is a deep sleep stage even though the EEG is similar to that of W; hence, it is also called "paradoxical" sleep. Dreams occur mainly during this sleep state. REM sleep is characterized by rapid eye movements, muscle atonia, and phasic changes in autonomic activity. REM sleep occupies 20%–25% of total sleep in adults and occurs approximately 90 minutes after the onset of sleep, a parameter known as REM sleep latency.[2] This latency decreases in pathological conditions such as narcolepsy and major depression.[6,7] REM sleep, as well as active W, is also characterized by theta (4–8 Hz) electrographic rhythm in the hippocampus; this signal is easily observed in rodents.

Nighttime sleep in humans is characterized by the presence of four to five sleep cycles. They comprise the period between the onset of sleep until the end of the first episode of REM sleep, or the period from the end of an episode of REM sleep to the end of the subsequent REM sleep episode. The average duration of sleep cycles is approximately 90 minutes in adults.[2]

The polysomnographic sleep patterns described above differ in the newborn; sleep matures along with the development of the brain.[8,9]

4.3 MOST FUNCTIONS ARE MODIFIED DURING SLEEP

When passing from one behavioral state to the other, the following main functions are deeply affected:

1. Cognitive functions. As mentioned earlier, we are conscious during W but during deep NREM sleep (N3) cognitive activity (dreams) is

scarce. On the contrary, dreams are the cognitive counterpart of REM sleep[3–5]; this "bizarre" cognitive activity has been equalized with a natural psychosis. In fact, according to Hobson (1997), "dreaming is, by definition, a psychosis."[10]

Cognitive activities (consciousness and dreams), and the different EEG rhythms that support these functions, are mainly generated by the activity of cortical and thalamic neuronal networks, which are mutually interconnected. Thalamic neurons have a complex electrophysiology that allows them to operate differently according to their level of polarization.[11] When hyperpolarized, the thalamic neurons that project to the cortex (thalamocortical neurons) oscillate at low frequency (0.5–4 Hz), and tend to block the sensory information that travels toward the cortex. This "oscillatory mode" of function synchronizes the cortical neurons and, accompanied by other phenomena of cortical origin, generates the slow waves of NREM sleep.[12,13] On the contrary, when these neurons are relatively depolarized, they enter in the "tonic mode" of function. In this condition, the thalamocortical neurons transmit sensory information toward the cortex in a reliable way. This mode of function occurs during W and REM sleep. Therefore, the thalamus is critical for the generation of part of the slow waves of NREM sleep. Moreover, the reticular nucleus of the thalamus is the site of generation of the sleep spindles that characterize N2 sleep.[13,14] When the thalamus is lesioned, as occurs in the "fatal familial insomnia," the generation of these electrographic signs is suppressed and deep NREM sleep does not occur.[15]

2. Motor functions. Whereas movements and high muscle tone characterize W, the tone of the somatic muscles decreases during NREM sleep. REM sleep is distinguished because of the deep muscle atonia, mainly of antigravity muscles. Due to the brain being very active during REM sleep, the atonia caused by the hyperpolarization of motoneurons is a protective mechanism that prevents acting out the dreams. The main respiratory muscle, the diaphragm, is not affected by the atonia. However, respiratory activity (frequency and tidal volume) is deeply affected during the sleep–waking cycle.[16]
3. Visceral functions. Autonomic and endocrine activity is highly dependent on the behavioral state; hence there are profound modifications on visceral activity during sleep.[17] For example, a hallmark of NREM sleep is the increase in tonic parasympathetic activity; this fact determines heart-rate adjustments during this state.[18]

4.4 SYNOPSIS OF WAKING AND SLEEP MECHANISMS

Thalamocortical, premotor/motor, autonomic, and hypothalamic endocrine neuronal networks are highly affected during the waking–sleep cycle, determining the functional aforesaid adjustments. However, the "primary engines" that determine changes in these neuronal networks are distributed in what are known as W-promoting (activating) and sleep-promoting systems. The location of the main components of these systems is shown in Fig. 4.1. The waking and the NREM sleep promoting neuronal networks have reciprocal inhibition (Fig. 4.2). The pattern of activity in the NREM sleep and W promoting regions has been modeled as a flip-flop electrical switch[19]; that is, periodic activation of either the W-promoting or NREM-promoting neuronal groups, with reciprocal inhibition between them. Interestingly, the structures that are critical for REM sleep generation mostly overlap with the neuronal networks that promote W.

The sleep–wake cycle is regulated by a circadian component (process C) and an homeostatic component (process S).[20] In humans, the propensity to sleep increases during the night (determined by process C) and increases proportionally to the duration of the episode of W (determined by the process S). Hence, the tendency to sleep is reproduced by mathematical models that include these two processes.

The circadian master-clock, the suprachiasmatic nucleus (SCN) of the hypothalamus, is the key component of the process C.[21] Both gene expression and electrical activity of the neurons of this nucleus (mostly GABAergic) oscillate with a 24-hour period, in the absence of environmental cues.[22] The SCN receives information about the environmental light directly from the retina. In diurnal animals, such as humans, SCN neurons promote W, probably by facilitating and inhibiting the activity of the W-promoting and NREM-promoting neurons, respectively (Fig. 4.2). Experimental evidence suggests that the pathway from the SCN for W and sleep regulation is mediated by the subparventricular zone and the dorsomedial hypothalamic nuclei.[23,24]

It is considered that the homeostatic process S is initiated by substances, such as adenosine, that are released into specific areas of the central nervous system (CNS) during W and promote NREM sleep[25,26] (Fig. 4.2).

W is enhanced during fasting, whereas sleep is favored after food intake.[27,28] In fact, metabolic signals affect sleep. For example, glucose activates the NREM-promoting neurons of the ventrolateral preoptic area (VLPO) and decreases the activity of the W-promoting hypocretinergic neurons.[29,30]

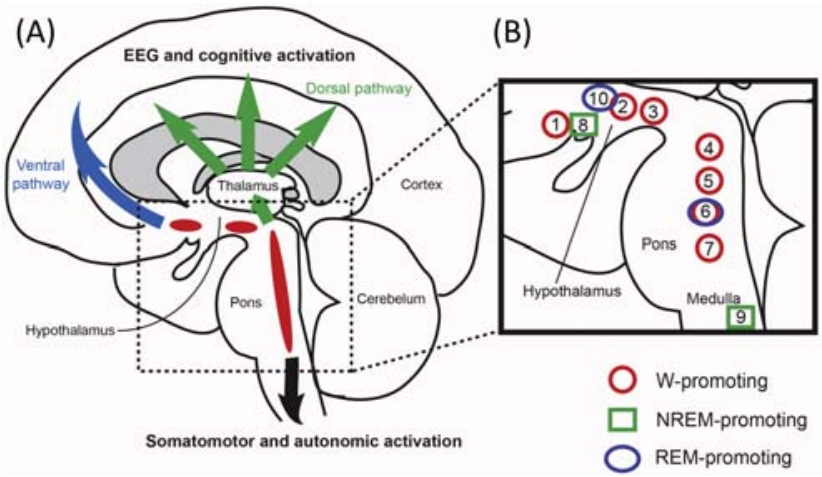

FIGURE 4.1 Scheme of the wakefulness and sleep-promoting systems. (A) Activating systems. The approximate anatomical location of the activating systems is shown in *red*. Activating systems are a heterogeneous group of neurons that use different neurotransmitters. The dorsal ascending activating pathways (that reach the thalamus influencing this on the cerebral cortex) and ventral (directly reaching the cerebral cortex) are shown in *green* and *blue*, respectively. Through these routes, the activating systems modulate the level of vigilance, cognitive functions, and EEG activity. In turn, descending projections regulate motor, respiratory, and autonomic activity. By projections to the hypothalamus (not shown) the activating systems also regulate the endocrine activity. (B) Outline of the main wakefulness, REM, and NREM sleep promoting nuclei. The neurons that form the activating systems (in *red*) are found in the basal forebrain, posterolateral hypothalamus, and mesopontine reticular formation, and use different neurotransmitters. The numbers identify different neuronal groups (approximate location): (1) Basal forebrain, cholinergic neurons. (2) Posterolateral hypothalamus, hypocretinergic neurons. (3) Tuberomammillary nucleus of the hypothalamus, histaminergic neurons. (4) Ventral tegmental area and substantia nigra, dopaminergic neurons. (5) Dorsal and medial raphe nucleus, serotonergic neurons. (6) Latero-dorsal and peduncle-pontine tegmental nucleus (LDT-PPT) neurons, cholinergic neurons. (7) Locus coeruleus, noradrenergic neurons. In *green*, the NREM sleep promoting regions are indicated; the preoptic region of the hypothalamus (8) and the parafacial zone (9). The cholinergic neurons of LDT-PPT (6) and the MCHergic neurons of the posterolateral hypothalamus (10) that promote REM sleep are shown in *blue*. The MCHergic neurons (10) also promote NREM sleep.

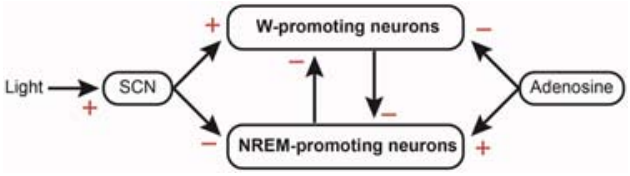

FIGURE 4.2 Scheme of the reciprocal inhibition between the wakefulness-promoting and NREM-promoting neuronal networks, and the regulation by the suprachiasmatic nucleus (SCN, process C) and by adenosine (process S). W, wakefulness. +, −, activation and inhibition, respectively.

Since Moruzzi and Magoun's classical report it is considered that sensory stimulation promotes W by activation of the W-promoting system[31]; however, repetitive sensory stimulation may also promote sleep.[32–34]

It is important to note that although both the standard EEG and behavior may denote W, local populations of neurons in the cortex may show a NREM sleep firing profile with negative consequences for performance. This phenomenon is called local seep, and local sleep homeostasis may be involved in this process.[35,36] In fact, a recent study has shown that local cortical activity of sleeping mice could be converted to the EEG profile of W by imposing a change in the extracellular ion composition.[37]

Very little is known about the neuronal bases involved in the transition from NREM sleep to REM sleep. It has been proposed that the mesopontine peribrachial region, which is activated during NREM sleep, could be involved in promoting the transition between these two sleep states.[38]

4.5 NEURONAL MODELS OF SLEEP AND WAKEFULNESS

Early studies, mainly performed in cats, pointed to the cholinergic and monoaminergic neuronal networks as the main structures responsible for the generation and maintenance of W (and REM sleep, see below). More recent studies in rodents, which employed powerful optogenetic and chemogenetic tools, have suggested that glutamatergic and GABAergic neurons, whose soma are widespread in different regions of the brain, are the main elements for the generation of behavioral states. The authors who support this model consider monoaminergic, cholinergic, and also neuropeptidergic neurons as regulators, but not as the main engine for the generation of the behavioral states. In this work, we will review the main structures and neurotransmitters involved in W and sleep.

4.6 WAKEFULNESS-PROMOTING NEURONAL NETWORKS AND NEUROTRANSMITTERS

The critical neural systems for the generation and maintenance of W are known as W-promoting or activating systems.[39] These are composed of neuronal groups located mainly within the mesopontine reticular formation, posterolateral hypothalamus, and basal forebrain (BF). All of

them project to the thalamus and/or cerebral cortex, producing cortical activation. The ascending projections of these neuronal groups are organized in a dorsal and ventral pathway. The dorsal pathway goes through the thalamus and is mainly involved in the generation of the content (cognitive counterpart) of W, while the ventral pathway goes through the lateral hypothalamus and BF toward the cortex and has been related to the generation of W per se.[40] The activating systems are summarized in Fig. 4.1.

There is an important anatomical and functional interrelation between the neuronal groups that are part of the activating systems. Because there are different types of W, different activating neuronal groups participate more in the generation of one type of W than another. For example, noradrenergic neurons (see below) would have a preponderant role during W that supports attentional processes, serotonergic neurons would sustain W that is accompanied by stereotyped and automatic motor activity, while dopaminergic and hypocretinergic neurons would maintain a waking state with high motivation.

The firing rate of the W-promoting neurons and the release of their neurotransmitters into the synaptic cleft tend to be maximal during W and decreases during NREM sleep (Table 4.1). Since REM sleep is characterized by activation of the EEG associated with oneiric activity, it is expected that part of the activating systems remain active in this state. In fact, cholinergic neurons increase their activity during this behavioral state (Table 4.1).

The activity of these neuronal networks that employ different neurotransmitters promotes a synaptic neurochemical milieu that determines the promotion of W. Below, we will review the main neurotransmitters and neurochemical systems that are involved in the generation of W.

4.6.1 Noradrenaline

In the CNS, noradrenaline is found almost exclusively in the neurons of the locus coeruleus (LC), located in the dorsolateral mesopontine region (Fig. 4.1). These noradrenergic neurons have a "W-ON," "REM-OFF" profile[41] (Table 4.1). This profile is in accordance with the pattern of synaptic release of noradrenaline into the cerebral cortex.[42] During W these neurons increase their firing rate in response to a novel stimulus, but this response is reduced after habituation,[43] which led to the proposal that this neuronal group regulates attentional processes. Experiments in mice have shown that optogenetic stimulation of noradrenergic neurons rapidly awakes the animals, while inhibition of these neurons promotes transition into NREM sleep and reduces W.[44]

TABLE 4.1 Main Neurotransmitters/Neuromodulators That Have an Active Role in the Generation of Wakefulness and Sleep

Neurotransmitters/ neuromodulators	Localization of the neurons	Activity profile
	WAKEFULNESS-PROMOTING	
Hipocretins/Orexins	Posterolateral hypothalamus	W-on
Acetylcholine	LDT-PPT and BF	W/REM-on
Serotonin	Dorsal raphe nucleus	W-on
Noradrenaline	Locus coeruleus	W-on
Dopamine	VTA and SN	Burst discharge during W and REM[a]
Histamine	TMN	W-on
GABA[b]	Nucleus pontis oralis	W-on
Glutamate[b]	Nucleus pontis oralis	W-on
	NREM-SLEEP PROMOTING	
Melanin-concentrating hormone (MCH)	Posterolateral hypothalamus	NREM-on
Adenosine	c	c
GABA[b]	POA	NREM-on
	REM-SLEEP PROMOTING	
Acetylcholine	LDT-PPT and BF	W/REM-on and REM-on
Melanin-concentrating hormone (MCH)	Posterolateral hypothalamus	REM-on
Glutamate[b]	Nucleus pontis oralis	W/REM-on

[a] *During the sleep–wake cycle, the pattern but not the frequency of discharge changes.*
[b] *The role of GABAergic and glutamatergic neurons depends on their location; only the main examples were included in the list.*
[c] *The extracellular release of adenosine increases with prolonged wakefulness, but the origin of adenosine (metabolic, glial, or released by neurons as neurotransmitter) is still not clear.*
BF, basal forebrain; *LDT-PPT*, latero-dorsal and peduncle-pontine tegmental nucleus; *POA*, preoptic area of the hypothalamus; *SN*, substantia nigra; *TMN*, tuberomammillar nucleus of the hypothalamus; *VTA*, ventral tegmental area; *W*, wakefulness.

Interestingly, when rats with LC lesions were introduced into a socially and physically complex environment, they had less W than controls.[45]

Pharmacological note. Alpha-1 adrenergic antagonists such as prazosin facilitate the generation of sleep, and alpha-2 agonists such as dexmedetomidine, which inhibit the activity of LC neurons, are used as sedatives.[46,47]

4.6.2 Dopamine

Dopamine is found in neurons whose soma is located in mesencephalic substantia nigra pars compacta and ventral tegmental area (VTA) (Fig. 4.1). VTA dopaminergic neurons project to the prefrontal cortex, while both neuronal groups project to the striatum.[48] Dopaminergic neurons do not change their firing rate during the sleep–wake cycle, but their temporal pattern of discharge is highly modified (Table 4.1). During W, dopaminergic neurons discharge high frequency "bursts or trains" in response to a motivational stimulus, which produces a large release of dopamine into the synaptic space.[49,50] During REM sleep, this firing pattern is also observed in dopaminergic neurons of the VTA; the dopaminergic release in the nucleus accumbens (ventral striatum) also increases during REM sleep.[51,52] Interestingly, dopamine active transporter (DAT) knockout mice showed a significant increase of W and a reduction of NREM sleep, probably related with an increase in dopamine in the synaptic cleft.[53] Optogenetic activation of VTA dopaminergic neurons has been found to induce and maintain W during a period of high sleep pressure, while chemogenetic inhibition of these neurons during the dark phase, when W predominates, induces NREM sleep.[54]

Lu and coworkers have described a group of dopaminergic neurons within the ventral periaqueductal gray that may also be important in the generation and maintenance of W.[55] This group of neurons is probably functionally similar to the dopaminergic neurons of the rostral region of the dorsal raphe (DR); in fact, a recent study has shown that optogenetic activation of these neurons promotes W.[56]

Pharmacological note. Dopamine agonists and antagonists have been shown to modify sleep variables in preclinical and clinical studies.[57,58] In this respect, several second-generation antipsychotic drugs including clozapine, olanzapine, and paliperidone that block the dopamine D_2 receptor cause a significant reduction of sleep latency, and an increase of total sleep time and N2 when administered to schizophrenia patients.[59,60]

The piperidine derivative methylphenidate has been approved for the treatment of attention deficit hyperactivity disorder in children and adults, and as a second-line treatment for narcolepsy in adults.[61] This drug is also useful for the treatment of idiopathic hypersomnia and excessive daytime sleepiness (EDS) related to Parkinson's disease, multiple sclerosis, and myotonic dystrophy.[62] The compound is a mild CNS stimulant that shares the pharmacological actions of amphetamines including potential for abuse.[63] Methylphenidate blocks the reuptake of

dopamine and noradrenaline by presynaptic neurons.[46,64] Insomnia and nervousness are the most commonly described side effects.

Modafinil is also employed for the pharmacological treatment of EDS. This drug also blocks the reuptake of dopamine and increases the synaptic levels of dopamine.[53]

4.6.3 Serotonin

Serotonin is synthesized by neurons located in several nuclei of the midline brainstem known as raphe nuclei.[65–68] Among them, the most involved in behavioral state control are the DR and medial raphe; these nuclei are located in the mesopontine region and project directly to thalamus and cortex (Fig. 4.1). These serotonergic neurons are characterized by being active during W and turn off during REM sleep[69]; the release of serotonin as measured by microdialysis has the same profile[70] (Table 4.1). Subgroups of these serotonergic neurons have a specific activation when the experimental animal is performing stereotyped movements, such as locomotor activity or grooming.[71] Electrical stimulation of the DR produces a marked activation of the EEG.[72] In addition, photoactivation of serotonergic neurons of the DR increases W and enhances patience to wait for a delayed reward.[73,74]

Based on genetic, electrophysiological, neurochemical, and neuropharmacological approaches, it is currently accepted that serotonin is involved in the promotion of W and the inhibition of REM sleep. The serotonergic receptors can be classified into at least seven classes termed 5-HT_{1-7}.[58] The 5-HT_{1A} receptor is a somatodendritic autoreceptor, while the 5-HT_{1B} receptor is located at presynaptic sites (serotonin axon terminals). In addition, both receptor subtypes are localized at postsynaptic sites. Mutant mice that do not express 5-HT_{1A} or 5-HT_{1B} receptor exhibit greater amounts of REM sleep than their wild-type counterparts. Moreover, direct infusion of a 5-HT_{1A} receptor agonist into the DR enhances REM sleep in laboratory animals. Systemic injection of full agonists of postsynaptic 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, 5-$HT_{2A/2C}$, 5-HT_6, and 5-HT_7 receptor increases W and reduces NREM sleep and REM sleep. Similar effects have been observed after intracerebroventricular administration of a 5-HT_3 receptor agonist.[68]

Pharmacological note. Agitation and hypervigilance accompany the serotonin syndrome, a potentially life threatening condition produced by adverse reaction or overconsumption of serotonergic drugs.[75]

Clinical studies have shown that the nonselective serotonin 5-$HT_{2A/2C}$ receptor antagonists such as ritanserin, ketanserin, and seganserin increase N3 sleep in subjects with normal sleep. Ritanserin also produced

an increase of N3 sleep in poor sleepers, patients with a chronic insomnia disorder, and psychiatric patients with a generalized anxiety disorder or a mood disorder. More recent evidence indicates that the selective 5-HT_{2A} receptor antagonist volinanserin, and the 5-HT_{2A} receptor inverse agonists nelotanserin and pimavanserin, significantly increase N3 sleep in subjects with normal sleep. Nelotanserin was also shown to augment N3 sleep in patients with a chronic insomnia disorder. N2 sleep tended to decrease in most of these studies, while REM sleep showed no significant changes. Thus, the coadministration of a selective 5-HT_{2A} receptor antagonist or inverse agonist along with a hypnotic drug could be a valid clinical approach for normalizing sleep induction and maintenance, as well as for promoting N3 sleep in patients with an insomnia disorder.[76]

4.6.4 Histamine

Histamine, acting via H_1 and/or H_3 receptor, has a crucial role in the regulation of the behavioral states. Histaminergic neurons are found only in the tuberomamillar nucleus of the posterior hypothalamus[77] (Fig. 4.1). These neurons also have a "W-ON" and "REM-OFF" firing profile[78] (Table 4.1). It is worth mentioning that knockout mice lacking histidine decarboxylase (enzyme involved in the synthesis of histamine) or H1 receptor are unable to stay awake when placed in a new environment.[79,80] On the contrary, drugs that increase synaptic levels of histamine augment W.[81] An optogenetic in vitro study also showed that stimulation of histaminergic neurons inhibits the NREM-promoting VLPO neurons, supporting the sleep–wake "flip-flop switch" hypothesis, and a role for histamine favoring W.[82]

Pharmacological note. Drugs that antagonize the H_1 histaminergic receptor and are prescribed as antiallergic, including diphenhydramine, hydroxyzine, and triprolidine, produce somnolence, an increased the likelihood of reduce vigilance and falling asleep.[83,84] These effects led to the use of these drugs as over-the-counter medications to promote sleep. Doxepin is the histamine H_1 receptor antagonist approved by international agencies for the treatment of an insomnia disorder. While prescribing guidelines for doxepin as an antidepressant goes as high as 300 mg daily, the approved insomnia doses are just 3 and 6 mg. This is because at low doses, this compound has minimal pharmacological activity on other neurotransmitter systems.[85]

The H_3 receptor functions as an autoreceptor, and regulates the synthesis and release of histamine. Activation of H_3 receptor reduces histamine release and promotes sleep. Conversely, blockade of H_3

receptor induces W.[86] Pitolisant, a histaminergic H_3 receptor inverse agonist, is a W-promoting drug that has been proposed for the treatment of hypersomnia.[87]

4.6.5 Acetylcholine

Cholinergic neurons involved in the maintenance of W are found in the laterodorsal and pedunculopontine tegmental nuclei (LDT-PPT), and in the BF (Fig. 4.1).[88–90] While LDT-PPT neurons project into the thalamus, the BF neurons project mainly to the cerebral cortex.

During W, and in close relationship with cortical activation, there is an increase in cholinergic neuronal firing as well as an increment in the release of the acetylcholine at cortical levels.[91–93] These neurons suppress their discharge during NREM sleep and are reactivated during REM sleep (Table 4.1).

Drugs that increase synaptic levels of acetylcholine, such as physostigmine, are capable of reversing the state of general anesthesia produced by sevoflurane in humans.[94] Recent optogenetic and "designer receptors exclusively activated by designer drugs" (DREADD) approaches have shown that direct activation of the cholinergic neurons of the BF tend to reduce slow EEG activity during NREM sleep, while inhibition of them increases the slow EEG rhythms but without an important decrease in the amount of W.[95–100]

It is considered that cholinergic neurons of the BF regulate sensory information processing, attention, and memory during W. It is important to note that the cognitive disorders characteristic of Alzheimer's disease are related, in part, to the degeneration and loss of this neuronal group.[101]

Cholinergic neurons of the medial septum and the vertical limb of the diagonal band (components of the BF) contribute to the generation of theta activity during active W (as well as during REM sleep).

Cholinergic neurons of the LDT-PPT are active mainly during active W,[91] and selective activation of the cholinergic neurons of the PPT by a chemogenetic approach suppresses EEG slow activity during NREM sleep.[102]

Pharmacological note. Cholinergic muscarinic receptor antagonist (such as atropine and scopolamine) display a dissociated state characterized by behavioral W, associated with high amplitude slow oscillations and spindles in the EEG, similar to those that occur during NREM sleep.[103] The most outstanding example of this cognitive dysfunction is the criminal use of anticholinergic substances that are present in Datura plant extracts (called "burundanga"), to induce amnesia and submissive behavior or "obedience" in victims.[104,105]

4.6.6 Hypocretins (orexins)

The hypocretins 1 and 2 (also called orexins A and B) are neuropeptides used as nonclassical neurotransmitters or neuromodulators by neurons located in the posterior and lateral hypothalamic region[106,107] (Fig. 4.1). Hypocretins act on two types of metabotropic receptors, exerting postsynaptic and presynaptic excitatory effects.[108]

The intracerebral or intraventricular administration of hypocretins facilitates the generation of W.[109] Furthermore, several experimental approaches have shown that these neurons are activated mainly during W when there is motivation. For example, experimental studies using Fos protein as an index of neuronal activity have shown that the hypocretinergic neuronal activity increases during W with motor activity related to the motivation to explore a new environment, but not during quiet wakefulness or forced locomotion.[110–112] Opto- and chemogenetic activation of these neurons also promotes W.[113–115]

This system is of great clinical importance, since the degeneration of hypocretinergic neurons is the pathogenic basis of narcolepsy with cataplexy.[7]

Pharmacological note. Intranasal hypocretin administration restored the olfactory dysfunction in patients with narcolepsy with cataplexy.[116] In addition, dual orexin receptor antagonist (DORA), suvorexant, is currently approved for the treatment of insomnia in the United States and Japan.[117]

4.6.7 Glutamate

Glutamate is the most ubiquitous neurotransmitter in the CNS. Several glutamatergic neurons located in different areas play an important role in the control of the sleep–wake cycle. With respect to W, glutamatergic neurons in the mesopontine nuclei form part of the activating systems. Some of these glutamatergic neurons are activated during W and REM sleep, while others become functionally active only during W.[91] In this regard, chemogenetic activation of glutamatergic neurons of the PPT increases W.[102] Glutamatergic neurons of the nearby medial parabrachial area are also involved in the generation of this state.[40,118] Furthermore, chemogenetic activation of glutamate-releasing neurons (Vglut2) in the supramammillary nucleus of the caudal hypothalamus produces sustained EEG activation and behavioral arousal, an effect that is virtually suppressed by genetic disruption of glutamate release from these neurons.[119] Studies in rodents have also pointed out that glutamatergic neurons of the BF also play a role in W.[97,99]

Pharmacological note. Ketamine, an NMDA receptor antagonist, inhibits W and produces sedation, hypnosis, or pharmacological coma.[120]

4.6.8 GABA

GABAergic neurons are widely distributed in the CNS.[121] Classically it was considered that GABA was a NREM sleep promoting substance. However, it is now accepted that different groups of GABAergic neurons play a variety of roles in the control of behavioral states.[122]

Experimental evidence suggests that an increase in synaptic GABA release in the nucleus pontis oralis (NPO, also called sublaterodorsal nucleus, which is the nomenclature currently more utilized in rodents), the executive area for REM sleep generation, is necessary to induce W.[123] In addition, the application of GABAergic receptor agonists into the NPO generates W.[124] Furthermore, local increase of GABA levels in the NPO prolongs the time necessary to induce general anesthesia, while isoflurane anesthesia reduces GABA levels within the NPO.[125] A group of GABAergic neurons of the BF is also involved in the generation of W; in fact, opto- and chemoactivation of GABAergic neurons that colocalize parvalbumin increase the W and fast EEG activity (gamma band, 30–60 Hz) that characterize W.[97,99,126,127]

W-promoting GABAergic neurons have also been found in the lateral hypothalamus; these neurons may induce W by inhibiting the NREM-promoting VLPO neurons, or the reticular thalamic nucleus that is critical for the generation of sleep spindles.[128,129]

GABAergic neurons of the VTA also increase their firing rate during arousal (and REM sleep)[130]; these neurons are probably involved in reward-related arousal.[122]

4.7 NEURAL SYSTEMS THAT GENERATE NREM SLEEP

Since Von Economo's early studies on the brains of patients who had died of lethargic encephalitis, the anterior region of the hypothalamus has been recognized as a critical area for sleep generation.[131] However, as reviewed below, other neuronal networks also seem to play a role in NREM sleep generation.

4.7.1 Preoptic Area

Neurons from the preoptic area (POA) of the hypothalamus are critical in the generation and maintenance of NREM sleep[132–135] (Fig. 4.1). These neurons increase their firing rate during NREM sleep, and have been identified mainly in the median POA and VLPO (Table 4.1). Most of these neurons are GABAergic, and also colocalize with the

neuropeptide galanin.[136] These cells project in monosynaptic form toward the activating nuclei; in fact, electrical stimulation of the POA and adjacent BF inhibits the W-promoting neurons and induces NREM sleep.[137] Moreover, optogenetic activation or inhibition of the GABAergic VLPO neurons that project toward the W-promoting histaminergic neurons, enhances or decreases sleep, respectively.[138] Also, optogenetic stimulation of GABAergic neurons of the POA directly inhibits the hypocretinergic neurons.[139] On the other hand, experimental evidence suggests that W-promoting neurons inhibit VLPO neurons.[82,140] This reciprocal inhibition between activating and hypnogenic neurons is critical for the transition between sleep and W, and the basis of the flip-flop state switch model[19] (Fig. 4.2).

4.7.2 Medullary Reticular Formation

Early transection studies have suggested that the caudal brainstem may promote NREM sleep.[141] A recent study has identified the parafacial zone (located ventral and lateral of the genu of the facial nerve) in the medullary reticular formation as a critical area for the generation of NREM sleep[142] (Fig. 4.1). GABAergic and glycinergic neurons within this area are active during NREM sleep, and activation or inhibition of these neurons promote or suppress NREM sleep, respectively.[142,143] Furthermore, GABAergic neurons within this area directly inhibit the W-promoting medial parabrachial area. However, Sakai (2017) has shown that none of these neurons discharge maximally during NREM sleep[144]; hence, this finding does not support a role of these neurons in the control of NREM sleep. New studies are needed to reach a definite conclusion about these neurons.

4.7.3 Other NREM Sleep Promoting Areas

Neurons in the lateral habenula project to several arousal-regulating nodes. In a recent study, Gelegen and colleagues used an elegant tissue-specific genetic approach to probe the role of glutamatergic neurons in the lateral habenula, in the regulation of sleep and anesthetic states.[145] Blocking glutamatergic output from the lateral habenula fragmented NREM sleep, increased the resistance to the sedative actions of propofol, and blocked the increase in EEG power during propofol sedation. This evidence suggests that glutamatergic neurons in the lateral habenula play a role in the sedative actions of propofol, and are necessary for the consolidation of NREM sleep.

4.7.4 Critical Role of GABA in the Generation of NREM Sleep

GABAergic neurons and receptors are distributed within the activating and NREM sleep promoting system. In addition, these neurons are located in the reticular nucleus of the thalamus, where sleep spindles are generated, as well in the cortex, where they play a critical role in the generation of EEG rhythms.[146] We mentioned above that several of these GABAergic networks play an important role in the inhibition of the activating system and, as a result, the occurrence of NREM sleep.

Pharmacological note. The importance of GABA in NREM sleep generation is highlighted with the fact that benzodiazepine and nonbenzodiazepine receptor allosteric modulators (Z-drugs; zolpidem, eszopiclone, zaleplon), which are used as hypnotics, potentiate the action of GABA by acting on GABA-A receptors.[147] Also, most of the general anesthetics (such as barbiturate, etomidate, and propofol) suppress W by enhancing chloride conductance at GABA-A receptors.[148] These drugs would promote NREM sleep, sedation, or anesthesia, at least in part, by reducing the activity of the activating systems, reproducing the effect obtained by the experimental activation of the GABAergic neurons of the POA and the parafacial zone. In addition, these drugs enhance the activity of GABAergic POA neurons that inhibit the activating systems.[148]

4.8 NEURAL SYSTEMS THAT PROMOTE THE GENERATION OF REM SLEEP

4.8.1 Mesopontine Reticular Formation

The neural networks necessary and sufficient for the generation and maintenance of REM sleep are found in the mesopontine reticular formation (Fig. 4.1).[149] In fact, most of the mesopontine neurons that play a role in the maintenance of W coincide with the neurons that are responsible for the generation of REM sleep.

How does this mesopontine neuronal network generate REM sleep? Two main structural models dominate the scene. The cholinergic-aminergic model has been built from data that were originally obtained mostly from cats.[150] The other, the GABA-glutamatergic model, has been constructed from data gathered mainly from rodents.[151]

Cholinergic-aminergic model. McCarley and Hobson (1975) constructed a structural and mathematical model in which an interaction between "REM-ON" and "REM-OFF" neurons determined the REM-NREM ultradian cycle.[152] A newer version of this model, with new neuronal actors, has been also proposed.[150]

Mesopontine noradrenergic and serotonergic neurons (of the LC and DR, respectively) that are active during W turn off their activity during REM sleep ("REM-OFF" neurons) (Table 4.1). These neurons are considered "permissive" for the generation of REM sleep; that is, to generate REM sleep these neurons must be inhibited. During W, these neurons inhibit the "REM-ON" neurons of the LDT-PPT and NPO.[153–155]

Cholinergic neurons of the LDT-PPT not only increase their firing rate during W, but also do so during REM sleep[91] (Table 4.1). Optogenetic stimulation of LDT-PPT cholinergic neurons promotes transition from NREM to REM sleep.[156] Cholinergic "REM-ON" neurons of the LDT-PPT project to the NPO, the REM sleep "executive area." The release of acetylcholine within this area promotes REM sleep.[157,158]

Cholinergic neurons activate glutamatergic neurons of the NPO, which are operational during REM sleep and seem to coordinate different aspects of this state.[157,159,160] For example, these neurons may activate glycinergic neurons of the medullary reticular formation that generate the muscle atonia or, via ascending projections, contribute to the thalamocortical activation that characterize REM sleep.

New versions of the model consider that mesopontine GABAergic neurons may contribute to the inhibition of the monoaminergic neurons during REM sleep, and/or to inhibit the "REM-ON" neurons of the NPO during W.[124,150,161–167]

GABAergic-glutamatergic model. This model emphasizes the connections between "REM-OFF" GABAergic neurons of the ventrolateral periaqueductal gray (vlPAG) that modulates the "REM-ON" glutamatergic neurons of the NPO (or sublaterodorsal nucleus). Hence, GABAergic vlPAG neurons are active during W and project to the NPO.[55,151,161] In fact, bilateral inhibition of the vlPAG and adjacent areas promotes REM sleep.[166] It has been hypothesized that inhibition of vlPAG neurons during the transition from NREM to REM sleep disinhibits "REM-ON" glutamatergic neurons in the NPO triggering REM sleep. Consistent with this hypothesis, calcium imaging and unit recordings across sleep–wake states demonstrated that the activity of most GABAergic neurons in the vlPAG is strongly suppressed during REM sleep.[168] Of note is that this model, guided mostly by experiments in rodents, considers cholinergic influence on REM sleep not as determinant, but only regulatory.[169]

Pharmacological note. Most serotonin or noradrenaline reuptake inhibitors used as antidepressants tend to suppress REM sleep.[6] The inhibition of REM sleep by these drugs is used to block cataplexy (produced by the same mechanisms responsible for the REM sleep atonia) in narcoleptic patients.[64]

In humans, increasing synaptic levels of acetylcholine by acetylcholinesterase inhibitors produces W and cortical activation, while REM

sleep precipitates if this drug is applied during NREM sleep.[170] These data support a bimodal role of cholinergic neurons, promoting both the generation of W and REM sleep.

4.8.2 Medullary Reticular Formation

The medullary reticular formation plays a critical role in the generation of REM sleep atonia. One accepted model considers that glutamatergic neurons in the NPO generate motor atonia by activation of glycinergic neurons in the ventromedial medulla. These neurons produce a glycinergic postsynaptic inhibition onto alpha motoneurons.[171] GABAergic neurons within this area may also play a role in the generation of REM sleep atonia.[161,172]

GABAergic neurons of the dorsal and lateral paragigantocellular nuclei inhibit "REM-OFF" neurons of the mesopontine region, and have been proposed to be also involved in the promotion of REM sleep.[173,174]

4.8.3 Other Areas Involved in REM Sleep Generation

As mentioned earlier, dopaminergic neurons of the VTA change their firing profile (from tonic to burst discharge type) and increase the release of dopamine in the nucleus accumbens and prefrontal cortex during REM sleep. These neurons may contribute to the EEG activation. In addition, ascending projections from the VTA have been suggested to be critical for the generation of dreams.[175]

The hypothalamus also participates in the control of REM sleep. Histaminergic neurons are "REM-OFF" and are probably also permissive for REM sleep generation. Furthermore, Lu and coworkers have identified a region of the POA that is active during REM sleep, the "extended" VLPO, and may promote this state.[176] However this REM sleep promoting area was not observed in the cat.[133]

Chemogenetic activation of hypocretinergic neurons suppresses REM sleep.[115] Moreover, hypocretinergic neurons decrease their firing rate during "tonic" REM sleep[177,178]; however, Fos protein and microdialysis studies conducted in cats suggest that these neurons may be active during the "phasic" components of REM sleep, and may contribute to the induction of twitches, rapid eye movements, and autonomic instability that characterize this behavioral state.[179] The role of the hypothalamic melanin-concentrating hormone (MCH) will be described in the next section.

Cholinergic and noncholinergic BF neurons are not only active during W but also during REM sleep. The latter may contribute to the cortical activation that characterizes REM sleep.[92,99,100]

Pharmacological note. Dopamine agonists induce vivid dreams, while antipsychotic drugs, which block the action of dopamine, suppress dream experiences.[175,180,181]

4.9 THE MELANIN-CONCENTRATING HORMONE: A NREM AND REM SLEEP PROMOTING SYSTEM

Neurons in the posterolateral hypothalamus and incertohypothalamic area utilize the neuropeptide MCH as a neuromodulator.[182–185] These neurons project throughout the CNS, including toward major W-promoting nuclei[185,186] (Fig. 4.1). MCH exerts its biological functions through two metabotropic receptors but only one is active in rodents.[187]

These neurons fire scarcely during W, increase their firing rate during NREM sleep, and reach a maximum during REM sleep.[188] Optogenetic and chemogenetic studies strongly suggest that this system plays a critical role in the generation of sleep.[189,190] Since the administration of MCH into the cerebral ventricles, POA, BF, DR nucleus, LC, and NPO facilitates the generation of NREM sleep and/or REM sleep, it is possible that MCHergic neurons inhibit the activity of the activating systems and/or activate the hypnogenic nuclei to promote sleep.[191–196] For example, MCHergic neurons inhibit DR serotonergic neurons and decrease serotonergic release[197,198]; this finding may explain, at least in part, the promotion of REM sleep induced by MCH.[191] The suppression of the serotonergic activity by MCH could explain also the pro-depressive effect of this neuropeptide.[199–203]

A recent chemogenetic study suggests that when MCHergic neurons are physiologically recruited, NREM sleep depth is increased and the extinction of NREM sleep episodes is accelerated, strengthening the probability for natural NREM to REM sleep transition.[204]

On the other hand, W-promoting neurotransmitter/neuromodulators tend to silence the MCHergic neurons.[183]

Pharmacological note. Experimental evidence strongly suggests that MCH antagonists may be a therapeutic approach to treat depression and anxiety.[205]

4.10 OTHER SUBSTANCES THAT PARTICIPATE IN THE CONTROL OF WAKEFULNESS AND SLEEP

4.10.1 Melatonin

Melatonin is a hormone that is secreted during the night from the pineal gland.[206] As mentioned, commands from SCN promote sleep during the night (and/or W during daytime, process C) in diurnal

animals. This nucleus, in addition to modulating W and sleep promoting areas, regulates the release of melatonin, through indirect modulation of the sympathetic system. Hence, melatonin is a hormone that signals the absence of light, and prepares the individual physiology to the night period.[207] In humans, melatonin has a weak sleep-promoting effect; recently, an inhibitory effect of melatonin onto the hypocretinergic neurons has been described.[208]

Pharmacological note. Because melatonin is the physiological marker of the night, it is usually indicated for circadian maladjustments such as jet lag. Also, melatonin and melatonin receptor agonists including ramelteon and tasimelteon are used to treat certain types of insomnia.[147] In this respect, ramelteon has a specific indication for difficulty with sleep onset, while tasimelteon is indicated for the treatment on non-24-hour circadian rhythm sleep–wake disorder. Finally, agomelatine, marketed as an antidepressant, has multiple receptor effects that include melatonin receptor agonist activity.[85]

4.10.2 Adenosine

Process S determines an increase of sleep pressure during a prolonged W period. Different lines of research have shown that during W, NREM sleep promoting substances such as adenosine are released into the synaptic space, at least in part, from astrocytes (gliotransmission).[25,26,209] Adenosine promotes sleep by inhibiting the activating systems and stimulating the NREM-promoting neurons of the POA.[26,210–212]

Recent experimental evidence suggested that GABAergic neurons of the nucleus accumbens (ventral striatum) that express the adenosinergic A2a receptor and dopaminergic receptors are critical for sleep and W regulation.[213,214] In fact, opto- or chemogenetic activation of these neurons induces NREM sleep.[215]

Pharmacological note. Caffeine, the world's most consumed psychostimulant, promotes W by blocking adenosine receptors.[216] Caffeine is usually obtained from different sources such as coffee, cola drinks, and caffeine pills.[217] In addition, several natural products that are consumed as tea have an important amount of caffeine. An example is the W-promoting *Ilex paraguariensis*, known as yerba mate, a traditional beverage in the south of Latin America that has now expanded to other world regions.[218,219]

4.10.3 Cytokines

It has been shown that loss of sleep distorts immune function. In fact, messenger molecules of immune function (cytokines) are present in the

normal brain and interact with the neurochemical systems that regulate the sleep–wake cycle.[220–222] The cytokines interleukin-1 (IL-1) and tumor necrosis factor (TNF) promote NREM sleep, increasing the activity of the NREM-promoting neurons of the POA. Part of this effect seems to be mediated by prostaglandin D2, which is another NREM-promoting factor. The role of cytokines in the generation of NREM sleep could occur under normal conditions, but it is potentiated in pathological conditions where the synthesis of these cytokines increase; for example, IL-1 and TNF would be involved with the hypersomnia that accompanies infection and fever.

4.10.4 Endocannabinoids

The predominant transmitters for the endocannabinoid system are anandamide (AEA) and 2-archidonylglycerol (2-AG). These molecules are ubiquitous in the CNS and are released during periods of neuronal activity.[223] These neuromodulators produce the majority of their central effects by activating the cannabinoid receptor 1 (CB1); activation of this G-protein-coupled receptor reduces neurotransmitter release at many synapses. Administration of exogenous AEA consistently increases REM and NREM sleep. However, conflicting results arise from attempts to increase endogenous AEA levels. A recent study suggests that endocannabinoid signaling through CB1 is necessary for NREM stability but it is not necessary for sleep homeostasis.[224]

Pharmacological note. Since antiquity, cannabinoids have been used as a treatment for insomnia[225]; however, there is not enough experimental and clinical evidence yet to support the use of cannabis for this condition.

4.10.5 Nitric Oxide

Several groups of neurons produce nitric oxide (NO); among them, the cholinergic neurons of the LDT-PPT that play a critical role both in W and REM sleep.[226]

Mariño and Cudeiro (2003) suggested an activating role of NO.[227] However, the intracerebroventricular injection of the precursor of NO, L-arginine, produces an increase in NREM sleep in rats.[228] Similar effects have been seen with the use of NO donors in rats and cats.[229–231] Other studies have shown that inhibitors of NO synthase (which decreases the release of NO) produce a decrease of sleep,[228,229,232] and attenuate the homeostatic "rebound" of sleep that follows its deprivation.[233] Neurons that contain NO synthase (and colocalize with GABA) in the cerebral cortex are active during

NREM sleep.[234] These neurons are thought to synchronize slow cortical electrical rhythms during NREM sleep, probably in relation with homeostatic sleep drive.[235,236] Finally, the release of NO increases during W or sleep according to the region where it is studied.[237]

In summary, available data suggest that NO promotes W or sleep depending on the neuronal network under study.

4.10.6 Other Substances

There is experimental evidence that substances such as various neuropeptides (neuropeptide Y, neuropeptide-VF, nesfatin-1, etc.)[238–240] and hormones (GHRH, female reproductive hormones, etc.)[241,242] also have a regulatory role in the sleep–wake cycle. For example, Jego et al. (2012) have shown that the neuropeptide nesfatin-1 is coexpressed with MCH in the lateral hypothalamic area.[243] These authors also showed that disruption of the brain nesfatin-1 signaling suppressed REM sleep with only small alteration of NREM sleep.

4.11 PHARMACOLOGICAL APPROACHES IN SLEEP PATHOLOGY

Knowing the neurobiological basis of W and sleep provides the clinician with the frame to understand sleep pathologies and the pharmacological approaches for their treatment. Below we discuss some of the neurochemical rationale for the therapeutic approach for paradigmatic sleep conditions.

4.11.1 Insomnia

An inability to fall or stay asleep, and daytime complaints such as somnolence and fatigue that occurs no less than three times per week, for at least 3 months, characterize the chronic insomnia disorder in adults.[1]

An imbalance between the W and NREM sleep promoting mechanisms is likely behind this disorder. Behavioral approaches and sleep hygiene may be enough to balance this disorder. If pharmacological treatment is needed, the medications approved for the treatment of this disorder include benzodiazepine (BZD) receptor allosteric modulators, either BZD (triazolam, temazepam, flurazepam) or non-BZD (zolpidem, eszopiclone, zaleplon) agents. These drugs promote sleep, at least in part, by reducing the activity of the activating systems. The melatonin

receptor agonist ramelteon and low-dose doxepin, whose mechanism of action is mainly related to the blockade of histamine H1 receptor, are also employed for the treatment of insomnia. These drugs improve sleep onset latency (zolpidem immediate-release, zaleplon, ramelteon) and/or sleep maintenance (temazepam, flurazepam, zolpidem extended-release, eszopiclone, low-dose doxepin). However, during their administration, N3 sleep and REM sleep do not regain normal levels or can be even further reduced.[76,147]

A new pharmacological approach for the treatment of an insomnia disorder is now available. It refers to the dual orexin (hypocretin) receptor antagonist (DORA) suvorexant that blocks the effect of the W-promoting orexin. In this respect, suvorexant administration was associated with significant improvements in time to sleep onset, total sleep time, and subjective quality of sleep in young and middle-aged patients with chronic insomnia. The greater amounts of total sleep time were related to an increase in REM sleep and N2 sleep.[117,147]

4.11.2 Hypersomnia

Hypersomnia disorder is a term used for a group of disorders in which the primary characteristic is EDS in the presence of normal or longer than normal nocturnal sleep.[244] These disorders are currently classified as central disorders of hypersomnolence.[1] Among these disorders, the most common is narcolepsy. The management of this pathology includes several behavioral approaches and pharmacological treatment. The most common symptom is EDS, and the first pharmacological approach is to use modafinil. This drug blocks the DAT, increasing dopamine synaptic levels. As mentioned before, increasing dopamine levels has a wake-promoting effect. Of note is that genetic ablation of the DAT abolishes the wake-promoting effect of modafinil. However, there are other possible sites of action of this drug.[245] Amphetamine-like drugs such as methylphenidate, that also increase the synaptic monoamines, are used, in addition, to reduce sleepiness.[246]

A new therapeutic approach is the administration of pitolisant, an inverse agonist/antagonist of the histamine H3 receptor that is an inhibitory autoreceptor. As a result, pitolisant increases the histaminergic tone, promoting W. Pitolisant decreases EDS and cataplexy rate in narcoleptic patients.[247,248]

4.11.3 Parasomnias

Parasomnias are unpleasant or undesirable behavioral phenomena that occur during the sleep period. There are different types of

parasomnias, that are classified in REM and NREM sleep parasomnias.[1,249] One of them is the REM sleep behavior disorder (RBD). During RBD the REM sleep atonia does not occur, and the patients act out their dreams. Severe injuries can occur during the REM without atonia episodes. About 90% of patients with chronic RBD respond well to clonazepam (0.5–2 mg) administered half an hour before sleep time.[250] Clonazepam is a benzodiazepine whose mechanism of action for the RBD is still unknown. It has been tentatively proposed that the improvement of sleep would depend upon a reduction of REM sleep time and/or intensity.

4.11.4 Circadian Disorders of the Sleep–Wake Cycle

Delayed and advanced sleep phase disorders are the most common circadian conditions. These are characterized by bedtimes and wake-up times that are delayed or advanced 3 or more hours, respectively. The free-running disorder occurs predominantly in severely blind individuals and is characterized by steady daily delaying drift of the major sleep period.

The goal of the therapy is to align the timing of the circadian clock (the SCN) with the desired light-night cycle. Sleep hygiene and chronotherapy with light and/or melatonin (or melatonin agonists) are usually indicated.[251]

4.11.5 Jet Lag and Shift Work Disorder

Jet lag and shift work disorder are circadian rhythm sleep–wake disorders resulting from altered sleep–wake schedule in relation to the external environment. As for the circadian disorders, the treatment aim is also to realign the internal circadian clock with the external environment. Behavioral therapies such as sleep hygiene and management of the light-dark and sleep schedule are indicated. Pharmacologic agents are used to treat insomnia and excessive sleepiness, and melatonin (or melatonin agonists) is used to facilitate sleep and circadian realignment.[252]

4.11.6 Neurological and Psychiatric Disorders That Affect Sleep

Several neurological and psychiatric and general medical disorders may affect sleep. Paradigmatic examples of a psychiatric and a neurological disorder that affect sleep are depression and Parkinson's disease.

Depression is associated with disturbed sleep, including disturbances of sleep continuity, reduced N3 sleep, and altered REM sleep parameters. Activating antidepressants may worsen sleep, which is related

to their mechanism of action including inhibition of serotonin and/or noradrenaline reuptake, and activation of serotonin 5-HT_{1A} and 5-HT_2 and noradrenaline α_1 receptors. Worsening of sleep in patients with a diagnosis of depression has been described following treatment with the activating tricyclic antidepressants imipramine, desipramine, and protriptyline; the selective serotonin reuptake inhibitors fluoxetine and paroxetine; the selective noradrenaline reuptake inhibitor reboxetine; and the serotonin and noradrenaline reuptake inhibitors venlafaxine, duloxetine, and milnacipran. Sedative antidepressants include the tricyclic derivatives amitriptyline, nortriptyline, trimipramine, and doxepin, and the serotonin reuptake inhibitors trazodone and nefazodone; their actions on sleep variables depend upon the blockade of serotonin 5-HT_{2A} and histamine H_1 receptors.[6,253–255]

Parkinson's disease is a neurological pathology that courses with degeneration of dopaminergic neurons.[256] Insomnia is the most frequent sleep disorder in Parkinson's disease, and is linked to motor symptoms that characterize the pathology. The sleep disorder is mainly characterized by increased sleep latency and intra-sleep awakenings. The administration of L-Dopa (administered together with the dopamine decarboxylase inhibitor carbidopa) may improve sleep-associated motor symptoms that contribute to insomnia. The dopamine agonists ropinirole, pramipexole, rotigotine patch, and the monoamine oxidase B inhibitor rasagiline have also been shown to recover insomnia in Parkinson's disease patients.[257]

4.12 CONCLUSIONS

A detailed knowledge of the neurochemistry of the activating and hypnogenic systems is important to understand and treat sleep pathologies. An exemplary achievement in relation to the activating systems has been the unveiling of the pathogenesis of narcolepsy. This pathology is caused by the degeneration of hypocretinergic neurons,[7] which prompted paraclinical studies such as the titration of hypocretin-1 in the cerebrospinal fluid for diagnostic confirmation of narcolepsy, and therapeutic advances such as intranasal hypocretin-1 administration for the treatment of some aspects of the disease,[116] as well as hypocretin antagonist for the treatment of insomnia.[258]

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