Sleep-Wake Neurochemistry

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KEYWORDS

• Neurotransmitters • Neuromodulators • Glutamate • Acetylcholine • Norepinephrine • Dopamine • GABA • Adenosine

KEY POINTS

- Behavioral states alternate between wakefulness, rapid-eye movement and non-rapid eye movement sleep.
- Waking and sleep states are highly complex processes, elegantly fine-tuned by cerebral neurochemical changes in the neurotransmitters and neuromodulators glutamate, acetylcholine, γ-amino-butyric acid, norepinephrine, dopamine, serotonin, histamine, hypocretin, melanin-concentrating hormone, adenosine, and melatonin.
- No single neurotransmitter or neuromodulator, but rather their complex interactions within organized neuronal ensembles, regulate waking and sleep states and drive their transitions.
- Dysregulation or medications interfering with these neurochemical systems can lead to sleep-wake disorders and functional changes of wakefulness and sleep.
- The neurochemical pathways presented here provide a conceptual framework for the understanding of the effects of currently used medications on wakefulness and sleep.

INTRODUCTION

Based on behavioral and (neuro) physiologic characteristics derived from polysomnographic recordings, the 3 distinct vigilance states of wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep can be unambiguously defined in mammals. Wakefulness with eyes closed is typically associated with electroencephalographic (EEG) activity in the alpha range (8–12 Hz) and with high-frequency, desynchronized activity greater than 40 Hz. In a normal sleep episode, voluntary muscle control is gradually lost and NREM and REM sleep episodes alternate in a cyclic pattern. In NREM sleep, the EEG shows slow, high-amplitude activity reflecting widespread, synchronous oscillations of neurons exhibiting alternating periods of firing and silence (burst-pause firing pattern).[1] The so-called EEG delta activity (<4.5 Hz) is under tight homeostatic control and exhibits a declining trend in the course of the night, which reflects the dissipation of sleep need and the decline in sleep intensity.[2] The EEG in REM sleep (sometimes called paradoxic sleep) is partly reminiscent of EEG activity in drowsy wakefulness, yet it is characterized by muscle atonia with occasional muscle twitches and rapid eye movements.

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Distinct neurotransmitter nuclei and neuronal pathways modulate and maintain these three behavioral states. First insights were reported by Constantin von Economo[3] (1876–1931) who studied patients with a type of viral encephalitis that was never seen before, encephalitis lethargica. von Economo discovered that the encephalitis was associated with lesions to distinct brain areas in the midbrain and brainstem reticular formation. Lesions of the ventral periaqueductal gray and posterior hypothalamus were associated with severe hypersomnia, whereas lesions of the hypothalamic anterior preoptic area extending into the basal ganglia were associated with insomnia. These findings were the first in a series of fundamental studies eventually leading to the postulation of an ascending reticular activating system (ARAS).[4] The ARAS arises from a network of neuronal clusters in the brainstem, which activates forebrain, thalamus, and cortex, mainly in wakefulness but to some extent also in REM sleep. Today, the ARAS is no longer seen as a loose reticular system but, instead, as consisting of a network of individual nuclei expressing distinct neurotransmitters that promote arousal (**Fig. 1**). The key modulatory neurotransmitters of the ascending activating system include acetylcholine (ACh), several monoamines (norepinephrine [NE], serotonin [5-hydroxy-tryptamine, 5-HT], histamine [His], dopamine [DA]), and the slow-acting neuropeptide hypocretin (Hcrt; aka orexin). More recently, the fast-acting amino acid glutamate has been proposed to be the main regulator of arousal.[5] Together with GABA (γ-amino-butyric acid), these neurochemicals play important roles in promoting waking and sleep states, which provide a useful conceptual framework to understand the effects of medications on wakefulness and sleep. With the recent advent of powerful optogenetic and chemogenetic tools, experimental in vivo control of neuronal activity by stimulating or inhibiting distinct neuronal ensembles permitted exciting new insights into the causal underpinnings of brain state transitions. A comprehensive summary of these insights are beyond the scope of this article; this has been the topic of excellent recent overviews.[6,7] Nevertheless, some recent progress in current understanding of sleep-wake neurochemistry made by investigating sleep-wake circuits with optogenetic techniques are covered.

THE NEUROCHEMICAL UNDERPINNINGS OF WAKEFULNESS

Acetylcholine

ACh-releasing nuclei in the pedunculopontine (PPT) and laterodorsal tegmental nuclei (LDT) of the pons project primarily to the basal forebrain (BF), as well

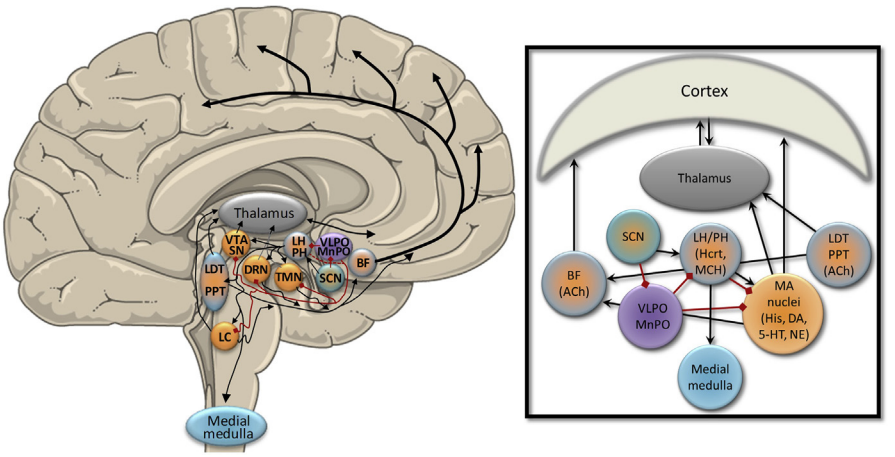

Fig. 1. Anatomical locations of major neurotransmitter nuclei (left) and simplified overview of their major connections relevant for sleep-wake regulation (right). Wakefulness (orange): Cholinergic (Ach) tegmental (LDT or PPT) neurons and monoaminergic (MA) neurons of upper brain stem and hypothalamus innervate thalamus and basal forebrain (BF). The MA neurons have a pronounced role and directly innervate the cerebral cortex. Hypocretin (Hcrt) neurons of lateral or posterior hypothalamus (LH or PH) reinforce the activity of this ascending arousal pathway and directly excite the (BF). NREM sleep (purple): GABA-ergic VLPO and MnPO nuclei, which inhibit the ascending arousal pathways, are active in NREM sleep. REM sleep (cyan): Ach-ergic neurons of LDT or PPT promote REM sleep, during which NE and 5-HT neurons are silent. Entry into REM is inhibited by Hcrt neurons and facilitated by the VLPO. Connections from the SCN are important in regulating the timing of wakefulness and sleep. Black arrows indicate an excitatory connection. Red squares and lines indicate an inhibitory connection. Please refer to main text for full list of abbreviations.