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Review Article

Biogenic Amines and Their Role in the Brain

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Abstract

The purpose of the review is to summarize and systematize the literature data on the metabolism, functions of biogenic amines in the brain, as well as their biochemical structure and classification. Biogenic amines play an important role in brain metabolism and its functioning. This is due to the exceptional role of biogenic amines as sources of synthesis of a large number of biologically important compounds, such as neuropeptides and hormones, and their participation in synaptic transmission as neurotransmitters and neuromodulators. Determination of the activity of enzyme systems of their metabolism can serve as an important diagnostic marker of the reaction of the central nervous system to damage in cerebral pathology.

Key words: Biogenic amines; Brain; Neurotransmitters

Introduction

Biogenic amines are organic substances that are formed in the body from amino acids by their decarboxylation (removal of the carboxyl group), decarboxylase enzymes and have high biological activity.

The group of biogenic amines includes: dopamine, norepinephrine, 5-hydroxytryptophan, normetanephrine, serotonin, histamine [1-5].

Dopamine

Dopamine is involved in the regulation of many body functions: in the modulation of blood pressure, cognitive processes, control of emotions and motor activity [6].

The nigro-strial system is responsible for the initiation and control of locomotor manifestations of vital activity.

The loss of dopaminergic neurons of the midbrain (substantia nigra) leads to the development of Parkinson's disease, which is expressed in a violation of inhibitory control over the contraction of striated muscles. Dopamine deficiency is noted in Alzheimer's disease, and excess - in schizophrenia. On the contrary, hyperactivity of dopaminergic systems of the brain is observed in the development of manic states and hallucinations. Modulation of the autonomous centers of the hypothalamus under the action of dopamine causes changes in food and water intake, hormonal status (due to an indirect effect on the pituitary gland) [5].

Projections of dopaminergic neurons of the blue spot are part of the ascending reticular activating system that regulates attention, arousal and circadian rhythms. On the periphery, dopamine determines the functioning of the sympathetic department of the autonomic nervous system, the effects of various stressful effects on the body: control over the work of the cardiovascular system, increased glycogenolysis in the liver, etc [7,5].

Norepinephrine

Tyrosine is converted into catecholamines by hydroxylation with the participation of tyrosine-3-hydroxylase. This reaction is the slowest in the biosynthesis of catecholamines, so its speed determines the speed of the entire biosynthesis of catecholamines. Next, dihydroxyphenylalanine is decarboxylated to form dopamine with the participation of the enzyme dopa-decarboxylase. Dopa-decarboxylase is in excess in the brain. Its greatest concentration is in the hypothalamus and the midbrain, and the smallest is in the cerebellum and in the cerebral cortex. In the microvascular bed of the brain, there is also a high activity of this enzyme. Therefore, DOPA does not penetrate into the brain, but is converted into dopamine, the patency of which through the BBB is very difficult [7,8-10]. Dopamine, being a precursor of norepinephrine, ensures the functioning of the brain as a neurotransmitter.

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The metabolic pathway of norepinephrine

Phenylalanine → Tyrosine → L-DOPA → Dopamine → Norepinephrine

Norepinephrine is synthesized in the body of a neuron, which, with the help of axonal current, passes into vesicles and nerve endings. Norepinephrine in vesicles is divided into three groups: strongly bound, labile bound and cytoplasmic. The first group is a spare and can be released by the influence of various reactions, determining the content of norepinephrine in the brain as a whole. The second group makes up 13% of the total norepinephrine and, being the active form, participates in conducting a nerve impulse, since it has a high level of metabolism. It is restored by the breakdown of norepinephrine of the first group, the absorption of norepinephrine of the third group and by biosynthesis. The third group is insignificant in volume, and has an intensive metabolism [5].

Dopamine is converted to norepinephrine by hydroxylation with the enzyme dopamine-β-hydroxylase, which is located in vesicles. Vesicles contain catecholamine and the enzyme activity requires the presence of ATP, NAD, NADP and Ca^{2+} in vesicles. The synthesis of catecholamines ends with the methylation of norepinephrine into the tertiary hormone adrenaline under the action of the enzyme phenylethanolamine-N-meltransferase. The biosynthesis of adrenaline is weak due to the low activity of the enzyme [11,12].

The enzymes are Monoamine Oxidase (MAO) and Catechol-Oxymethyltransferase (COMT). COMT, along with MAO, plays an important role in the inactivation of catecholamines. Unlike MAO, which catalyzes the oxidative deamination of catecholamines inside the presynaptic space, COMT destroys catecholamines in the synaptic chain [12,13,5].

Normetanephrine

Normetanephrine is a metabolite of norepinephrine. It is formed due to the action of catechol-O-methyltransferase on norepinephrine. Normetanephrine is excreted in the urine, and is also found in other tissues. It can be used to diagnose tumors that secrete catecholamines, for example, pheochromocytoma [7,14,5].

5-hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is a natural amino acid, which is also called oxy-tryptan. It participates in the biosynthesis of serotonin, being its precursor and intermediate [15,16,17].

Oxytriptan is formed by the action of the enzyme tryptophan hydroxylase on tryptophan. Tryptophanhydroxylase is one of the aromatic amino acid hydroxylases that depend on biopterin [18].

5-HTP, when decarboxylated with aromatic L-amino acid decarboxylase, is converted into serotonin with the participation of vitamin B6. This transformation takes place in the liver and nervous tissue [19,7,5].

Serotonin (5-oxy-tryptamine, 5-HT)

The highest amount of serotonin is found in the cells of the gastrointestinal tract, spleen, platelets, brain, performing hormonal and mediator functions. Serotonin regulates processes such as circadian rhythms, inflammation, affects the emotional background and vascular tone. Like norepinephrine, most serotonin is found in the hypothalamus and midbrain, and least of all in the cerebellum. The content of serotonin in gray matter exceeds its content in white by two times [20].

Serotonin is localized everywhere in the brain, isolated from the bridge and midbrain. Serotonergic nuclei are localized in the nuclei of the suture, the reticular formation of the medulla oblongata [21].

An increase in the concentration of serotonin in animals causes impaired coordination, stupor and catalepsy. A decrease in concentration causes aggression. Serotonin has opposite effects to catocholamines in the central nervous system.

The half-life of serotonin is 10-30 minutes. Serotonin penetrates poorly through the BBB, but 5-oxy-tryptophan penetrates well through it [22].

The limiting stage of serotonin synthesis in serotonergic neurons is the formation of 5-oxy-tryptophan and depends on tryptophan entering the brain through the BBB. The coenzyme of tryptophan-5-hydroxylase is pyridoxal phosphate [23].

Serotonin metabolism

Depolarization of neurons causes the release of accumulated serotonin, which can bind to presynaptic (5-HT receptors) or postsynaptic (autoreceptor) receptors. Binding to postsynaptic receptors causes a negative feedback. The highly selective serotonin transporter SERT, which is located on the presynaptic membrane, is used to remove serotonin from the synaptic cleft. When it enters the presynaptic neuron, serotonin is transported to the presynaptic vesicles, protecting itself from chemical changes. Metabolism occurs under the action of MAO in the cytosol of the cell.

Inactivation of serotonin is carried out by its reuptake by terminals and the action of MAO with the formation of 5-hydroxyindolacetic acid [24].

In the nervous tissue, under conditions of increased $NADH_2$ formation, serotonin can turn into 5-oxy-tryptophol. Sideways of serotonin metabolism are compensatory and are detected under conditions of MAO inhibition in pathology.

In other tissues, there are ways to exchange tryptophan and serotonin through the formation of melatonin, tryptamine and kynurenine [25,5].

The melatonin pathway. Serotonin turns into melatonin in the epiphysis, being a tissue hormone, it also affects the regulation of the sleep-wake cycle there [7].

The Kynurenine way. Almost all tryptophan of the body in the liver forms kynurenin, which, being an antagonist of serotonin and tryptamine, inhibits the accumulation of tryptophan in the brain. A change in metabolism from the serotonin to the kynurenine pathway may be the cause of mental depression.

The tryptamine pathway. Tryptiamine in the brain (cerebellum, cortex, basal ganglia) is formed from tryptophan during its decarboxylation. In the liver, tryptamine continues its metabolism and turns into 6-oxy-tryptamine [7,5].

Reserpine is a tryptamine antagonist. This pathway plays an important role in the genesis of schizophrenia. Confirmation of the participation of serotonin in the activity of the central nervous system and the connection with the occurrence of psychosis is confirmed by the picture of poisoning by the competitive serotonin antagonist Lysergic Acid Diethylamide (LSD)

contained in ergot alkaloids, It is assumed that the central psychogenic effect of LSD is caused by its competition with serotonin for serotonin receptors in the brain [7].

Serotonin affects the sleep-wake cycle. Sleep begins with the "orthodox stage", which lasts 60-90 minutes in humans, and then comes the "paradoxical" stage (≈20 minutes) with desynchronization of the electrical activity of the cerebral cortex, frequent rhythmic eye movements. At this stage, the most vivid dreams appear. Serotonin increases the duration of the orthodox stage of sleep, and a decrease in its content in the brain causes insomnia, which is relieved by the introduction of the immediate precursor of serotonin - 5-oxy-tryptophan, and depression [2,5].

Histamine

The appearance of histamine in the body is provided by basophils and mast cells in response to allergies. Histamine neurons in the central nervous system are located in the gray hillock and the intermediate brain. Collaterals can reach the cortex, hippocampus, thalamus, trunk.

There are also mast cells in the interstitial brain that produce histamine. It is formed from histidine by decarboxylation using the enzyme L-histidine decarboxylase [5].

The half-life is about 30 minutes, which is the limiting factor of accumulation in tissues.

The mechanisms of reuptake are unknown [7,2,5].

There are three groups of histamine receptors:

1). H1 receptors are a glycoprotein consisting of 490 amino acid residues located on the postsynaptic membrane of cells. The highest concentration is in the thalamus, hippocampus, cerebellum (Purkinje cells). The action is caused by increasing the formation of cAMP and increasing the amount of calcium inside the cells.

H1 receptor antagonists are used to treat allergies. They can penetrate through the BBB and cause a sedative effect associated with the blockade of histamine receptors.

2). H2 receptors are a glycoprotein consisting of 358 amino acid residues located on the postsynaptic membrane of cells. The greatest concentration is found in the large hemispheres (cortex, caudate nucleus, shell, tonsils), glial cells. The action is caused by an increase in the formation of cAMP due to the connection with G-proteins.

H2 receptor antagonists are used to treat allergies. They cannot penetrate the BBB, so they cannot cause sedation.

3). H3-receptors – their isolation into a separate group was carried out on the basis of pharmacological properties. They are located in the membrane of presynaptic terminals (autoreceptors), participating in the regulation of histamine synthesis and release. The highest concentration is in the areas of the frontal lobe of the cortex, basal nuclei and substantia nigra of the midbrain. Their activation leads to inhibition of the secretion of acetylcholine, dopamine, serotonin and norepinephrine. Intracellular effects are caused by activation of G-proteins [7,24,5].

Being the main mediator of inflammation and allergies, histamine can penetrate through the walls of blood vessels and regulate the regulation of cerebral circulation and the permeability of the walls of blood vessels of the brain.

Histamine is involved in the regulation of the wakefulness cycle, energy balance, body temperature, food intake, various emotions, following extensive innervation of the components of the limbocyte system. A lack of histaminergic neurons can cause Alzheimer's disease [2,23].

H1- and H2-receptors can cause significant changes in the functioning of the cardiovascular system. H2-receptors cause an increase in heart rate, cause vasodilation, and with the action of H1-receptors, the permeability of the vessels of the microcirculatory bed increases due to the reduction of actin filaments of the endothelium. Histamine can also cause bronchospasm and contraction of the smooth muscles of the gastrointestinal tract, but it does not have a strong effect on the smooth muscles of the eye and genitourinary system. Histamine stimulates the secretion of gastric juice by activating the H2 receptors of the parietal cells of the stomach [5].

Thus, due to the multifunctionality of biogenic amines in the brain, it is important to study shifts in the pool of biogenic amines both in normal and pathological conditions, including as markers of various pathological processes.

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