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# Functional Neurochemistry of the Sleep–Waking Cycle in the Pathogenesis of Neurological Diseases

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This review addresses contemporary experimental data on the functioning of the main neurotransmitter systems of the brain involved in arousal reactions and the maintenance of waking.

**Keywords:** sleep, sleep–waking cycle, neurotransmitters, sleep and waking impairments.

Despite the "addressed" nature of the access of most neurotransmitters to specific neurons and their binding with receptor proteins, reuptake, and disposal, some persist for some period of time and diffuse through the intercellular fluid, i.e., the biochemical medium of the brain as a whole. In the three main states (waking, slow-wave sleep and fast-wave sleep[1]), this medium has cardinal differences (Table 1) [1–3]. As shown in Table 1, the intercellular fluid in the waking phase is saturated with transmitters with mainly activatory (depolarizing) actions on the postsynaptic membrane.

Orexins (hypocretins) are two oligopeptides formed from a single common polypeptide precursor – proorexin – which in turn is a fragment of a longer protein, preproorexin; this latter is secreted by neurons located in the perifornicеal (posterolateral and dorsomedial) area of the hypothalamus. Orexinergic cells are very few in number (no more than 80,000 in the human brain), though their axons branch extensively, innervating other hypothalamic nuclei, the limbic system, the thalamus, the neocortex, the brainstem, and the spinal cord. Orexinergic neurons project mainly to the noradrenergic cells of the locus ceruleus, inducing depolarization, i.e., activation, or "arousal." Insufficiency of this activation has the result that neurons in the locus ceruleus acquire the ability to suddenly fall silent not only during fast-wave sleep, but also during waking, leading to attacks of narcolepsy/cataplexy [1–4]. It is interesting that cells in the "sleep center" in the ventrolateral preoptic area do not contain orexin receptors, which apparently increases the reliability of the hypothalamic "trigger" [5].

The orexinergic system receives a multitude of activatory afferents from the glutamatergic system: the preceruleus/parabrachialis and the dorsomedial nucleus – the higher hypothalamic "command center" – and from dopaminergic neurons in the ventral tegmentum. Activatory cholinergic spikes arrive from orexinergic neurons in the rostrally located nuclei of the basal part of the anterior brain – the basal areas of the frontal lobes (the substantia innominata, etc.) In addition, a number of modulatory peptides (arginine-vasopressin, cerebral cholecystokinin, neurotensin, oxytocin) also have activatory influences on orexinergic transmission. This is also activated by the occurrence of hunger due to decreased glucose and increased ghrelin levels in the blood [6, 7].

Inhibitory influences on the orexinergic system come from the serotoninergic system of the raphe nuclei (presumptively direct), the noradrenergic system of the locus ceruleus (presumptively mediated by GABAergic neurons), nociceptive elements of the amygdala, and, of particular importance, the GABA/galaninergic "sleep center" in the preoptic area. The activity of the orexinergic neurons is suppressed by increases in glucose levels and the appearance of leptin in the blood [6, 8].

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[1] The terms slow-wave and fast-wave have around ten pairs of synonyms. There is no universally accepted English-language terminology. In this review we use the paired Russian-language terms recommended by the founder of Russian sleep medicine and human sleep physiology Academician of the Russian Academy of Medical Sciences A. M. Vein (1928-2003).

TABLE 1. Simplified Scheme of the Release of the Main Transmitters in the Brain during the Sleep–Waking Cycle

| Neurotransmitters | Locations | Waking | Slow-wave sleep | Fast-wave sleep |
|---|---|---|---|---|
| Acetylcholine | LDT/PPT+BF | ↑↑ | ↓→↓↓ | ↑↑ |
| Glutamate | PC/PB+BF | ↑↑ | ↓→↓↓ | ↑↑ |
| Noradrenaline | LC | ↑↑ | ↓→↓↓ | ↔ |
| Serotonin | DR | ↑↑ | ↓→↓↓ | ↔ |
| Histamine | TMN | ↑↑ | ↓→↓↓ | ↔ |
| Dopamine | VTA/SNpc/vPAG | ↑↑ | ↓ | ↑ |
| GABA | RTN | ↓ | ↑↑ | ↓ |
| | NC | ↑ | ↑↑ | ↑ |
| | VLPO/MnPO | ↓↓ | ↑→↑↑ | ↑↑ |
| | BF (GABA+PV) | ↑↑ | ↓→↓↓ | ↑↑ |
| | BF (GABA+SOM) | ↓ | ↑→↑↑ | ↓ |
| | vlPAG | ↓ | ↑↑ | ↔ |
| | MPZ | ↓ | ↑↑ | ↓ |
| | VMZ | ↓ | ↓ | ↑↑ |
| Orexin | LHA | ↑↑ | ↔ | ↔ |
| Galanin | VLPO/MnPO | ↓ | ↑↑ | ↑↑ |
| MCH | LHA/PH | ↓ | ↓ | ↑↑ |

↑ – increased release; ↑↑ – significantly increased release; ↓ – decreased release; ↓↓ – significantly decreased release; → – gradual decrease/increase in release; ↔ – cessation of release.

However, the greatest level of inhibition of the orexinergic system comes from the so-called melaninergic system. Orexinergic neurons in the hypothalamus closely intertwine and interact with morphologically similar cells containing another peptide neurotransmitter, melanin concentrating hormone, MCH). MCH-containing neurons are located mainly in the lateral hypothalamus and zona incerta; small quantities of this peptide are also found in the reticular formation of the pons and the caudal part of the laterodorsal tegmentum. Neurons containing orexin and MCH form mutually overlapping projections in the structures identified above [9, 10]. The MCH system is inhibitory, reciprocal in relation to orexin neurons: MCH neurons are not active in waking and discharge weakly in the slow-wave sleep phase; they are highly active in fast-wave sleep ("REM-on sleep") In patients with narcolepsy, the MCH system remains unaffected; degradation of MCH-containing neurons is currently regarded as one possible cause of the development of Parkinson's disease. The MCH system is regarded as responsible, in particular, for inhibiting the mechanisms of arousal and regulation of fast-wave sleep [9–11].

The effects of orexinergic neurons are mediated by two types of activatory metabotropic receptors. Mice with double knockout of the preproorexin gene or the genes of both receptors (dual orexin receptor antagonists, DORAs) demonstrate a narcoleptic-cataleptic phenotype, including fragmentation of waking. Central and systemic administration of DORAs induces soporific effects with corresponding changes on the electroencephalogram (EEG). Orexinergic neurons are of the "wake-on" type, i.e., they are very active during waking (especially during intense movement) but hardly discharge at all in slow- and fast-wave sleep. Orexinergic neurons show phasic activity in waking; the greatest discharge frequency in mice is seen in responses with positive reinforcement. In humans, the maximum orexin level in the cerebrospinal fluid (CSF) is seen during the experiencing of positive emotions and during social interactions [12, 13].

Impairment to orexinergic transmission is seen not only in narcolepsy, but also in Alzheimer's disease and Parkinson's disease, as well as in craniocerebral trauma. This may be the cause of the signs (the inability to maintain normal levels of waking for prolonged periods) common to these very different types of pathology (Table 2). Thus, typical symptoms in narcoleptics and patients with Parkinson's disease are excessive daytime drowsiness and so-called sleep attacks. The cause of narcolepsy is known to consist of loss of orexinergic neurons, which is particularly signif-

TABLE 2. Impaired Release of the Main Neurotransmitters in Various Diseases

| Disease | Neurotransmitter | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Histamine | Glutamate | Serotonin | Orexin | Noradrenaline | Dopamine | Acetylcholine | GABA | MCH |
| Alzheimer's disease | | | | ↓ | ↓ | | ↓ | ↓ | |
| Parkinson's disease | ↑ | | | ↓ | | ↓ | | | ↓ |
| Craniocerebral trauma | ↓ | | | ↓ | | | | | |
| Narcolepsy | ↑ | | | ↓ | | | | | |
| Primary insomnia | | | | ↑ | | | | | |
| Primary hypersomnia | ↓ | | | | | | | ↑ | |
| Anxiety | | | | ↑ | | | | | |
| Endogenous depression | | | ↓ | | ↓ | | | | |
| Schizophrenia | | ↓ | ↓ | | ↓ | ↑ | | | |

↑ – increased release; ↓ – decreased release.

icant in type 1 narcolepsy (with cataplexy); gradual degradation of these neurons also occurs in Parkinson's disease. Recent data, including the finding of new types of narcolepsy after immunization with H1N1 antiserum in Finland and other countries, supports the view that narcolepsy is an autoimmune disease. Orexinergic neurons play a major role in coordinating the activity of the aminergic systems of the brain, integrating incoming circadian-optic spikes on the one hand, and nutritional-metabolic spikes on the other. Results from a recent study [14] showed that prolonged optogenetic activation of orexinergic neurons in mice increases activity in the hypothalamus-hypophysis-adrenal cortex axis and induces stress behavior.

In craniocerebral trauma, most patients have sharp decreases in orexin levels in the CSF, combined with impairments to arousal, but if the patient recovers, the level of this peptide recovers within six months, though the impairment may persist. This may be linked with irreversible damage to histaminergic neurons in many types of trauma [14].

Typical impairments to arousal and sleep in Alzheimer's disease, as in Parkinson's disease, are insomnia, fragmentation of nocturnal sleep, and excessive daytime drowsiness. Lesions in this disease affect arousal centers, both cholinergic (basal parts of the frontal lobes) and noradrenergic (locus ceruleus). Orexinergic neurons have been seen to play a major role in the pathogenesis of this disease. Increases in CSF orexin levels in patients with Alzheimer's disease preceded impairment of the sleep–waking cycle and cognitive abilities [14].

Aminergic neurons produce histamine, serotonin, and noradrenaline. Histaminergic neurons whose bodies are located in the tuberomammillary nuclei (TMN) of the posterior hypothalamus, serotoninergic neurons in the dorsal raphe nucleus, and noradrenergic neurons in the locus ceruleus of the brainstem are characterized by tight groupings of relatively small numbers of cells with unusually extensive ascending and descending projections. Ascending projections reach the thalamus, hypothalamus, basal nuclei of the forebrain, and neocortex. Descending projections are to the cranial nuclei of the visceromotor and somatomotor nerves. In terms of their characteristics, these neurons belong to the so-called "REM-off" group: they discharge tonically during waking and gradually slow their discharge frequency as slow-wave sleep deepens and stop (or almost stop) activity in the fast-wave sleep phase. Drugs able to promote the release of these three aminergic transmitters or inhibit their reuptake are activatory and suppress sleep. Antagonists of the postsynaptic receptors of these transmitters have sedative properties. Having a multitude of mutual connections, the aminergic systems of the brainstem form a self-organizing network, a kind of orchestra, in which orexinergic (hypocretinergic) neurons play the role of conductor and histaminergic neurons that of first violin [3, 5, 15, 16].

The typical morphological features of histaminergic neurons are: several fine primary dendrites with overlapping branches and few axodendritic synaptic contacts, and the tight contact of these dendrites with the glia, their penetration through the ependyma and contacts with the CSF for secretion into it and uptake from it of a variety of regulatory substances. The biochemical characteristics of histaminergic neurons are the unusual diversity of neurotransmitter system markers such as glutamate decarboxylase (a GABA synthesis enzyme); adenosine deaminase (a cytoplastic enzyme involved in inactivating adenosine); a multitude of peptides: galanin (a peptide colocated with GABA and all monoamines), ($Met^5$)enkephalyl-$Arg^6Phe^7$ (a peptide cleaved from proenkephalin-A protein), substance P, thyroliberin, and brain natriuretic peptide. These TMN neurons contain the enzyme monoamine oxidase B, which deaminates tele-methylhistamine, the main metabo-

lite of histamine in the brain. Finally, these neurons can take up and decarboxylate exogenous 5-hydroxytryptophan (serotonin precursor) synthesized by other cells. The existence of so many cotransmitter functions in the same neurons is a unique property of the TMN. Like most such activatory systems, the histaminergic system of the TMN is constructed on the ancient principle that a small number of magnocellular (25–35 μm) neurons (64,000 in the human brain) innervate billions of cells in the neo- and paleocortex and subcortical structures due to the colossal branching of their nonmyelinated axons (each axon forms hundreds of thousands of branches). Ascending TMN fibers form two pathways: the lateral (via the lateral bundle of the forebrain) and the periventricular, coming together in the diagonal band of Broca to form a common projection (mainly ipsilateral) to multiple structures of the forebrain, including the cortex, olfactory bulb, hippocampus, caudate nucleus, nucleus accumbens, globus pallidus, and amygdaloid complex. Several hypothalamic nuclei also have saturating innervation from TMN neurons: the suprachiasmatic, supraoptic, semicircular, and ventromedial [3, 5, 15–17].

The most extensive ascending projections are directed to the neurohypophysis, the close-lying dopaminergic areas of the ventral tegmentum, the compact part of the substantia nigra, the basal parts of the frontal lobes (the magnocellular nuclei of the substantia innominata, which contain acetylcholine, glutamate, and GABA), the striatum, neocortex, hippocampus, amygdala, and midline thalamic nuclei; the descending projections run to the cerebellum, pons, medulla oblongata, and spinal cord, including the nuclei of the cranial nerves (trigeminal nerve), the central gray matter, the colliculi, the substantia nigra, the locus ceruleus, and the dorsal raphe nucleus. In addition, a reciprocal connection between the suprachiasmatic nuclei and the TMN has been demonstrated [3, 5, 15–17].

In turn, histaminergic neurons in the TMN receive afferents from the infralimbic cortex, the lateral area of the septum, the septodiagonal complex, the hippocampus, the preoptic area of the anterior hypothalamus, adrenergic cells C1–C3, noradrenergic neurons A1–A3, and serotoninergic cells B5–B9 (the ventrolateral and dorsomedial parts of the of the medulla oblongata, the dorsal raphe nucleus). The most powerful inhibitory (GABA/galaninergic) projections to the TMN come from the so-called sleep center (the ventrolateral preoptic area), and the most powerful excitatory projections come from orexin/hypocretinergic neurons in the lateral hypothalamus. It is interesting that only occasional fibers reach the TMN from noradrenergic cells in the locus ceruleus and dopaminergic neurons in the ventral tegmentum of the midbrain (VTM) and the compatible part of the substantia nigra. However, in Parkinson's disease, which is associated with degradation of dopaminergic transmission, there is a twofold increase in the histamine concentration arriving from the TMN and the compact part of the substantia nigra and its projection – the globus pallidus [3, 5, 15–17].

The greatest discharge frequency of orexin neurons, like aminergic neurons, is seen in the state of active waking, while the lowest (null) frequency is seen in the fast-wave sleep phase. Activation of histamine neurons is one of the most important functions of the orexinergic system. However, histamine neurons evidently do not have any immediate effects on the arousal of orexin neurons, such that direct interactions between the two systems is unidirectional in nature. The two transmitters (histamine and orexin) act synergistically, playing a unique role in maintaining waking [3, 5, 15–17].

A tight interaction in the regulation of arousal occurs between the histaminergic and the other two aminergic systems – the noradrenergic and the serotoninergic. All these neurons belong to the "waking-on" group and are activated only during waking, with sharp decreases in spike frequency in slow-wave sleep and complete cessation of activity in fast-wave sleep. The details of this interaction have received insufficient study, though experiments on mutant dogs – "narcoleptics" [1, 14] – have shown that histaminergic neurons, evidently responsible for elements of "consciousness," are associated with the thalamocortical and other systems of the forebrain, while noradrenergic and serotoninergic cells are more associated with maintenance of muscle tone during waking.

An interesting property of all histamine receptors is their high so-called "constitutive" activity, i.e., their spontaneous activity in the absence of histamine. This activity plays an important regulatory role in the brain, taking part in controlling sleep–waking and cognitive functions by modulating the release or synthesis of histamine and other neurotransmitters. Several reversible $H_3$ receptor agonists, able to block histamine, have undergone clinical trials in patients with schizophrenia, epilepsy, narcolepsy, obesity, and Alzheimer's disease [3, 5, 15–17].

The histaminergic system also plays an important role in forming the narcoleptic phenotype, as histamine levels in the CSF of patients with narcolepsy and primary hypersomnia are sharply reduced or absent. However, post mortem studies of patients with narcolepsy showed increases in the numbers of histaminergic neurons in the brain, probably due to the actions of compensatory processes in response to loss of orexinergic cells. Although narcolepsy itself is linked with insufficiency of orexin transmission, experimental studies have shown that histaminergic neuron activity persists during cataplexic attacks, while that of serotoninergic neurons decreases sharply and that of noradrenergic neurons ceases. $H_3$ receptor antagonists decrease excessive drowsiness and cataplexic attacks, evidently blocking the inhibitory autoreceptors supporting negative feedback, which leads to an increase in histamine release in synaptic clefts. Some substances of this type have undergone clinical trials as drugs for the treatment of narcolepsy [3, 5, 15–17].

In addition, modulation of the histaminergic system can be used for the treatment of other impairments to the

sleep–waking cycle. Thus, the tricyclic antidepressant doxepin not only inhibits noradrenaline and serotonin reuptake, but is also an antagonist of $H_1$ and $H_2$ receptors, such that it is used successfully for the treatment of sleeplessness in older patients. Conversely, excessive drowsiness can be suppressed by giving $H_3$ receptor antagonists. Thus, the histaminergic system is an important target for developing novel therapeutic agents required for the treatment of, particularly, narcolepsy and Parkinson's disease [4, 13, 15, 18].

Dopaminergic neurons involved in regulating the sleep–waking cycle are located in the compact part of the substantia nigra and adjacent area of the ventral tegmentum. At the level of the projection of dopaminergic neurons in the striatum, effects are diverse: activatory receptors involved in the mechanisms of arousal and waking are located in the nucleus accumbens of the septum, while dopaminergic transmission in the outer part of the globus pallidus is involved in regulating slow-wave sleep. Furthermore, an important dopaminergic waking center is present in the ventral part of the periaqueductal gray matter. Inactivation of dopamine in the brain occurs mainly as a result of its reuptake by transporter protein. Psychostimulators (amphetamines and modafinil) block this protein, suppressing dopamine reuptake. Thus, the global effect of dopamine on systemic administration is activatory. Antipsychotics (antagonists of dopaminergic receptors) have sedative properties [3, 11, 14, 17, 19–21].

Impairment of dopaminergic transmission occurs in pathologies such ads Parkinson's disease, restless legs syndrome, and excessive daytime drowsiness. This is supported by clinical pharmacological data. For example, restless legs syndrome is effectively treated with dopamine agonists, and its antagonists worsen symptoms. Neural scanning (positron emission tomography (PET) and single-photon scanning (SPECT)) of the dopamine transporter and the saturation of dopamine receptors in patients with restless legs syndrome do not give concordant results. It was suggested that the neuroanatomical pathways involved in restless legs syndrome include the so-called diencephalic-spinal group of dopaminergic neurons (A11). These cells, which have tight connections with the circadian oscillator in the suprachiasmatic nucleus and take part in antinociceptive reactions form a relatively poorly studied descending conducting pathway, which integrates subcortical influences on the spinal cord [14].

Parkinson's disease is known to involve degeneration of the dopaminergic nigrostriatal system. Pharmacological data have confirmed the role of this system in maintaining normal waking, as insufficiency of the dopaminergic system is probably the cause of the development of excessive daytime drowsiness. In addition, at the late stages of Parkinson's disease, the development of hypersomnia is also linked with degradation of the orexinergic system [3, 11, 14, 17, 19–21].

Cholinergic neurons are located in the dorsal part of the pontomesencephalic reticular formation, including the area of the pedunculopontine and laterodorsal tegmentum, as well as in the basal parts of the frontal lobe. Cholinergic neurons in the pedunculopontine and laterodorsal tegmentum project mainly to the thalamus and hypothalamus, while cells in the basal parts of the frontal lobes project to the limbic cortex and neocortex. Cholinergic neurons in both groups belong to the "REM-waking-on" type – they discharge intensely both in waking and in fast-wave sleep, but gradually become silent as slow-wave sleep deepens. Cholinergic neurons in the basal parts of the frontal lobes are involved in generating the EEG $\gamma$ rhythm in behavioral activation. Ontogenetic experiments have shown that laser stimulation of neurons in the basal parts of the frontal lobes during slow-wave sleep induces short-latency behavioral and EEG arousal [3, 14, 18, 20, 22–24].

Individual groups of glutamatergic neurons are distributed through the reticular formation of the midbrain and pons. The most important of these is in the area of the precerular/parabrachial nucleus, from which monosynaptic projections are sent to the basal areas of the frontal lobes. Recent studies have confirmed the exclusive role played by this system in maintaining waking and consciousness not only in model animals, but also in humans. Glutamatergic neurons, like cholinergic neurons, are members of the "REM-waking-on" type and are involved in regulating not only waking, but also fast-wave sleep [3, 7, 14, 25, 26].

Thus, individual parts of the reticular ascending activatory system releasing transmitters such as glutamate, acetylcholine, orexin, and catecholamines (dopamine, histamine, serotonin, noradrenaline) detected by experimental methods in model systems have received complete confirmation in neurological and imaging studies in humans. These data, obtained by basic scientific studies, constitute the necessary basis for studies of diseases such as narcolepsy, Alzheimer's disease, Parkinson's disease, and craniocerebral trauma [3, 5, 14, 15, 17, 21, 23, 27].

On transfer to slow-wave sleep (to the "kingdom of GABA"), all these molecules rapidly disappear from the intercellular medium of the brain and are replaced by the main inhibitory transmitter of the brain (GABA), whose concentration increases as slow-wave sleep becomes deeper [3, 20].

The biochemical medium of brain has an exclusive feature in the fast-wave sleep phase. High acetylcholine and glutamate levels are combined with the complete absence of orexin (hypocretin) and brain amines – noradrenaline, serotonin, and histamine, with the exception of dopamine, whose concentration can even be greater than that in waking. A new transmitter appears – the peptide MCH – which mediates the hypothalamic-pontine level of regulation of fast-wave sleep. Release of GABA in general decreases significantly, but remains high at locations of groups of orexinergic (median hypothalamus), histaminergic (tuberomammillary nucleus of the posterior hypothalamus), serotoninergic (dorsal raphe nucleus), and noradrenergic (locus ceruleus) neurons. In these systems, GABAergic neurons

play the role of a lock preventing these cells from undergoing depolarization throughout the period of fast-wave sleep [2, 3, 14, 21, 26].

Such a radical shift in the biochemical medium of the brain during the sleep–waking cycle is combined with global changes in the operation most of the neuronal systems, as laid out in detail in reviews [1–3, 5, 14, 17, 20, 21, 23, 26–28] and, thus, with radical mental changes in humans. In this regard, sleep medicine based on fundamental somnology acquires ever greater social significance because serious disorders of the circadian rhythm and sleep impairments are seen in both mental and neurodegenerative diseases [29].

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