Understanding the Interplay between Neurobiochemistry of Sleep-wake Systems and Cognition

**Corresponding Author:**
Dr. Mohammad Torabi Nami,
MD, PhD Neuroscience, Institute for Cognitive Sciences Studies, Neuroscience Research Center, ICSS,
17Pezeshkpour St., Valiasr Ave. - Iran (Islamic Republic of)

**Submitting Author:**
Dr. Mohammad Torabi Nami,
MD, PhD Neuroscience, Institute for Cognitive Sciences Studies, Neuroscience Research Center, ICSS,
17Pezeshkpour St., Valiasr Ave. - Iran (Islamic Republic of)

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Understanding the Interplay between Neurobiochemistry of Sleep-wake Systems and Cognition

Author(s): Torabi Nami M, Sadeghniaat K

Abstract

A body of evidence and critical concepts has contributed to our current understanding of the brain circuitry and the neurotransmitters that regulate the daily cycles of wakefulness and sleep. The neurochemistry of brain circuitries involved in sleep and wake systems plus the interrelation between sleep parameters and cognitive functions are the focus for this brief review. Wakefulness is promoted by hypothalamic and brain stem neurons producing hypocretin, histamine, noradrenaline, serotonin, dopamine and acetylcholine. Coordinated activity in these distinct neuronal groups activates the thalamus and cerebral cortex by ventral pathway (aminergic) and a dorsal pathway (cholinergic), to insure full alertness and cortical activation. Rapid eye movement (REM) sleep and non-rapid eye movement (nonREM) sleep are controlled by the cholinergic neurons in the pons, and the gamma amino-butyric acid (GABA) and galanin containing neurons in ventro-lateral pre-optic area of the hypothalamus. Mutual interaction between these wake- and sleep-promoting regions likely permit to maintain consolidated periods of wakefulness and sleep. Sleep architecture and, in particular, nonREM sleep intensity are further modulated by the prior duration and quality of wakefulness. Genetically determined differences in adenosine metabolism and activity dependent secretion of brain derived neurotrophic factor (BDNF) contribute to robust inter-individual differences in sleep intensity in human. Sleep parameters including its microstructure and consequently its efficiency is known to be correlated with the neurocognitive aptness in terms of attention and concentration, visuo-spatial and constructional skills, sensory perceptual function, language, memory, executive and intellectual functions. To understand this correlation better, neurobiochemistry of sleep and cognitive functions provide an open realm for research in cognitive neuroscience.

Review

The ideas behind defining the neural circuitries in the brain which govern sleep and wake systems. During the first half of the last century, clinicians and neuroscientists began to identify neural structures that regulate behavioral state. One of these clinicians was Constantin von Economo, an Austrian psychiatrist and neurologist. He found that patients with “encephalitis lethargica” (slept for more than 20 hours a day, arising only briefly to eat and drink) had lesions of the posterior hypothalamus and rostral midbrain. By contrast, patients with an injury to the anterior hypothalamus had unrelenting insomnia. Based on these observations, he hypothesized that the anterior hypothalamus contained neurons that promoted sleep, whereas neurons near the hypothalamus brainstem junction helped promote wakefulness. Moreover, he suggested that a region between the two, including the lateral/posterior hypothalamus, caused narcolepsy when lesioned. Von Economo proposed that there was an ascending arousal system originating in the brainstem that kept the forebrain awake.

During the years after the Second World War, the neuroscientists Moruzzi and Magoun also focused on these wake-promoting regions. They demonstrated that stimulation of the brainstem reticular formation changed the synchronized EEG activity of anesthesia and sleep to the desynchronized activity of waking. They showed that this effect was mediated by an ascending arousal pathway that begins in the rostral pons and runs through the midbrain reticular formation. Their concept of the “ascending reticular activating system” (ARAS) as a loose collection of neurons was born. However, much work during the last decades has explored these ideas and identified several neurochemically distinct systems that contribute to the regulation of wakefulness and sleep (1-3). These well-defined cell groups with identified neurotransmitters will be the focus of this review.

The circadian clock and sleep homeostasis determine the sleep-wake cycle. The sleep-wake cycle is regulated by the interaction of a circadian oscillator and a sleep-control mechanism, which has been referred to as sleep homeostasis. Many characteristics of human physiology in general and the sleep-wake cycle in particular reflect circadian rhythms. Circadian is Latin and means approximately...
one day. These rhythms are produced, in part, by a complex transcriptional-translational feedback loop of so-called clock genes and clock proteins that have been shown to be present in every cell and be conserved throughout evolution. The major zeitgeber and synchronizer of the endogenous rhythms with the environment is the light-dark cycle. When the endogenous rhythms are out of synchrony with the environmental light-dark cycle, such as for example with jet lag or shift work (social time), sleep-wake disturbances and impaired mood and cognitive performance can occur.

Circadian rhythms are governed by an endogenous circadian master clock located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus (4).

SCN and its connections when regulating sleep-wake systems

The SCN helps to time wakefulness and sleep through local hypothalamic circuits. The circadian information is likely conveyed by SCN-derived peptides such as prokineticin-2 or transforming growth factor-β that act in a humoral or synaptic fashion on adjacent regions including the supraventricular zone (SPZ; ventral: vSPZ & dorsal: dSPZ). This signal is then relayed to the dorsomedial nucleus of the hypothalamus (DMH), which integrates it with behavioral (e.g., sleep, activity, feeding) and endocrine (e.g., corticosteroid levels). A wake-promoting signal is relayed through excitatory projections to the lateral hypothalamic area (LHA), as well as through inhibitory projections to the ventro-lateral preoptic (VLPO) area. The latter are mostly GABA-containing neurons that promote wakefulness by inhibiting sleep (1,3,4).

The importance of these pathways is demonstrated by lesions of the SPZ or DMH that markedly reduce the circadian rhythms of wakefulness and sleep (Fig-1). Neurons in the LHA are the site of the exclusive production of two neuropeptides which are essential regulators of wakefulness and sleep: hypocretin 1 and hypocretin 2. It was shown roughly 12 years ago that the symptoms and pathophysiology of narcolepsy are caused by Hcrt-deficiency (von Economo). Moreover, these neurons activate wake-active monoaminergic and cholinergic cell groups in hypothalamus and brainstem.

Today, these well-defined nuclei with identified neurotransmitters are considered the key elements of ARAS which was proposed by Moruzzi and Magoun. Thus, the ARAS is a complex structure including monoaminergic and cholinergic projections. These include (1): The norepinephrine pathway originates from the locus coeruleus (LC) and related brainstem nuclei. (2): The histaminergic pathway originates from neurons in the tuberomammillary nucleus (TMN) of the posterior hypothalamus. (3): The serotoninergic neurons originate from the raphe nuclei within the brainstem and (4): The dopaminergic neurons originate in ventral tegmental area (VTA). Norepinephrine, histamine, serotonin, and dopamine have complex modulatory functions and, in general, promote wakefulness. Another important component of the ARAS is the cholinergic pontine tegmentum in the brainstem known as PPT/LDT (3,4).

The two major pathways providing arousing signals that produce wakefulness

The ascending arousal system has two major branches. The first branch originates in the PPT/LDT and projects to the thalamus, lateral hypothalamus and basal forebrain. These cholinergic neurons depolarize the thalamic relay cells and thereby activate thalamocortical signaling. This activation of the thalamus is necessary for the desynchronized EEG activity in wakefulness (and REM sleep).

The second branch originates from monoaminergic neurons in the upper brainstem and caudal hypothalamus, including LC, dorsal raphe, TMN, and VTA. This pathway bypasses the thalamus, but activates neurons in the lateral hypothalamic area and BF, and throughout the cerebral cortex. Activation of this ventral pathway may be required for the expression of waking behaviors. Lesions along this pathway, particularly in the LHA and rostral midbrain, produce the most profound and long-lasting forms of sleepiness or even coma (encephalitis lethargica [von Economo]) (Fig-2,5).

The VLPO and its adjacent regions; active during sleep

Economo’s second major observation was an opposite response in a small percentage of patients with encephalitis lethargica. Rather than being sleepy, they became insomniac. Typically, they were extremely tired, but found it difficult to fall asleep. These patients had lesions involving the basal ganglia and adjacent anterior hypothalamus. Later experiments in animals identified a hypothalamic site involving the lateral pre-optic area where lesions caused similar insomnia. Many of these cells are within a small cluster known as the ventro-lateral preoptic area (VLPO), but sleep-active cells also reside within adjacent regions of the preoptic area and basal forebrain. These preoptic neurons are active during sleep, especially deep nonREM sleep. Most VLPO neurons contain the inhibitory neurotransmitters, γ-aminobutyric acid (GABA) and galanin. They innervate wake-promoting brain regions such as the LHA, TMN, LC, dorsal raphe, and PPT/LDT. Through these projections, VLPO neurons produce sleep by coordinating the inhibition of
many arousal regions. It appears that these neurons are necessary for the normal production of sleep, and sedating drugs such as benzodiazepines and barbiturates may promote sleep by enhancing GABA-signaling in these descending pathways(4-6). The VLPO also receives afferents from each of the major monoaminergic systems. Both NE and 5-HT inhibit VLPO neurons. The latter do not have histamine receptors, but the TMN neurons also contain GABA, which is inhibitory to the VLPO neurons. Therefore, the VLPO can be inhibited by the very same arousal systems that it inhibits during sleep. During wakefulness, the monoaminergic nuclei inhibit the VLPO, thereby relieving the inhibition of the monoaminergic cells, and that of the Hcrt neurons (LHA/PH) and the cholinergic PPT/LDT. Because the VLPO neurons do not have Hcrt receptors, the Hcrt neurons serve primarily to reinforce the monoaminergic tone, rather than directly inhibiting the VLPO on their own. During sleep, the firing of the VLPO neurons inhibits the monoaminergic cell groups, thereby relieving their own inhibition. This also allows it to inhibit the Hcrt neurons, further preventing monoaminergic activation that might interrupt sleep. Thus, Hcrt neurons stabilize wakefulness and sleep and help prevent sharp, unstable transitions between the vigilance states(1,5,6).

REM sleep with wake and sleep like characteristics
REM sleep is, on one hand is a sleep state, but on the other hand, is associated with neocortical EEG characteristics of wake. In parallel with these two sides of REM sleep, it has been shown that arousal systems can be classified into two different types, and they are illustrated in Fig-3 (the numbers of black dots are proportional to the activity of the aminergic and cholinergic systems during the stages of wakefulness and sleep).

Neurons in each of the monoaminergic brainstem nuclei contributing to the ascending arousal system are “off” in REM sleep and are befitting the sleep-like property of REM sleep. Thus, LC, dorsal raphe, TMN fire fastest in wakefulness, slow down in NREM sleep, and stop altogether in REM sleep. The Hcrt neurons in the LHA are less active in NREM sleep than in wakefulness, but it is controversial whether they are active in REM sleep (Fig-3).

The release of neurotransmitters and neuromodulators at nerve terminals is initiated by the propagation of action potentials. Thus, neurotransmitter release is correlated with the discharge rate of neurons. Thus, while diffuse brain structures are involved in NREM sleep, the neuroanatomy of REM active structures is relatively circumscribed. The primary oscillator that drives REM sleep is located in and near the PPT/LDT region. Lesions of this region abolish REM sleep. In wakefulness and NREM sleep, these REM-on cholinergic cells are inhibited by NE, 5-HT, and Histamine. These aminergic neurons fall silent during REM sleep, thus disinhibiting the REM-generating cells. These cholinergic neurons also produce the atonia of REM sleep by activating the medial medulla, which inhibits motor neurons (Fig-4)(7).

Pharmacological elimination of REM sleep
The knowledge of these pathways provides insights into how certain medications suppress REM sleep. For example, classic antidepressants are known to enhance aminergic signaling and thereby reduce, or may completely suppress, REM sleep.

Sleep promoting endogenous neurochemicals and adenosine metabolism
In the last part of this review, we would address a possible neurochemical mechanisms of Process S, or sleep homeostasis including adenosine, prostaglandin-D2, muramyl dipeptide, cytokines such as interleukin-1 and TNF, and growth hormone releasing hormone. All these substances induce sleep in laboratory animals. The most consistent evidence, which accumulated during the last 10-15 years suggests that adenosine is a key factor in the homeostatic control of sleep need. For example, Tarja Porkka-Heiskanen and her co-workers conducted microdialysis experiments in freely moving cats. They showed that the extracellular adenosine concentration in the cholinergic basal forebrain increased during prolonged wakefulness and slowly decreased during subsequent recovery sleep. These data suggest that at least some effects of sleep deprivation are mediated by adenosine. This molecule could constitute a neurochemical correlate of sleep homeostasis.

The extracellular adenosine concentration is balanced with the intracellular concentrations by selective nucleoside transporters.

Adenosine is formed during wakefulness by the break-down of energy-rich compounds such as adenosine tri-phosphate (ATP) and adenosine-mono-phosphate (AMP). The main metabolic pathway of adenosine are the formation of AMP by adenosine kinase (AK) and inosine by adenosine deaminase (ADA)(9).

Extracellular adenosine acts via four different classes of G-protein-coupled adenosine receptors. The molecule, however, has the highest potency at the A1 and A2A receptors. If adenosine is bound, excitatory neurotransmission is either reduced (A1 receptors), or the sleep-active cells in the VLPO of the hypothalamus are disinhibited or actively stimulated via the excitatory
A2A receptor.
Adenosine deaminase catalyzes the irreversible formation of adenosine to inosine. This enzyme plays an important role in regulating extracellular adenosine levels. The effect of a G to A transition at nucleotide 22 of the ADA gene has been investigated. This polymorphism is found in approximately 10% of a healthy Caucasian population. It leads to an amino acid change at codon 8 of the ADA protein. It was shown that the variant allele has 30% lower enzymatic activity in erythrocytes and leucocytes than the more common isof orm of the enzyme.

The investigators of one of the pivotal studies in this realm hypothesized that the carriers of the G/A genotype exhibit elevated extracellular adenosine. For this reason, they expected them to have deeper sleep than subjects with the G/G genotype and this was what was found and reported (Fig-5)(9,10). The interaction of caffeine with sleep deprivation study has also been investigated. Caffeine is an adenosine receptor antagonist and is hypothesized that blockade of these receptors during wakefulness attenuates the build-up of homeostatic sleep pressure.

Caffeine is shown to attenuate the build-up of theta activity in the waking EEG. Theta activity is considered a measure of sleepiness and sleep need during wakefulness.

In the placebo condition, it remained low during the first day of sleep deprivation and increased sharply towards the end of the subjects' habitual sleep period. On the second day, it remained elevated, and also a circadian modulation was clearly present. It has been found that this increase from the first to the second day of wakefulness was significantly attenuated by the two doses of 200 mg caffeine. These data suggest that caffeine interacts with sleep-wake physiology. It appears to attenuate the build-up of sleep need during wakefulness. Thus, these and other data are consistent with an important role for adenosine and its receptors in sleep homeostasis(1,10).

Sleep and cognition
Sleep parameters including its microstructure and consequently its efficiency is known to be correlated with the neurocognitive aptness in terms of attention and concentration, visuo-spatial and constructional skills, sensory perceptual function, language, memory, executive and intellectual functions (11,12).

Summary and conclusion
To summarize, the suprachiasmatic nucleus as the central body clock, sends signals to hypocretin neurons via the dorsomedial hypothalamus (DMH). The hypocretin neurons in the lateral hypothalamus (LHA) and posterior hypothalamus (PH) are anatomically well placed to provide a link among monoaminergic, cholinergic, and GABA-ergic neurons in the brainstem and the hypothalamus. The monoaminergic cell groups are wake-active, cells in the ventro-lateral preoptic region are sleep-active, and the cholinergic pontine tegmentum promote REM sleep. It appears that the hypocretin neurons play a central role in stabilizing the vigilance states. They maintain wakefulness through stimulation of the monoaminergic nuclei, are inhibited by the VLPO in NREM sleep, and excite the cholinergic pedunculo pontine neurons in REM sleep. Above all, adenosine and other neuromodulators play a modulatory role reflecting sleep homeostasis.

Future directions:
To understand the interplay between neurobiochemistry of sleep-wake systems and cognition, there is room for fundamental research on animal and human subjects. Diseases like Parkinson’s, Alzheimer’s, Multiple Sclerosis, Schizophrenia, Depression, Anxiety and Post Traumatic Stress Disorders have impaired sleep. These impairments are partly resulted from disrupted neurochemical, anatomical and electrophysiological symmetry in the brain leading to an inefficient sleep and inappropriate vigilance with incompetent cognitive functions. Knowing the pathophysiology of these conditions in a more comprehensive fashion in terms of neurobiochemistry of sleep and cognitive functions provide an open realm for research in cognitive neuroscience.

Abbreviations:
ADA: Adenosine Deamiase
ARAS: Ascending reticular Activating System
DA: Dopamine
DMH: Dorsomedial Hypothalamus
dSPZ: Dorsal Supraventricular Zone
GABA: Gamma Amino Butyric Acid
5HT: 5-Hydroxy Tryptamine
Hcrt: Hypocretin
LC: Locus Coeruleus
LHA/PH: Lateral hypothalamic Area/Posterior Hypothalamus
NE: Nor epinephrine
NREM: Non-Rapid Eye Movement
PPT/LDT: Pedunculo-Pontine tegmental area/Latero-Dorsal tegmental area
REM: Rapid Eye Movement
SCN: Suprachiasmatic Nucleus
SWA: Slow Wave Activity
TMN: Tubero-mammillary Nucleus
VLPO: Ventrro-Lateral Pre-optic area
vSPZ: Ventral Supraventricular Zone
VTA: Ventral Tegmental Area

References

Illustrations

Illustration 1

Connections of suprachiasmatic nuclei (SCN) to sleep-wake regulatory systems

Illustration 2

Two major pathways provide arousing signal that produces wakefulness
Illustration 3

REM sleep (paradoxical sleep) exhibits “wake-like” and “sleep-like” characteristics

Illustration 4

REM sleep is driven by cholinergic neurons (pedunculopontine/laterodorsal tegmental area)
Illustration 5

Regulation of extracellular adenosine levels
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