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THE NEUROBIOLOGY OF SLEEP AND WAKEFULNESS

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SYNOPSIS

Since the discovery of Rapid Eye Movement (REM) sleep in the late 1950s, identification of the neural circuitry underlying wakefulness, sleep onset and the alternation between REM and non-REM (NREM) sleep has been an active area of investigation. Synchronization and desynchronization of cortical activity as detected in the electroencephalogram (EEG) is due to a corticothalamocortical loop, intrinsic cortical oscillators, monoaminergic and cholinergic afferent input to the thalamus, and the basal forebrain cholinergic input directly to the cortex. The monoaminergic and cholinergic systems are largely wake-promoting; the brainstem cholinergic nuclei are also involved in REM sleep regulation. These wake-promoting systems receive excitatory input from the hypothalamic hypocretin/orexin system. Sleep-promoting nuclei are GABAergic in nature and found in the preoptic area, brainstem and lateral hypothalamus. Although the pons is critical for the expression of REM sleep, recent research has suggested that melanin-concentrating hormone/GABAergic cells in the lateral hypothalamus "gate" REM sleep. The temporal distribution of sleep and wakefulness is due to interaction between the circadian system and the sleep homeostatic system. Although the hypothalamic suprachiasmatic nuclei contain the circadian pacemaker, the neural circuitry underlying the sleep homeostat is less clear. Prolonged wakefulness results in the accumulation of extracellular adenosine, possibly from glial sources, which is an important feedback molecule for the sleep homeostatic system. Cortical neuronal nitric oxide (nNOS) neurons may also play a role in propagating slow waves through the cortex in NREM sleep. Several neuropeptides and other neurochemicals likely play important roles in sleep/wake control. Although the control of sleep and wakefulness seemingly involves multiple redundant systems, each of these systems provides a vulnerability that can result in sleep/wake dysfunction that may predispose to physical and/or neuropsychiatric disorders.

Keywords

EEG; synchronization; homeostasis; slow wave activity; NREM sleep; REM sleep; neurotransmitter; hypocretin; orexin; adenosine

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Our understanding of the neural control of sleep in large part parallels the history of the field of neuroscience. As new tools and methodologies have become available to the research community, sleep researchers have been quick to take advantage of such techniques. Thus, the description in the following sections progresses from relatively crude methods such as brain transections and lesion studies to the application of molecular biology and genetics to create transgenic models. The approach in this section will be largely historical, illustrating the insights and principles that have emerged as research has progressed.

The advent of inducible transgenic mouse strains and viral-mediated transfection has enabled the ability to target cell populations in a phenotype-, location- and time-specific manner. This added precision eliminates many of the caveats associated with more traditional lesion (impossible to isolate heterogeneous cell populations) and knockout methodologies (developmental confounds; lack of anatomical specificity). Recently, opto- and chemogenetic methods have enabled manipulation of specific cell populations with unprecedented precision using light or synthetic ligands, respectively. In optogenetics, neurons of interest are genetically engineered to express light-sensitive opsins that control specialized ion channels. Subsequent illumination of these cells (usually through surgically implanted optical fibers) by specific wavelengths of light can activate or inhibit the cells expressing that opsin without collateral activation of nearby cell types. For example, the blue light-sensitive channel rhodopsin-2 protein opens a Na^+ channel and, when stimulated, will depolarize a cell. Conversely, the yellow/green light-sensitive halorhodopsin opens a Cl^- channel and will thus inhibit cells when illuminated. Similarly, the DREADD (Designer Receptors Exclusively Activated by Designer Drugs) system relies on a modified G protein-coupled receptor that responds only to a (otherwise biologically inert) synthetic ligand. Following expression of the DREADD receptor in a cell population of choice, the ligand can be injected systemically to activate only that population. This combination of powerful tools for precisely manipulating neuronal activity with the specificity of genetic targeting is revolutionizing the study of neural circuits and their control of behavior.

Cortical Activity During Sleep and Wakefulness

The electrical activity of the cerebral cortex has been used to distinguish sleep vs. wakefulness since the earliest EEG studies of sleep.[1] The firing rate of cortical neurons generally declines during non-Rapid Eye Movement (NREM) sleep relative to wakefulness and REM sleep,[2, 3] although a few studies have reported cortical neurons with the opposite firing pattern.[4, 5] EEG activity reflects the aggregate firing of large neuronal ensembles, and is conventionally referred to by bandwidths with the following approximate frequencies: alpha (9-12 Hz), beta (12-30 Hz), delta (0.5-4.0 Hz), low (30-60Hz) and high (60-100 Hz) gamma and theta (5-9 Hz). Several neural circuits have been implicated in the synchronization and desynchronization of cortical activity that distinguish NREM sleep from wakefulness and REM sleep. For example, input from the basal forebrain (BF), likely from both cholinergic and non-cholinergic neurons, is critical for the desynchronized EEG characteristic of wakefulness and REM.[6, 7]

Synchronization of the EEG during NREM depends on a corticothalamocortical loop[8] as well as intrinsic cortical oscillators,[9] whose activities are modulated by a number of

subcortical systems. Here, our primary focus will be how interactions between these subcortical systems produce sleep and wake and their electrophysiological correlates at the cortical level.

Historical Overview

Classical brainstem transection studies

The first investigations relevant to the neurobiology of sleep and wakefulness were conducted in the 1930s. Bremer transected the cat brainstem, observing that sleep/wake cycles remained intact after a low medullary level transection (*encephale isolé*), whereas transection between the pons and midbrain (*cerveau isolé*) yielded chronic drowsiness.[10] Conversely, electrical stimulation of the midbrain reticular formation caused alerting of the cortex.[11] From these observations arose the concept that the forebrain was kept alert by tonic activity in the reticular formation. This ascending reticular activating system (ARAS) is comprised of cholinergic laterodorsal and pedunculopontine tegmentum (LDT/PPT), noradrenergic locus coeruleus (LC), serotonergic (5-HT) Raphe nuclei and dopaminergic ventral tegmental area (VTA), substantia nigra (SN) and periaqueductal gray projections that stimulate the cortex directly and indirectly via the thalamus, hypothalamus and BF.[6, 12-18] These aminergic and catecholaminergic populations have numerous interconnections and parallel projections which likely impart functional redundancy and resilience to the system.[6, 13, 19]

In contrast, transecting the pons rostral to the trigeminal nerve induced constant wakefulness,[20] suggesting that input from a sleep "center" in the lower pons or medulla inhibited a wakefulness "center" in the rostral pons. This result established that sleep is an active state of the brain;[21] however, the identity of this lower brainstem “sleep center" remained a mystery. Although “sleep active” neurons were reported in the nucleus tractus solitarius,[22] their location has proven to be elusive. More recently, the medullary parafacial zone (PZ) adjacent to the facial nerve was identified as a sleep-promoting center on the basis of anatomical, electrophysiological and chemo- and optogenetic studies.[23, 24] GABAergic PZ neurons inhibit glutamatergic parabrachial (PB) neurons that project to the BF,[25] thereby promoting NREM sleep at the expense of wakefulness and REM sleep. As we shall see below, these populations exert much of their effects via projections to the BF and hypothalamus.

Encephalitis lethargica: Insights into sleep/wake control from neuropathology

After World War I, a worldwide influenza epidemic claimed an estimated 25-40 million fatalities. One variant of this disease was *encephalitis lethargica*, in which patients entered a coma that often resulted in death. The neuropathologist Constantin von Economo identified distinct types of brain lesions associated with equally distinct effects on sleep and waking. Lesions in the posterior hypothalamus extending into the mesencephalic reticular formation were associated with persistent coma, whereas lesions in the anterior hypothalamus and the adjacent BF were associated with chronic insomnia. von Economo concluded that the posterior hypothalamus was important for the maintenance of wakefulness and the anterior hypothalamic/BF region important for sleep induction.[26]

Nauta subsequently demonstrated that anterior hypothalamic transections severely disrupted sleep and wakefulness,[27] providing direct experimental evidence for von Economo's clinical observations. Sterman, McGinty and others found that preoptic/basal forebrain lesions decreased sleep,[28] whereas stimulation of this region facilitated sleep onset.[29] Sleep-active neurons were later described in the BF, particularly the substantia innominata and the horizontal limb of the diagonal band of Broca.[30] Subsequent electrophysiological, Fos activation, tract tracing and lesion studies identified the GABAergic ventrolateral preoptic area (VLPO) and median preoptic area (MnPO) as being sleep-active neuronal populations that project to and inhibit wake-active cell groups.[31-38] These preoptic sleep-promoting groups are themselves inhibited by wake-active monoaminergic stimulation.[39, 40] It should be noted that the BF also contains cortically-projecting cholinergic neurons distributed across the diagonal band of Broca, nucleus basalis and substantia innominata.[41, 42] These neurons have been extensively studied for their role in promoting cortical activation and wakefulness. In addition, much research has examined the role of the BF, including the cholinergic neurons therein, in regulating sleep homeostasis; this work will be discussed in detail in a later section.

Also consistent with von Economo's earlier observations, lesions of the posterior lateral hypothalamus (PLH) were found to increase sleep in rats, cats and monkeys.[27, 43, 44] Histaminergic (HA) cells were subsequently identified in the tuberomammillary nuclei (TM) and found to be wake-promoting.[45] Antihistamines have long been known to be soporific, and knockout mice lacking the enzyme responsible for histamine synthesis are hypersomnolent.[46, 47] Inhibitory VLPO neurons project to HA TM neurons[48], and HA neurons project widely throughout the brain including to wake-promoting populations in the brainstem and to the cortex.[49] Injections of the $GABA_A$ agonist muscimol into the posterior hypothalamus increased NREM sleep and suppressed REM sleep, whereas injections in the ventral PLH increased both NREM and REM sleep.[50] Together, these results supported the hypothesis that sleep results from functional blockade of a posterior hypothalamic waking center. Although the neurons inactivated by muscimol were thought to be the HA cells, the PLH contains another wake-active neuronal population, the hypocretin/orexin cells, that were yet to be described.

REM sleep: The role of the Pons and Acetylcholine

REM sleep was first described by Aserinsky and Kleitman[51-53] and was described in animals in 1959.[54] As cellular neurophysiology entered the neurobiologist's toolbox in the '60s and early '70s,[55-57] sleep physiologists characterized the firing rates of cells in specific brain regions across the arousal state continuum from wakefulness to NREM to REM sleep. These "arousal state profiles" showed that monoaminergic cell groups decrease their firing from wakefulness to REM and are thus called "REM-off" cells. In contrast, a smaller set of brainstem regions had maximal firing rates during REM ("REM-on" cells). Since these cell groups were anatomically localized, Hobson and McCarley[58, 59] proposed that the NREM/REM cycle arises from a reciprocal interaction between these aminergic REM-off cell groups and cholinergic REM-on cell groups in the medial pons. More recent versions of this model recognize that the REM-on and REM-off cells are distributed in a variety of brain regions[60-62] and include both glutamatergic and GABAergic populations.[63, 64]

The pons is both necessary and sufficient to generate REM sleep[65, 66] and the dorsolateral pons, in particular, is crucial for the genesis of REM sleep.[67, 68] Neurons in this region have a “REM-on” profile with their highest discharge rate occurring during REM sleep.[69, 70] Microinjections of carbachol, a mixed cholinergic agonist, into the dorsolateral pons results in a prolonged REM-like state, and pontine acetylcholine levels are increased during REM sleep relative to NREM and wakefulness.[71] Cholinergic input for REM sleep generation comes from the more rostral PPT and LDT, which project to the cholinoceptive subcoeruleus or sublaterodorsal tegmental nucleus (SLD) and the subjacent nucleus pontis oralis.[72, 73] During REM sleep, activation of the dorsolateral pons regulates the varied physiological manifestations of REM sleep, e.g., EEG desynchronization and theta activity, ponto-geniculo-occipital (PGO) waves, rapid eye movements and atonia. More recent studies have implicated the melanin-concentrating hormone (MCH)/GABAergic neurons of the hypothalamus as providing critical input to the pontine generator of REM sleep.[64, 74]

Lesions of the dorsolateral pons produce REM sleep without atonia in cats: the cats orient, locomote, and engage in what appears to be prey-catching behavior - as if they were "acting out their dreams".[75, 76] Cholinoceptive dorsolateral pontine neurons project to the ventral medulla, where they form synapses with inhibitory neuronal populations that, in turn, project to and inhibit spinal motorneurons, thereby preventing muscle movement during REM. This descending inhibition is thought to be mediated by glycinergic mechanisms;[77] more recent work has implicated GABA[78, 79] as well as local inhibition in the ventral horn.[80] A similar condition, REM Behavior Disorder, exists in humans;[81] interest in the neurophysiological basis of REM Behavior Disorder has been potentiated by the finding that REM Behavior Disorder may be a risk factor or predictor of Parkinson’s disease and other neurodegenerative synucleinopathies.[82, 83]

Narcolepsy/Cataplexy

The other sleep disorder related to the dorsolateral pons is narcolepsy. Narcoleptic patients suffer from excessive daytime sleepiness, abnormalities of REM sleep, and sudden attacks of muscle atonia during wakefulness known as cataplexy. Cataplexy is primarily triggered by “positive” emotional stimuli (laughter, surprise, sexual arousal) that are processed by the limbic system; these stimuli appear to converge on the REM atonia pathway, likely through the prefrontal cortex and the amygdala.[84, 85] In narcoleptic dogs, cataplexy can be exacerbated by anticholinesterases, and the muscarinic cholinergic receptor is upregulated in the pons of these dogs.[86, 87] Although this upregulation likely affects the same REM atonia pathway described above, narcoleptic dogs have been particularly valuable for the insights that they provided into the role of the hypocretin/orexin system in sleep/wake control and muscle atonia.[88]

The Hypocretin/orexin System

Discovery of the Hypocretins and the Orexins

Hypocretins 1 and 2 (Hcrt1 and Hcrt2), also known as orexins A and B, are excitatory hypothalamic neuropeptides that were independently described by two groups in 1998.[89, 90] Since Sakurai et al.[91] confirmed the common identity of the Hcrts and the orexins, we will

use the term “Hcrt” here to refer to this system. While early studies emphasized the role of the Hcrt system in feeding and energy balance, subsequent research focused on sleep-wake regulation based, in part, on the discovery that Hcrt dysfunction underlies the sleep disorder narcolepsy.

Hcrt neurons are found exclusively in the PLH,[89, 90, 92] numbering between 4,000-5,000 in the rat[92-94] and 50,000-80,000 in humans.[95] The two Hcrt peptides are derived from a single precursor molecule by proteolytic processing and Hcrt1 and Hcrt2 are largely co-localized in the same neurons.[96] Hcrt neurons are co-extensive, but not co-localized, with MCH neurons.[92, 97, 98] The Hcrt neurons project widely throughout the brain and spinal cord[92, 96, 99, 100] including major projections to wake-promoting cell groups such as the HA cells of the TM,[101] the 5-HT cells of the dorsal Raphe nuclei (DRN),[101] the noradrenergic cells of the LC,[102] and cholinergic cells in the LDT, PPT, and BF.[101, 103] Afferent input to Hcrt neurons was mapped using a combination of retrograde and anterograde tract tracers;[104] these studies described major projections from the lateral septal nucleus, bed nucleus of the stria terminalis, preoptic area, dorsomedial, ventromedial and posterior hypothalamic nuclei, substantia nigra and VTA, and the DRN. Using transgenic mice expressing transneuronal retrograde tracers linked to the Hcrt promoter,[105] genetic tracing studies revealed a more circumscribed set of afferents to the Hcrt neurons from the amygdala, preoptic GABAergic neurons, and 5-HT neurons in the median/paramedian Raphe nuclei. Thus, the anatomy of the Hcrt system strongly suggests involvement in numerous physiological functions including sleep-wake, feeding, thermoregulation, blood pressure and neuroendocrine regulation.

To date, the Hcrt peptides have uniformly been reported as excitatory either by eliciting depolarization and/or increased spike frequency.[89] Hcrt directly excites cellular systems involved in waking and arousal including the LC,[102, 106, 107] DRN,[108, 109] TM,[110-112] LDT,[113, 114] cholinergic BF,[115] and both dopamine (DA) and non-DA neurons in the VTA.[116, 117] The excitatory effects of Hcrt are mediated by multiple ionic mechanisms[110, 118-125] which, combined with their capacity for neuromodulation,[109, 113, 118, 126-129] suggest that Hcrt exerts potent direct and indirect effects on a variety of physiological systems, particularly arousal systems. Some of these effects appear to be mediated by colocalized transmitters and modulators including, but not limited to, dynorphin, galanin and glutamate.[130-135] Cellular electrophysiological studies revealed that while Hcrt cells are excited by numerous substances,[136-145] they are inhibited by the aminergic transmitters NE, DA, and 5-HT,[136, 139, 146-148] as well as by GABA.[136, 139, 149]

Hcrt signaling is strongly associated with wakefulness. The region of the PLH containing the Hcrt cells has long been implicated in arousal state control.[27] Hcrt neurons are wake-active as measured by Fos expression,[150] electrophysiology,[151-153] or brain/CSF peptide content.[154-156] Hcrt1 increases arousal when infused into the brain,[106, 157-162] and optogenetic stimulation or inhibition of Hcrt signaling increases or decreases wakefulness, respectively.[163-167] Hcrt receptor antagonists promote sleep when administered systemically or directly into the brain.[168-171] Indeed, newly-developed dual Hcrt receptor antagonists exhibit promise for the effective pharmacological promotion of sleep without adverse side

effects such as cognitive performance deficits and dependence that are common to many sleep medications.[172, 173]

The Hcrt System and the Sleep Disorder Narcolepsy

Narcolepsy has a genetic component in both humans and dogs that has proven instrumental in identifying its unique pathology. In narcoleptic dogs, the *canarc-1* gene that transmits narcolepsy was identified as a mutation in the *hcrtr2* gene that results in a truncated, nonfunctional protein.[88] In a remarkable convergence, *Hcrt* null mutant mice exhibited a narcoleptic phenotype, including cataplectic "behavioral arrests", sleep-onset REM, and increased and fragmented NREM and REM sleep.[101] Thus, dysfunction of either the Hcrt ligand or one of its receptors can result in narcolepsy. In humans, the HLA Class II antigen HLA DQB1*0602 is present in more than 85% of narcoleptic patients with cataplexy but only 12-38% of the general population.[174] Such close association with the HLA system has led to the suggestion that narcolepsy may be an autoimmune disease.[175, 176] Narcoleptic humans exhibit undetectable levels of Hcrt1 in cerebrospinal fluid (CSF).[177] Postmortem studies revealed an absence of *prepro-hcrt* mRNA[178] and an 85-95% reduction in the number of Hcrt-containing cells in human narcoleptic brains[95] without any change in either MCH mRNA or the number of MCH cells. The presence of increased staining for glial fibrillary acid protein in the PLH of narcoleptic brains[95, 178] suggests that degeneration of the Hcrt cells may cause human narcolepsy. Consistent with this, animal models in which the Hcrt neurons are ablated by selective neurotoxins[179, 180] or engineered to degenerate postnatally[181, 182] also present a narcoleptic phenotype.

Models for the Role of the Hcrt System in Arousal State Regulation

The balance between sleep and wakefulness has been proposed to be maintained by the relative activation of the wake-active systems found in the BF, LDT/PPT, LC, DRN and TM and the sleep-active systems found in the VLPO.[13, 94] These relationships are summarized in Figure 1. In wakefulness, ascending monoaminergic projections from the ARAS nuclei activate wake-promoting cholinergic BF and histaminergic TM cells en route to the cerebral cortex, while inhibiting sleep-promoting VLPO and MnPO neurons. LDT/PPT cholinergic neurons ascend to the thalamus, which in turn stimulates the cortex. During NREM sleep, inhibitory, GABAergic output from the VLPO, MnPO and PZ inhibit these populations. REM sleep is driven by a combination of increased brainstem cholinergic ("REM-on") activity and inhibition of "REM-off" populations; MCH neurons in the LH are proposed to be a part of the REM control mechanism as well. Hcrt signaling promotes waking by activating brainstem and forebrain wake-active populations and is, in turn, inhibited by ascending 5-HT and NE inputs. Hcrt has also been proposed to consolidate waking and sleep states by stabilizing transitions between sleep and wakefulness in the "flip-flop switch" model.[13] When the Hcrt system is dysfunctional as occurs in human narcolepsy and transgenic mouse models, behavioral state instability results so that the affected individual cannot maintain extended periods of wakefulness of sleep and, instead, shifts rapidly between these states.[183] This "flip-flop switch" concept was subsequently extended to account for the alternation between NREM and REM sleep.[63]

Sleep Homeostasis and the Timing of Sleep and Wakefulness

Common knowledge, as well as scientific observations, suggest that sleep is a homeostatically regulated physiological response. The longer one is awake, the more likely one is to sleep or, at least, be sleepy. Sleep deprivation impairs cognition and prolonged sleep deprivation results in impaired physiological function, ultimately resulting in death.[184] This homeostatic property has been incorporated into the "two-process model" of sleep regulation[185, 186] which posits that the homeostatic sleep-related "Process S" integrates input from the circadian system ("Process C") to gate the occurrence of sleep and wakefulness across the day. Process S is proposed to be a neurochemical process(es) that begins to build up at the onset of wakefulness; once a threshold value is reached, sleep will ensue only if Process C is in the appropriate circadian phase. This seemingly simplistic model accounts remarkably well for the timing of sleep in humans and rodents.

EEG slow waves in the delta bandwidth (0.5-4.0 Hz) generated by thalamocortical interactions during NREM sleep increase in proportion to prior wake duration. The level of NREM delta power (NRD; also called EEG slow wave activity or EEG SWA) is highly dependent on the prior history of sleep and wakefulness: prolonged wakefulness dose-dependently increases NRD while both daytime naps and nighttime sleep decrease NRD, reflecting a diminution of Process S. Conversely, NRD itself is highly resistant to circadian modulation.[187, 188] Thus, EEG NRD has been suggested to reflect the cortical manifestation of the recovery from prior waking activities[185] and is commonly used as a quantitative measurement of Process S.

Anatomical substrates of the Two-Process model

The Suprachiasmatic Nuclei as the Basis for Process C

The hypothalamic suprachiasmatic nuclei (SCN) contain a master circadian pacemaker (or biological clock) in mammals,[189-192] and are commonly recognized as the source of Process C.[193-195] However, it remains unclear how SCN activity temporally organizes daily sleep-wake rhythms. Early studies relied on SCN lesions to functionally dissect circadian versus homeostatic regulation. The homeostatic response to sleep loss was intact in SCN-lesioned rats with no change in total sleep time per 24 h,[196, 197] whereas similar studies in SCN-lesioned squirrel monkeys and mice and in behaviorally arrhythmic Siberian hamsters reported increased sleep time per 24 h.[198-200] These results fueled ongoing debate over whether the SCN specifically promotes wakefulness (as in the “opponent process model”), sleep, or both.[199, 201] More recently, Hcrt was proposed as a point of integration between circadian and homeostatic mechanisms based on CSF Hcrt1 levels assayed across the day and in conjunction with sleep deprivation. However, it is unclear to what extent changing Hcrt1 levels in the CSF result from active (e.g., circadian or homeostatic) regulation[156, 202, 203] or are passively driven by increased locomotor activity.[204] Integration of circadian and homeostatic signaling may also occur within the SCN. Indeed, SCN neuronal firing rates are modulated by sleep-wake state and by sleep deprivation,[205, 206] and certain sleep-wake states (e.g., REM sleep)[207-209] and EEG spectral signatures[188] may be under stronger circadian control than others.

Circadian rhythms arise from interactions between a well-characterized set of dedicated "clock genes" found throughout the body and CNS.[210, 211] Genetic disruption of the clock via knockout yields increased waking, increased sleep or no change of daily sleep-wake amounts depending on the particular gene targeted.[212-216] Sleep deprivation can modulate extra-SCN clock gene expression and binding activity.[217-221] Together, these findings suggest that different clock genes may play distinct roles in regulating or integrating circadian and homeostatic aspects of sleep.

In Search of Substrates for Process S

Whereas the anatomical substrate for Process C had been identified prior to the development of the two-process model, a similar substrate for Process S has proven more difficult to identify. GABAergic neurons in the MnPO are sleep-active,[34, 222] project to wake-active brain regions including the LC, DRN, vlPAG and the Hcrt neurons,[38] and Fos immunohistochemical studies indicate that MnPO activation occurs during sleep deprivation prior to sleep onset,[223] suggesting that this region is responsive to homeostatic sleep pressure. MnPO neurons also exhibit increased Fos activation during REM sleep deprivation.[224]

A cortical neuronal population that expresses neuronal nitric oxide synthase (nNOS) has recently emerged as a candidate for involvement in Process S. Whereas the majority of cortical neurons express the immediate early gene product Fos during waking, cortical nNOS neurons express Fos during sleep, but not during wakefulness.[225] Cortical nNOS neurons, which also coexpress the Substance P receptor NK1, represent the rarest subset of GABAergic interneurons and are anatomically and functionally quite distinctive: they are the only nNOS-synthesizing neuronal population reported to be sleep-active,[226] they receive subcortical inputs from sleep-related cholinergic[227] and serotonergic[228] neurons, and send long-range rather than local circuit projections.[229-232] Functionally, nNOS cortical neuron activation is positively correlated with NR bout duration and NRD energy[233] and critically depends on elevated sleep pressure.[234] Furthermore, loss of nNOS signaling in nNOS null mutant mice fragments NR sleep, attenuates NRD power while increasing delta power in wake, and increases sleepiness while attenuating response to sleep deprivation. Cortical nNOS neurons thus appear to be critical integrators in the neuronal network linking state-dependent afferent inputs, homeostatic sleep drive and EEG SWA.[235]

Other Neurochemicals Involved in Sleep/Wake Control

Although functional neuroanatomical approaches, especially when combined with electrophysiology, have led to many fundamental insights into the control of sleep and waking, there is an equally impressive literature on sleep substances and their contributions to behavioral state. These "sparks vs. soup" approaches are highly complementary and valuable insights into the control of sleep and wakefulness have arisen from both approaches.

Cytokines and Sleep

A number of lymphokines (e.g., interleukin-1, tumor necrosis factor alpha), inflammatory molecules and growth factors promote NREM sleep.[236, 237] Interleukin-1 and tumor necrosis factor may regulate physiological sleep through direct, receptor-mediated modulation of the hypothalamus and serotonergic raphe nuclei. Other immune molecules, such as interleukin-6, promote NREM sleep and are elevated in sleep disorders with excessive daytime sleepiness as a symptom.

Peptides and Sleep

As indicated above, Hcrt has wake-promoting activity.[106, 160] A number of other neuropeptides have also been found to promote wakefulness. Corticotrophin-releasing factor (CRF)[238, 239] and adrenocorticotrophic hormone,[240] two core components of the hypothalamo-pituitary adrenal axis, promote wakefulness, possibly mediated by CRF activation of CRF receptor-1 on Hcrt cells.[141] Thyrotropin-releasing hormone (TRH) and TRH analogs are wake-promoting in rodents[241, 242] but, in a clinical study, TRH only exerted a “weak” effect on sleep efficiency.[243] Neuropeptide Y, a potent inducer of feeding behavior, exerts varied effects on rodent sleep ranging from sleep suppression to alterations in EEG spectral power.[244-246] In humans, intravenous NPY reduced sleep latency in young men[247] and older men and women.[248] Neuropeptide S[249] and urotensin[250] are also reported to promote wakefulness in rodents.

Among sleep-promoting peptides, growth hormone releasing hormone (GHRH) has been extensively studied,[238, 251, 252] in part because pharmacological stimulation of slow wave sleep (SWS) results in increased GH release.[253] However, studies of peptides related to the GH system have produced varying results.[246, 254-256] Intraperitoneal cholecystokinin-8 (CCK) reduced sleep latency and increased NREM sleep in rats and rabbits[257-259] and centrally-administered CCK restored sleep in cats rendered insomniac by serotonin depletion.[259, 260] α-melanocyte stimulating hormone is sleep-promoting as is corticotropin-like intermediate lobe peptide.[240] Both peripheral[261] and icv[262] infusion of insulin increases SWS in rats. These effects could be related to postprandial sleepiness. Insulin also stimulates insulin-like growth factor-1 (IGF-1) receptors, although the molar doses of IGF-1 needed to promote sleep are much lower than that of insulin.[263]

As indicated above, the hypothalamic neuropeptide MCH is coextensive, but not co-localized, with Hcrt cells.[92, 97, 98] MCH has profound effects on both SWS and REM sleep, in particular, when administered icv.[264] Fos is activated in MCH neurons during recovery from REM sleep deprivation.[264, 265] MCH neurons are inhibited directly by HA and indirectly by Hcrt via local GABA interneurons.[266, 267] Optogenetic studies have implicated MCH neurons in the control of REM sleep[268, 269] as well as sleep onset.[270] Other peptides with REM-promoting activity include prolactin,[271, 272] vasoactive intestinal polypeptide [272, 273] and pituitary adenylate cyclase-activating polypeptide.[274-277]

Extracellular Adenosine as an Indicator of Sleep Loss

Interest in adenosine (AD) as a potential modulator of sleep and wakefulness arose when the adenosine receptors were cloned and it was recognized that methylxanthines such as

caffeine, a potent wake-promoting substance, were antagonists at AD receptors.[278] AD is the ultimate breakdown product of ATP and, as such, there has also been great interest in a role for AD as a potential link between sleep and restoration of intracellular energy stores.[279, 280] Injections of AD or AD analogs typically promote sleep and NREM EEG delta power;[281-284] interestingly, such injections increase delta power even in sleep-satiated animals[285]. AD signaling regulates sleep and waking at targets including the BF, VLPO, Hcrt neurons, cortex and brainstem,[280] primarily via inhibitory A_1 receptors and excitatory A_{2A} receptors.[286-289]

Levels of extracellular AD accumulate with time spent awake and decline during recovery sleep in the BF and cortex but weakly, if at all, in other brain regions.[290, 291] In the BF, wake-related AD release appears to depend on cholinergic neurons, as cell-specific lesions of these neurons abolish AD increases induced by sleep deprivation.[292, 293] Together, these data suggest that AD is an important endogenous regulator of sleep and waking in the brain, and that the BF, in particular, is important for adenosinergic influences on sleep homeostasis.[294] While the source of AD in the BF has proven elusive, expression of inducible NOS (iNOS) in the cholinergic BF neurons appears to be important for the wake-related upregulation of AD.[295-297] Astrocytes may be an important source for AD induced by waking, as abolishing vesicular release specifically in astrocytes attenuated the homeostatic sleep response and blocked the sleep-suppressing effect of an adenosine A_1 receptor antagonist.[298, 299] Given the important role played by astrocytes in regulating neuronal energy stores, it is tempting to speculate that glial-neuronal interactions may be a critical component of regulating sleep need.[300-302]

Melatonin

Melatonin is produced by the pineal gland during the night in both diurnal and nocturnal species. Specific receptors for melatonin are found in the cortex, SCN, and hypothalamic regions involved in thermoregulation. Exogenous melatonin is a popular hypnotic available in both physiological (0.03 mg) and pharmacological (1-10 mg) doses. Physiologic doses can help in sleep onset processes when sleep initiation is attempted at abnormal times, such as occurs following travel across time zones. Melatonin helps to synchronize circadian rhythms in totally blind individuals.[303] Pharmacologic doses may work through non-melatonin receptors.

Prostaglandin D_2 and Sleep/Wake Regulation

Intra-cerebral administration of prostaglandin D_2 (PGD_2) induces sleep, especially SWS, in rats and monkeys.[304] Inhibition of the enzyme responsible for PGD_2 synthesis, PGD synthase (PGDS),[305, 306] markedly suppresses sleep and blockade of PGD_2 receptors inhibits physiological sleep.[307] CSF levels of PGD_2 undergo significant modulation by time of day in rats, with a daytime peak and a nighttime trough.[308] CSF levels of PGD_2 in rats increase during sleep deprivation and tend to increase along with an increasing propensity toward sleep under normal conditions.[309] The site of action for PGD_2 has been identified as a sleep-promoting zone (PGD_2-SZ) located on ventral surface of the rostral basal forebrain outside the brain parenchyma.[310, 311] Administration of a selective adenosine A_{2a}-R agonist (CGS21680), but not the selective adenosine A_1-R agonist cyclohexyladenosine, markedly

induces sleep when administered to the PGD_2-SZ.[312] The SWS-promoting effect of PGD_2 is inhibited by pretreatment with KF17837, a highly selective A_{2a}-R antagonist[312] and is blunted in adenosine A_{2a}-R-deficient mice.[289] It is therefore hypothesized that PGD_2 is coupled to A_{2a}-R adenosinergic signaling via the brain parenchyma and that the PGD_2-SZ plays an important role as an interface between these two systems.

Gonadal steroids and sleep

Sex and sex hormones have long been reported to modulate sleep and biological timing, but only recently have these phenomena begun to be studied on a more mechanistic level.[313] Women exhibit increased subjective sleep disturbance, particularly insomnia,[314] and increased spindle activity and SWA compared to men.[315-318] Sex differences in SWA are amplified by sleep deprivation, aging and major depression.[315, 319] Sleep spindle activity and REM sleep, but not SWA, also vary across the menstrual cycle.[320-322] Female rodents exhibit increased wakefulness in the dark (active) phase compared to males,[323-328] with the estrus cycle further modulating sleep in female rats,[329-331] but not mice.[325] Like humans, female mice exhibit increased spindle frequency activity and NRD compared to males.[324, 326] Circulating ovarian steroids, particularly estradiol and progesterone, are important for maintaining many of these effects.[327, 330, 332-334] Studies exploiting genetic tools to dissociate genetic and gonadal sex, along with use of classical neuroendocrine paradigms, recently showed that sex differences in sleep appear to be developmentally determined by a combination of genetic sex and gonadal hormone exposure.[335, 336] Estradiol downregulates the synthetic enzyme for PGD_2,[337] increases Hcrt and Hcrt receptor expression levels,[338, 339] and modulates Fos expression in the VLPO and TM.[331]

SUMMARY

Sleep is a regulated physiological state with clear implications for cognition, performance and overall well-being. Although beyond the scope of this review, numerous sleep disorders have been described that negatively impact these functions. Other chapters in this volume address the involvement of sleep disturbances in a number of psychiatric disorders. The neural substrates of sleep and wakefulness appear to be highly distributed and, to some extent, redundant systems distributed throughout the brain with monoaminergic and cholinergic systems largely promoting wakefulness and GABAergic systems in the preoptic area and brainstem promoting sleep. The hypocretin/orexin system appears to play a special role in the promotion of wakefulness and suppression of REM sleep by providing excitatory input to the monoaminergic and cholinergic systems. Sleep is not a unitary state but involves a cyclic alternation between NREM and REM sleep; the pons is critical for generating the multiple components (i.e., EEG synchronization, eye movements, muscle atonia, etc.) that characterize REM sleep. The timing of sleep and wakefulness is regulated by an interaction between the circadian pacemaker located in the hypothalamic SCN and a sleep homeostatic system whose anatomical location is yet to be convincingly identified. Among various neurochemicals, extracellular AD accumulates in the BF as wakefulness is extended and inhibits cortically-projecting cholinergic neurons, thereby influencing cortical activity. A corticothalamocortical loop plays a major role in generating SWA measured in the EEG; cortical nNOS/NK1 neurons may be important in coordinating and/or propagating SWA

within the cortex. Since the control of sleep and wakefulness involves a complex orchestration of the activity of many neural systems, it is readily apparent that many nodes for dysfunction exist that can have implications for both physical and mental health.

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LIST OF ABBREVIATIONS

5-HT	5-hydroxytrytamine (serotonin)
AD	Adenosine
ARAS	Ascending reticular activating system
BF	Basal forebrain
CRF	Corticotrophin releasing factor
CSF	Cerebrospinal fluid
DA	Dopamine
DRN	Dorsal raphe nuclei
EEG	Electroencephalogram
GABA	Gamma-aminobutyric acid
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
HA	Histaminergic
Hcrt	Hypocretin (orexin)
IGF-1	Insulin-like growth factor-1
iNOS	Inducible Nitric Oxide Synthase
LC	Locus coeruleus
LDT	Laterodorsal tegmental nucleus
LH	Lateral hypothalamus
MCH	Melanin-concentrating hormone
MnPO	Median preoptic area
nNOS	Neuronal Nitric Oxide Synthase
NREM	Non-rapid eye movement sleep
NRD	NREM delta power
PB	Parabrachial nucleus

PGD2	Prostaglandin D2
PGD2-SZ	Prostaglandin D2-sensitive zone
PGO	Ponto-geniculo-occipital
PLH	Posterolateral hypothalamus
PPT	Pedunculopontine nuclei
PZ	Parafacial zone
REM	Rapid eye movement sleep
SCN	Suprachiasmatic nuclei
SLD	Sublaterodorsal tegmental nucleus
SN	Substantia nigra
SWA	Slow wave activity
TM	Tuberomammillary nuclei
TRH	Thyrotropin-releasing hormone
VLPO	Ventrolateral preoptic area
VTA	Ventral tegmental area

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KEY POINTS

- Sleep is not a unitary state; Rapid Eye Movement (REM) and non-REM (NREM) sleep recur with a 90 min cyclicity in humans and more rapidly in other mammals.
- The monoaminergic systems of the brainstem, the cholinergic neuronal groups found in the brainstem and basal forebrain and the hypocretin/orexin cells of the hypothalamus are critical for the maintenance of wakefulness.
- Sleep is regulated by GABAergic populations in both the preoptic area and the brainstem; increasing evidence suggests a role for the melanin-concentrating hormone cells of the lateral hypothalamus.
- The pons has historically been viewed as critical for the production of REM sleep; recent research implicates descending projections from the hypothalamus and the periaqueductal gray as important for control of pontine REM generators.
- The hypocretin/orexin cells of the posterior and lateral hypothalamus provide excitatory input to all wake-promoting monoaminergic and cholinergic brain nuclei and both promote wakefulness and suppress REM sleep; loss of these cells results in the sleep disorder narcolepsy.
- The timing of sleep and wakefulness across the 24 h day/night cycle is due to the interaction between the circadian pacemaker located in the suprachiasmatic nuclei of the hypothalamus and a sleep homeostatic mechanism whose anatomical locus is yet to be conclusively defined.
- Sleep is a homeostatically-regulated process in which adenosine plays an important feedback role; the underlying neural circuitry is incompletely understood but may involve cortical nNOS/NK1 neurons.
- Synchonization of cortical activity as measured in the electroencephalogram (EEG) involves a corticothalamocortical loop and oscillators intrinsic to the cortex; EEG desynchronization results from monoaminergic and/or cholinergic input to the thalamus and cholinergic projections from the basal forebrain.

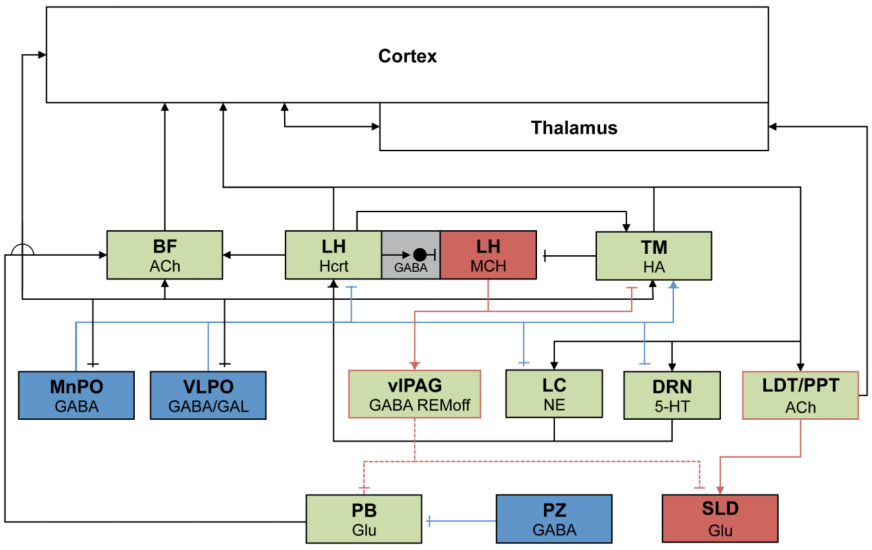

Figure 1.

Schematic depiction of major subcortical sleep-wake regulatory populations. Wake-promoting cell groups are green, NREM sleep-promoting cell groups are blue and REM sleep-related cell groups are red. Green boxes with red outlines indicated wake/REM-active populations. Gray boxes indicate local GABA interneurons. Excitatory connections are marked with arrowheads, and inhibitory connections are indicated by blunted terminals. Dotted lines indicate pathways that are inhibited during REM sleep.