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The Role of Histaminergic System of the Brain in the Regulation of Sleep–Wakefulness Cycle

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Abstract—The structure and the morphological and neurochemical connections of the histaminergic system of the brain, which plays one of the most important roles in maintaining wakefulness, are considered. The biochemistry of histamine metabolism and histamine receptors is briefly described. The special role of the relation between the histamine system and orexin/hypocretin system is noted. Some examples of the effects of experimental manipulations with the histaminergic system on the wakefulness–sleep cycle are given.

Keywords: wakefulness-sleep cycle, histamine, histamine receptors, orexin/hypocretin

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Since, in the late 1940s, Moruzzi and Magoun discovered the brainstem reticular formation, it became clear that the normal functioning of the brain's thalamocortical system, which provides all forms of mammalian behavior and the entire spectrum of conscious human activity, is possible only in the presence of powerful tonic effects from some subcortical structures, which are referred to as activating ones. Direct studies of neurons involved in the regulation of sleep–wakefulness conducted in the second half of the 20th century showed that, with these influences, membranes of the majority of cortical neurons in the awake state are depolarized by 5–10 mV compared to the resting potential (–68/–70 mV). Only in the state of tonic depolarization are these neurons able to process the information and respond to the signals coming from them from other nerve cells, both receptor and intracerebral ones. There are, apparently, no less than ten systems of tonic depolarization or ascending arousal systems (they may also be conventionally called the waking centers). They are located at all levels of the brain axis and release various chemical neurotransmitters, such as acetylcholine, glutamate, noradrenaline, serotonin, histamine, dopamine, and orexin/hypocretin. The structure and functioning of these systems are detailed in a series of recent Russian reviews [1–5].

A special role in these harmonious orchestra of the systems for maintaining wakefulness is played by the histaminergic system, located in the tubero-mammilar nucleus (TMN) in the posterior hypothalamus [6–12]. Due to methodological reasons, the exact location of this system and its projections in the brain of rats were described later, compared to other brain amines; only in 1983–1984, it was described by Japanese and American researchers [13, 14]. In 1977, Schwartz [15] from the Paul Broca Center in Paris hypothesized on the critical role of the brain's histaminergic system in the formation of the arousal reaction. Then, in 1988, the histaminergic arousal mechanism in the hypothalamus of the cat was found in the laboratory headed by Jouvet [16].

TMN is the only source of histamine in the brain of vertebrates; at the same time, histamine is the main transmitter secreted by neurons of TMN. However, apart from histamine, these cells also synthesize gamma-aminobutyric acid (GABA) and neuropeptides, such as galanin, enkephalins, thyroliberin, and substance P [10]. The tuberomamillary area of the rat is divided into the medial, ventral, and diffuse zones, which spread from the caudal hypothalamus to the middle of the third ventricle. The tuberomamillary area in humans is arranged similarly; however, in the large human brain, histaminergic neurons are more numerous and occupy a relatively larger part of the hypothalamus. Their characteristic morphological features are a few thin primary dendrites with overlapping branching and small axon-dendrite synaptic contacts, as well as the close contact of these dendrites with the glia, their penetration through the ependyma, and contacts with liquor for the secretion of various regulatory substances into it and extraction substances from the liquor [15]. The biochemical feature of histaminergic neurons consists in the extraordinary variety of markers of various neurotransmitter systems: glutamate decarboxilaze (GABA synthesizing enzyme); adenosine deaminase (cytoplasmic enzyme involved in the inactivation of adenosine); many peptides, such as galanin (a peptide colocalized with GABA and all monoamines), (Met^5)*enkephalylArg*^{6}*Phe*^{7} (a peptide cleaved from the

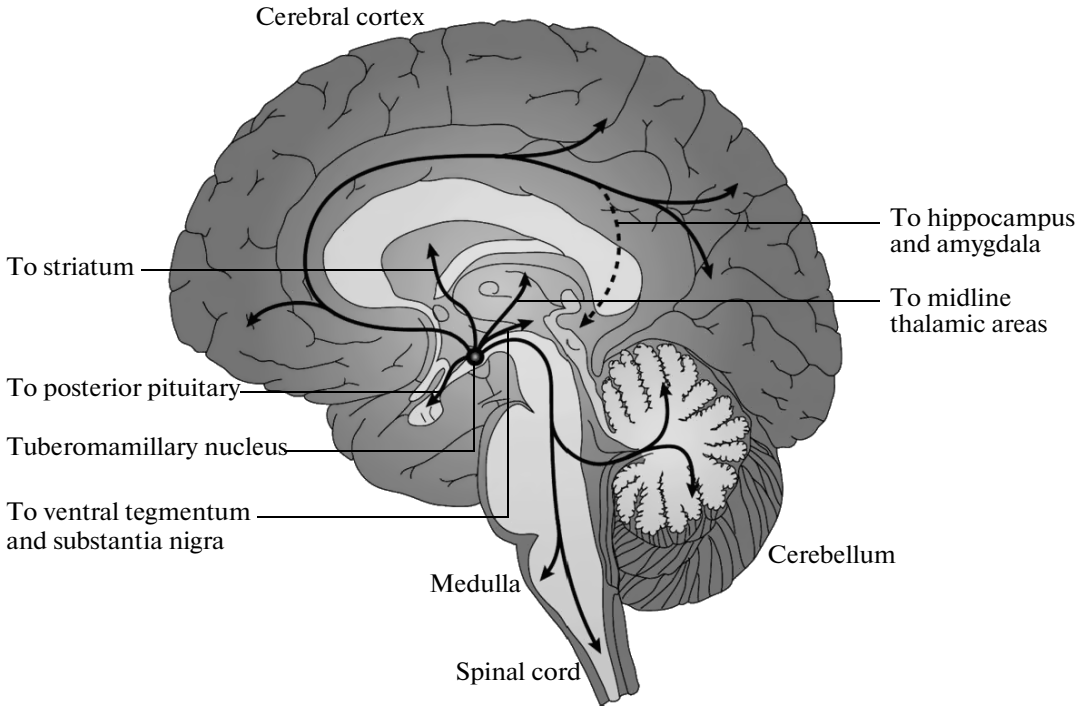

Fig. 1. Key projections of the histaminergic system of the human brain (cited from [6]).

protein proenkephalin A), substance P, thyrotropin-releasing hormone, and brain natriuretic peptide. TMN neurons also contain the enzyme MAO-B removing amines from tele-methylhistamine, which is the main metabolite of histamine in the brain. In addition, these neurons can capture and decarboxylate exogenous 5-hydroxytryptophan (a precursor of serotonin), synthesized by other cells. Such a large number of cotransmission functions in the same neurons is a unique feature of TMN [15].

Like most other activating systems, the histaminergic TMN system is tree-structured: a very small number of large cell (25–35 μm) neurons (in the rat brain, only 3000–4000 neurons; in the human brain, 64000 neurons) innervate billions of cells of the neocortex, paleocortex, and subcortical structures due to the enormous branching of their unmyelinated axons (each axon forms hundreds of thousands of branches). Ascending fibers of TMN break down into two pathways: the lateral pathway (through the lateral forebrain bundle) and the periventricular way, which come together in the diagonal Broca band to form the overall projection (which is, mainly, ipsilateral) on multiple structures of the forebrain, including the cortex, olfactory bulb, hippocampus, caudate nucleus, n. accumbens, globus pallidus, and amygdala. Many hypothalamic nuclei, such as suprachiasmatic, supraoptic, semicircular, and ventromedial nuclei, have been reported to be very rich innervated by the neurons of TMN [17].

The most powerful ascending projections run to the neurohypophysis, as well as to the nearby dopamine-containing areas of the midbrain ventral tegmental area (VTM) and to the substantia nigra/pars compacta (SNpc), to the basal forebrain region (large nuclei of the unnamed substance containing acetylcholine and GABA), to the striatum, neocortex, hippocampus, amygdala, and midline thalamic nuclei; the descending projections run to the cerebellum, pons, medulla, spinal cord, including the nucleus of the cranial nerves (trigeminal nucleus), central gray matter, colliculi, substantia nigra, locus coeruleus, midbrain and pons tegmental area, and dorsal raphe nuclei (Fig. 1). In rats and mice, histamine-containing neurons have been also found in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus, which is the main circadian pacemaker of the brain. In addition, a reciprocal relationship between SCN and TMN was recorded [18]. Detailed neuromorphological studies conducted in the laboratory headed by Jouvet, as well as in other laboratories throughout the world, on the brain of cats and rats, have shown that histaminergic neurons of TMN are also projected on the nuclei of the mesopontine tegmentum, producing acetylcholine (laterodorsal tegnmentum/pedunculopontine tegmentum, LDT/PPT) and noradrenaline (locus coeruleus, LC), and on the dorsal raphe nuclei synthesizing serotonin (dorsal raphe, DR) [17].

In turn, the histaminergic neurons of TMN receive afferents from the infralimbic cortex, the lateral area

of the septum, the septal diagonal complex, the hippocampus, the preoptic area of the anterior hypothalamus, C1–C3 adrenergic cells, A1–A3 noradrenergic neurons, and B5–B9 serotonergic cells (ventrolateral and dorsomedial medulla; raphe nucleus). The most powerful inhibitory (GABA/galaninergic) projections of TMN come from the sleep center VLPO, while the excitatory projections come from orexin/hypocretin-containing neurons in the lateral hypothalamus [6].

Interestingly, only a few fibers reach TMN from the noradrenaline-containing cells of the locus coeruleus and dopamine-containing neurons of VTM and SNpc [6, 15]. However, in patients with Parkinson's disease, which is associated with the destruction of dopaminergic transmission, there is a twofold increase in the concentration of histamine coming from TMN to SNpc and its projection, the globus pallidus [8].

Relationships between the histaminergic and orexin/hypocretinergic brain systems are extremely important [19]. Orexin neurons play a critical role in coordinating the activity of aminergic brain systems, integrating incoming circadian optical impulses, on the one hand, and nutritional metabolic impulses, on the other hand. In the active state of wakefulness, the discharge frequency of orexin neurons is maximal, as well as the discharge frequency of aminergic neurons; during REM sleep, it is minimal (zero). The activation of histamine neurons is one of the most important functions of the orexinergic system. The first time it was shown shortly after discovering the orexin/hypocretinergic system [1] when, in experiments with direct injection of orexin into the cerebral ventricles of rats, the subsequent increase in behavioral activity disappeared when histaminergic transmission was blocked. Furthermore, it was shown that the histamine content in the brain of mutant dogs (narcoleptics) and in the liquor of patients with narcolepsy differs from normal values [20].

Both neurotransmitters, histamine and orexin, act synergistically, playing a unique role in maintaining wakefulness. Orexin/hypocretin-containing neurons are located in the posterior-lateral hypothalamus and perifornical area in the immediate vicinity of the histamine neurons of TMN. Both nuclei overlap and form a functional unit. Both orexin/hypocretin stimulate directly histamine neurons through their type 2 receptors and activation of the sodium–calcium ion exchange. Orexin is often co-localized with dynorphin, which may also participate in the excitation of histaminergic neurons by inhibiting GABAergic inhibition. However, histamine neurons, apparently, do not directly affect the excitability of orexin neurons, so that a direct interaction between these two systems is one-sided [20]. On histamine neurons, there are also excitatory cannabinoid receptors; however, their role in the integrative activity of the brain is still unclear [20].

It is believed that histaminergic arousal effects are largely mediated by cholinergic activation. Unlike histaminergic neurons, cholinergic REM-waking neurons are very active in wakefulness and during REM sleep; they are responsible for EEG desynchronization in these states. The histaminergic system is involved in the genesis and maintenance of cortical activation not only directly but also through the excitation of corticopetal cholinergic neurons of the basal forebrain, as well as excitatory interaction with the cholinergic thalamic and hypothalamic projections coming from the mesopontine tegmentum [20].

There is also close cooperation in the regulation of wakefulness between histaminergic and the two other aminergic systems of the brain involved in the general ascending activating flow, namely, the noradrenergic and serotonergic systems. All their neurons belong to the waking group of neurons; i.e., they are active only during wakefulness, dramatically reduce their frequency of impulses during slow wave sleep, and completely stop it during REM sleep. The details of this interaction are not well understood, however, experiments on mutant narcoleptic dogs (see below) show that these histaminergic neurons may be responsible for the elements of consciousness related to the thalamocortical system and other systems of the forebrain; while the noradrenergic and serotonergic cells are mainly related to the maintenance of muscle tone during wakefulness [20].

There are almost no excitatory dopamine receptors (D1 and D2) on histaminergic neurons; however, these cells contain a large amount of transport proteins and enzymes, which are capable of capturing the precursor of dopamine, a natural dihydroxyphenylalanine (DOPA), in the extracellular environment, transport it into the cell, and convert it into dopamine [10].

Therefore, we assume that the histaminergic system and other aminergic systems of the diencephalon, midbrain, and brainstem are largely similar in their morphology, as well as in their cellular and systemic physiology. With their multiple interconnections, they form a self-organizing network, which may be compared to orchestra (as mentioned above), in which orexin (hypocretin) neurons play the role of a conductor, and histamine receptors play as the first violin [8].

As is well known, histamine is produced from the amino acid histidine, which is supplied to the body with food protein. In contrast to histamine, histidine passes the blood–brain barrier and is trapped by the protein transporter of natural amino acids, which transports it into the neuron. Neurons of TMN express the enzyme histidine decarboxylase (HDC), which cleaves carboxyl from the molecule of histidine and transforms it into histamine. HDC is most active in the neuron body; however, it is also contained in varicosities and axon terminals. The limiting factor in the rate of synthesis of histamine is the tissue concen-

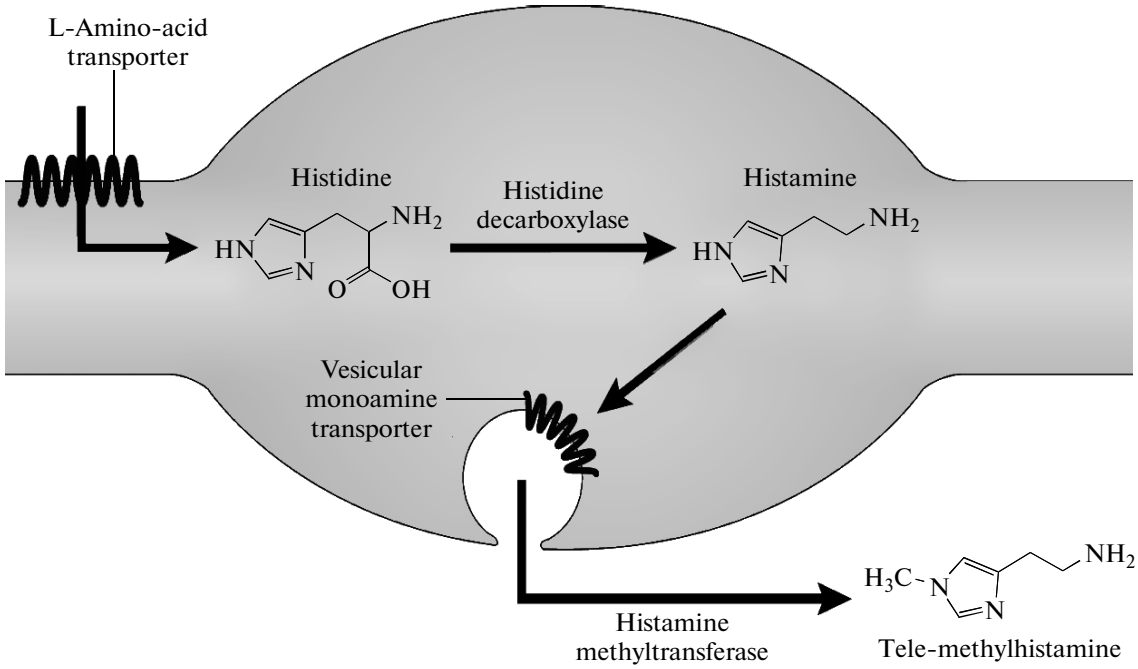

Fig. 2. Synthesis and metabolism of histamine in the brain (cited from [6]).

tration of its precursor, histidine. Histamine is transferred to the vesicles by a special protein, vesicular monoamine transporter type 2 (VMAT-2), and accumulates there. These vesicles are located not only in the cell bodies but also in the endplates and varicose swellings of axons. With the appearance of the action potential, the histamine is released via the Ca^{++}-dependent pathway. The histamine released into the synaptic cleft or extracellular space, which is not bound to the receptor, is inactivated by methylation by the enzyme histamine methyltransferase (synthesized postsynaptically or in glia), turning it into tele-methylhistamine. It undergoes oxidative deamination by MAO-B, turning into t-methyl-imidazolacetic acid (Fig. 2). There is no reuptake pathway for histamine. Typically, the half-life of neuronal histamine is about half an hour; however, it can be shortened dramatically under the effects of external factors, such as stress [6, 21].

Four types of metabotropic receptors of histamine associated with guanidine-linked proteins (G-proteins) are known: two excitatory receptors (H1 and H2) and two inhibitory receptors (H3 and H4) [22] (Fig. 3). Activation of postsynaptic H1 or H2 receptors, located on the target neuronal bodies, triggers intracellular molecular cascades associated with adenosine triphosphate (ATP), adenylyl cyclase, and cyclic adenosine monophosphate (cAMP); increases cell activity and excitability, either reducing the leakage K^{2+} current (I_{KL}) or posthyperpolarizing current (I_{AHP}) or increasing the hyperpolarization-activated cation current (I_H). Histamine also interacts with the polyamine area of the NMDA receptor, modulating excitatory postsynaptic potentials (EPSPs) [21, 22]. Presynaptic H3-type autoreceptors and heteroreceptors may be located on the cell bodies, dendrites, and axons, inhibiting the synthesis and release of histamine and other transmitters. As regards the postsynaptic receptors of type H3, they are located on the target cell bodies, e.g., in the striatum, and are often paired with D2 dopamine receptors, lowering their affinity for ligands [23, 24]. High constitutive activity, i.e., the spontaneous activity in the absence of histamine, is an interesting feature of histaminergic receptors. This activity plays an important regulatory role in the brain and is involved in the regulation of sleep–wakefulness and cognitive functions by modulating the synthesis or release of histamine and other neurotransmitters. Several reversible H3 receptor agonists that can block it are already used in clinical trials for patients with schizophrenia, epilepsy, narcolepsy, obesity, and Alzheimer's disease [25]. Another distinctive feature is the plurality of the isoforms encoded by the same gene and generated by alternative splicing. Receptors of the H1–H3 types are ubiquitous in the brain, while the H4 receptor is located mainly in the spinal cord [21, 25].

Interestingly, in addition to neuronal cells, mast cells, and microglia, histidine decarboxylase is expressed by ependymal cells of the brain. This histamine may be involved in the regulation of the formation of stem cells located under the ependymal layer. Neural stem cells in vitro react to the ligands of H1 and H2 receptors [21].

It is believed that the activating effect of neuronal histamine is mediated mainly via H1 receptors,

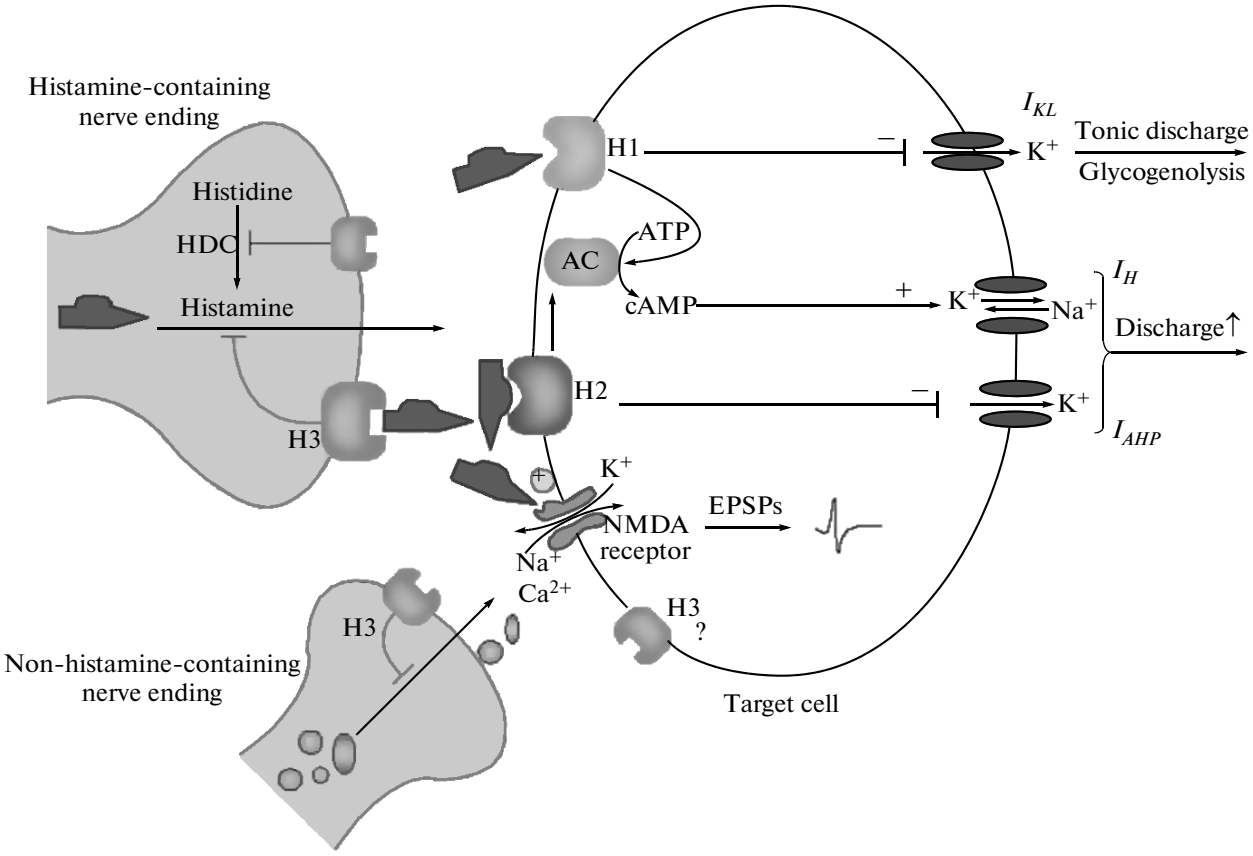

Fig. 3. Histamine-mediated transmission and cellular mechanisms involved in its operating (cited from [23]). See explanations in the text. Designations: HDC, histidine decarboxylase; H1, type 1 histamine receptor; H2, type 2 histamine receptor; H3, type 3 histamine receptor; AC, adenylate cyclase; ATP, adenosyl triphosphate; cAMP, cyclic adenosyl monophosphate; EPSPs, excitation postsynaptic potentials; I_{KL}, background K^+ leakage current; I_H, hyperpolarization-activated cation current; I_{AHP}, after-hyperpolarization current; Discharge↑, discharge enhancement.

because their greatest intensity is recorded in the frontal cortex and the amygdala, and the lowest intensity, in the cerebellum and spinal cord. These are the receptors responsible for the wake-up effect of the administration of histamine in cats. Furthermore, activating cholinergic neurons of the basal forebrain (n. basalis magnocellularis), which are projected to the cortex, also excite due to the exposure to H1 agonists [20]. Postsynaptic excitation resulting from activation of the H1 receptor, coupled with proteins of the *Gq*/11 group and phospholipase C, causes the formation of two secondary messengers, diacylglycerol (DAG) and inozitoltrisphosphate (IP3), as well as releasing Ca^{2+} ions from intracellular stores. All this gives rise to a whole cascade of events: (1) the opening of cation channels, which leads to depolarization; (2) activation of the electrogenic sodium-calcium exchanger (NCX), which also leads to depolarization; (3) the formation of NO and cyclic guanidinmonophosphate (cGMP); and (4) opening of Ca^{2+}-dependent K^+ channels, which results in hyperpolarization [10].

If K^+ leakage current is experimentally blocked by the direct action of G-protein, the thalamic relay nuclei open and the reaction of activation of the neocortex occurs. Direct stimulation of cortical neurons can also occur. It is believed that, for the excitation of septal cholinergic neurons, activation of tetrodotoxin-insensitive Na channels is required; whereas, for the excitation of the serotonergic neurons in the dorsal raphe nuclei, the activation of mixed cation channels is required. Activation of H1 receptors also leads to more frequent discharges of neurons of the suprachiasmatic nucleus and cholinergic basal nuclei of the forebrain [10].

At the same time, H2 receptors are primarily responsible for the processes of learning and memory; and their high intensity is observed in the cortex, basal ganglia, hippocampus, and amygdala. These activating receptors, like β-adrenergic receptors and type-2 serotonin receptors, are linked with Gs-protein, adenylyl cyclase, and protein kinase A, which phosphorylates proteins and activates the CREB transcription factor. Through this signal pathway, these transmitters block Ca^{2+}-dependent K^+ conductivity, which is responsible for the long-term post-hyperpolarization

and the accumulation of charge (exaltation). Thus, the reaction of target neurons in the cerebral cortex and hippocampus is modulated; the same stimuli can cause, depending on the levels of aminergic activation, a reaction consisting either of a small amount of action potentials or of numerous action potentials. At the level of consciousness, this potentiation of excitation is supposed to be needed for strengthening the attention [10].

The H3 receptors, as indicated above, function as autoreceptors on the bodies, dendrites, and varicosities of axons of histaminergic neurons, forming the negative feedback, which limits the synthesis and release of histamine. However, more importantly, they function as heteroreceptors located in the varicose axons of nonhistaminergic neurons (Fig. 4). Thus, they modulate the release of glutamate, GABA, noradrenaline, and acetylcholine. The H3 receptors are coupled to a Gq-protein and high-voltage Ca^{2+} channels, which are the typical mechanism for the release of a neurotransmitter [10].

Microdialysis of histamine in the preoptic area and the anterior hypothalamus of rats showed that its extracellular level undergoes circadian rhythms, where the maxima coincide with periods of wakefulness, when there is the greatest activity of histaminergic neurons. During periods of slow-wave sleep, there is a decrease in the histamine level; during REM sleep, it reaches the minimum. Sleep deprivation has no effect on histamine level, indicating that it reflects the circadian (rather than homeostatic) component of Borbely's bicomponent model [10, 26]. It is believed that, during prolonged wakefulness, sleep deprivation, and high activity of the central nervous system, adenosine is accumulated in the key areas of the brain responsible for the development of sleep. Adenosine receptors of A1 type, which are positively coupled with various K^+ channels and negatively coupled with Ca^{2+} channels and cAMP, cause postsynaptic and presynaptic inhibition of many centers of wakefulness, especially the cholinergic nuclei of the basal forebrain. Interestingly, adenosine has no effect on histaminergic neurons [10].

Histaminergic neurons are pacemakers and produce regular spontaneous low-frequency discharges (1–4 Hz). During waking and behavioral activation, their frequency increases; while during going to sleep and slow sleep wave, their frequency decreases; and during REM sleep, it disappears (Fig. 5). Inhibition of histaminergic neurons during sleep is mediated by GABAergic neurons of the sleep center in the ventrolateral preoptic area (VLPO) [21]. In addition, neurons of TMN are affected by inhibitory neuropeptides, such as galanin and endomorphin. There are no histaminergic receptors on VLPO, thus, a direct interaction between the histaminergic system of the waking center of TMN and the GABAergic VLPO sleep center is one-sided. It is believed that this type of interaction of the histamine system with the activation system (orexinergic, see above) and the inhibitory system (GABAergic) provides extra stability to the whole mechanism [27].

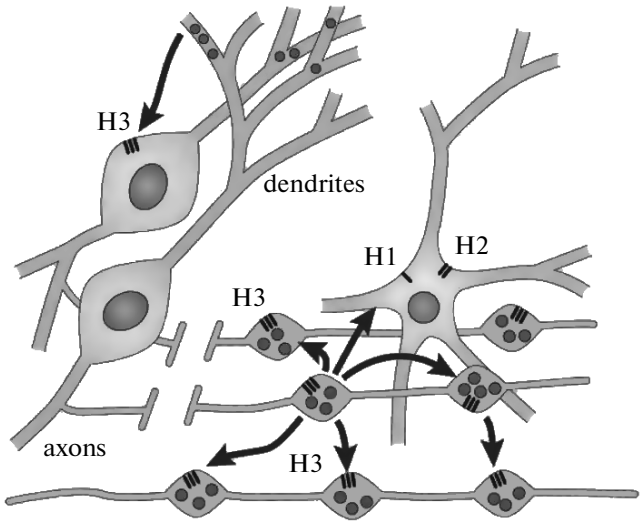

Fig. 4. Histaminergic neurons and their targets. H1 and H2 receptors are located on the bodies of target cells; H3 autoreceptors are located in the bodies, dendrites, and axons; H3 heteroreceptors are located on the axons. Histamine is released from dendritic and axonal vesicles (cited from [6]).

Neuronal histamine is involved in many functions of the brain: brain tissue homeostasis; regulation of certain neuroendocrine functions, behavior, biological rhythms, reproduction, temperature, and body weight; energy metabolism and water balance; as well as in the response to stress. In addition to maintaining wakefulness, the brain's histamine is involved in sensory and motor reactions and the regulation of emotion, learning, and memory [21]. With regard to the regulation of circadian rhythms, the histamine deficiency leads to a decrease in the overall level of behavioral activity and disorders of the rhythmic expression of the *mPer1* and *mPer2* clock-genes in the secondary oscillators, located in the neocortex and striatum. However, the activity of the primary oscillator of the body, located in the suprachiasmatic nuclei of the preoptic area of the anterior hypothalamus, remains unchanged. This indicates that histamine, apparently, modulates the behavior at the output of the circadian pacemaker [20].

Histamine was first assumed to be the hormone of wakefulness appeared after finding out, in the 1950s, that the first generation of antihistamines (H1 receptor antagonists), such as diphenhydramine, which pass the barrier, have side sleeping effects. It was further discovered that the neurons of TMN are active only in wakefulness but not in sleep. Finally, the effect on the

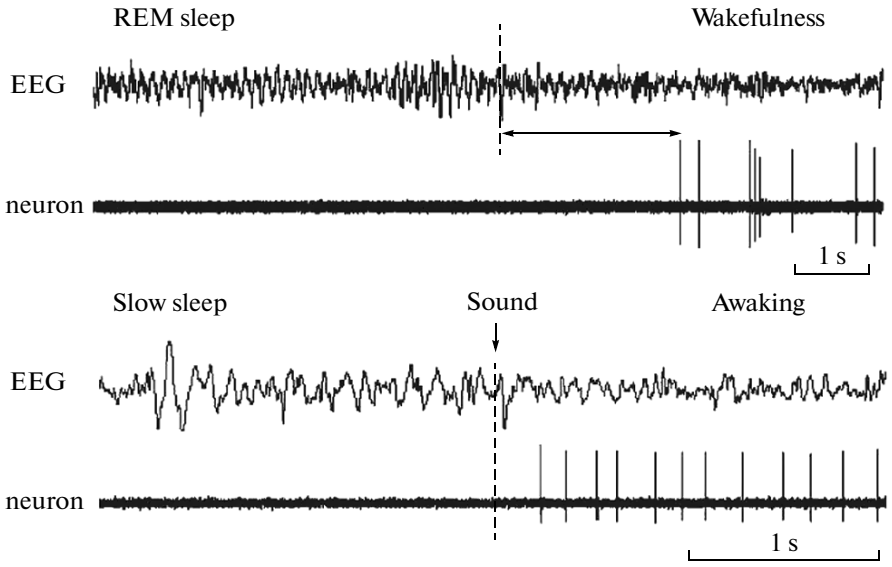

Fig. 5. Histaminergic neuron of the mouse in the cycle of wakefulness–sleep (cited from [6]).

histaminergic system, either by introducing H3 receptor antagonists, which activate the histaminergic system, or administration of α-fluoromethyl, which blocks the synthesis of histamine, or by deletion of the GDC gene in knockout mice, results in disorders of the sleep–wakefulness cycle in experimental animals [21]. The blockade of the synthesis of histamine by α-fluoromethyl histidine dramatically reduces the levels of histamine in the brain, suppresses wakefulness, and increases slow wave sleep in laboratory cats and rodents. At the same time, strengthening histaminergic transmission by inhibiting degradation of histamine, on the contrary, increases wakefulness [10]. Like orexin neurons, histamine neurons may be involved in the reaction of awakening caused by hypercapnia, because they are activated by short-term moderate hypoxia and acidosis [10]. Of all neuron systems currently known, the histaminergic system is the most sensitive to the changes in the level of wakefulness [10, 12].

In GDC gene knockout mice, there is an increase in the representation of REM sleep; a decrease in the power of the θ-rhythm during wakefulness, and a decrease in the power of the Δ rhythm during slow sleep; a decrease in the representation of wakefulness at night, and hypersomnia. Hypersomnia is manifested both as a decrease in reactivity, or the latency to sleep after the effect of awakening stimuli on the animal (lights off or placing the mouse in a new cage), and a decrease in the activity in the dark period compared to control mice (wild-type). In the daytime, GDC gene knockout mice and the H1 receptor gene knockout mice are more active than the control group. Interacting with the GABAergic system, the histaminergic system inhibits behavioral manifestations of sensitization (which is the opposite of tolerance) caused by chronic administration of methamphetamine [28, 29].

Until recently, it was believed that the histaminergic system is descending relative to the orexinergic system, which controls it through wide tree-like branching of its axons projected onto the neurons of TMN. However, recent experiments showed that the phenotype of homozygous GDC gene knockout mice described above is only partly similar to the phenotype of homozygous orexin knockout animals. Both mutant strains showed excessive sleep fragmentation and an increase in the representation of REM sleep; however, there are the following differences: (1) in mice without histamine, an increased percentage of REM sleep occurs in the light and less active period of a day, while in the mice without orexin, it occurs in the darker, more active period of a day; (2) unlike mice lacking histamine, the animals lacking orexin exhibit neither a reduction of wakefulness during the "twilight" period of the day (immediately preceding and immediately following the switching off of the light) nor EEG abnormalities, and they normally respond to being placed in a new environment by an increase in wakefulness; (3) the same animals, unlike animals lacking histamine, have narcoleptic-like attacks and, on being placed on a rotating wheel, show no motor activity [10].

The relationships between the histaminergic and melaninergic systems of the posterior hypothalamus have also attracted much interest. The neurons containing the peptide melanin concentrating hormone are located in the same place as orexinergic cells; however, they exhibit reciprocal orexinergic and histaminergic discharge [1–5]. They seem to play a special role

at the hypothalamopontine level of the regulation of REM sleep [10].

The histaminergic system plays an important role in the formation of the narcoleptic phenotype. Although the disease is due to the lack of orexin transmission, in experiments on narcoleptic dogs (Doberman Pinscher) showed that, during cataplexy attacks, the activity of histaminergic neurons persists, while the activity of serotonergic neurons dramatically decreases, and the activity of noradrenergic neurons stops [30]. At the same time, H3 receptor antagonists reduce excessive sleepiness and cataplexy attacks, apparently, by blocking the inhibitory autoreceptors, which provide negative feedback, thereby increasing the release of histamine in the synaptic cleft. Currently, a number of substances of the kind are undergoing clinical trials as drugs for narcolepsy [10].

Thus, according to the current concepts, the histaminergic activating system is primarily responsible for the cortical activation of EEG and the higher (cognitive) functions of the brain; whereas the orexinergic system, which is closely related to the histaminergic activating system, is responsible mostly for behavioral manifestations of waking up and wakefulness, such as muscular tone, postural and locomotor conditions, food consumption, and emotional responses. Orexin deficiency in humans is the direct cause of narcoleptic attacks, while histamine deficiency is the direct cause of excessive daytime sleepiness and sudden sleep attacks, which are not only the characteristic symptoms of narcolepsy but also of many other diseases, which are much more common, including Parkinson's disease [10].

In addition, modulation of the histaminergic system can be used for treating other disorders of the wakefulness–sleep cycle. For example, a tricyclic antidepressant doxepin not only inhibits the reuptake of norepinephrine and serotonin but also is an H1 and H2 receptor antagonist, and it has been successfully used for the treatment of insomnia in the elderly. Conversely, excessive sleepiness can be suppressed by introducing H3 receptor antagonists [10].

Studies on the TMN histaminergic systems in order to develop new substances that suppress sleepiness and enforce wakefulness led to the discovery of awakening properties of montireline, which is a nonhydrolysable analog of a thyrotropin-releasing hormone, which showed a good effect in the simulation of narcolepsy in dogs. TMN neurons express both known types of thyrotropin-releasing hormone receptors, which are excited by the thyrotropin-releasing hormone and montireline. At the same time, montireline has no effect on GDC-biknockout mice. Thus, the histaminergic system is the crucial target for the development of new stimulating drugs needed for treating, in particular, patients with narcolepsy and Parkinson's disease. In patients with Parkinson's disease, most of the centers of wakefulness gradually degenerate; however, the histaminergic system remains intact, so that the reversible H3 receptor agonist can cause wakefulness. In these patients, montireline is almost inefficient because of the destruction of the dopaminergic system [10].

However, note that the behavioral disorders in laboratory rodents caused by the selective destruction of the histaminergic cell bodies of the brain were not as striking as one might expect. For example, Blanco-Centurion et al. [31], working with large and strong Sprague–Dawley rats (aged up to 6 months and weighing up to 620 g), showed that local intracerebral injection of specific saporin-containing neurotoxins, which provide targeted chemical destruction of specific neuronal bodies, did not lead to significant disorders of wakefulness–sleep in the experimental animals. Up to 75% of Hist/TM neurons were destroyed by them, as well as up to 90% of NA/LC and Ach/BF neurons; at the same time, according to the results of the morphological control, provided by the authors, the injected substances did not affect the surrounding cells. It was found that the simultaneous destruction of one, two, or even three systems in the same animals resulted, after 20 days, in few changes in the sleep–wakefulness cycle; the most pronounced changes were a twofold reduction of the representation of wakefulness during the transition from the light to the dark period and in a decrease in the representation of REM sleep during the daytime [31]. The effect characteristic of GDC-knockout mice has been reproduced to a large extent [10].

Such a weak effect of the subtotal irreversible destruction of three key activating systems, including the histaminergic system, whose role in maintaining wakefulness has been, seemingly, irrefutably proved by numerous neuroanatomical, neurophysiological, neuropharmacological, neurochemical, neurogenetical, and neurological clinical data [4], makes us unsure about the above scheme of the ascending activating flows. It is possible that the activation of some of the neural systems, which is currently considered to be the cause for tonic depolarization of the cortex is actually a result of it, while the real cause is the activation of some other systems, which are still unknown [4]?

It has been suggested that such a small effect of chronic damage may be related, at least in part, to quite a significant period of the recovery time (compared to the duration of a rat's life); i.e., during three weeks after the destruction, strong recovery processes have time to occur in the brain [12]. However, the use of the latest optogenetic method provides a reversible short-term (acute) selective switching on and off the specific neuronal groups in laboratory mice without anesthesia in the free behavior. As a result of a reversible selective inhibition of noradrenergic LC neurons for 1 h in free-moving mice, only moderate effects,

such as a decrease in the representation of wakefulness and an increase in slow wave sleep in the dark period, were recorded. In the same experiments, selective activation of orexin neurons increased wakefulness and c-Fos expression in LC noradrenergic neurons and histaminergic TMN; however, it could not counteract sleep deprivation. In GDC-knockout mice, the behavioral effect was the same, i.e., an increase in wakefulness occurred in the total absence of histamine [32].

Thus, despite the enormous progress made in recent years in studying the regulation of the wakefulness–sleep cycle, the role of the histaminergic system of the brain in these mechanisms remains rather puzzling. As the talented Russian biologist Yu.A. Labas (1933–2008) wrote [33, 34],

> If some alien creatures, in the early twentieth century, had brought computers to Earth, humans, by any methods known at that time, would not have solved the mystery of the device, as they would have seen in front of them a ready-made instrument, not knowing all the previous years of the history of culture and information, and the purpose of these devices ... . Nature, creating more and more complicated nervous systems, took its evolutionary way; while the level of scientific understanding of the brain performance, even today, remains primitive. The analogy with the computer is just an analogy ... . The nerve cells and their connections are arranged quite differently from the micromodules of the computer, and the principle of their interaction is quite different. The programs on which the brain works are created by evolution; so, trying to understand them, we often come up against a blank wall ... .

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