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Mediators of the Nervous System Kinds Characteristic

Maksimovich N Ye[1], Bon E I[1,2]* and Kohan N V[1]

[1]*Grodno State Medical University, Republic of Belarus*

[2]*Candidate of biological science, Assistant professor of pathophysiology department named D.A. Maslakov, Grodno State Medical University, Belarus*

***Corresponding author:** Lizaveta I Bon, Candidate of biological science, assistant professor of pathophysiology department named D.A. Maslakov, Grodno State Medical University; Grodno State Medical University, 80, Gorky St., 230009, Grodno, Belarus

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ABSTRACT

A mediator (synaptic transmitter, neurotransmitter) is a physiologically active substance found in a nerve cell in a bound form, which is secreted from an excited nerve ending into the synaptic cleft and specifically acts on the receptors of the postsynaptic target cell. The data on neurotransmitters presented in the article create a fundamental basis for further research in this area and will serve as the basis for subsequent clinical trials to prevent and correct the pathology of the nervous system.

Keywords: Neurotransmitter; Synaptic Transmitter; Nervous System

Introduction

A mediator (synaptic transmitter, neurotransmitter) is a physiologically active substance found in a nerve cell in a bound form, which is secreted from an excited nerve ending into the synaptic cleft and specifically acts on the receptors of the postsynaptic target cell [1].

Evidence of the mediator role of compounds in the nervous system is:

1) Their selective localization in the bodies of neurons and, in especially high concentrations, in presynaptic formations, where they are deposited in synaptic vesicles.

2) Their action on the postsynaptic membrane, as a result which changes its permeability to ions.

3) A sharp increase in their number in the extracellular fluid and outflowing blood upon stimulation of the presynaptic nerve fiber.

4) The presence in the nerve endings of enzymes involved in the synthesis and breakdown of neurotransmitters.

5) Calcium-dependent secretion of the mediator from nerve endings during their depolarization (presynaptic stimulation) in quantity corresponding to the number of stimuli.

6) The identity of the action of low concentrations of exogenous mediator (application, microiontophoresis) and a natural endogenous transmitter to the receptors of the postsynaptic membrane, tested by the formation of an excitatory or inhibitory postsynaptic potential.

7) Pharmacological agents (lytic or mimetic agents) acting on the receptors of the postsynaptic membrane should block or, accordingly, reproduce the effects of the intended transmitter.

8) The presence of a highly selective active capture system mediator to the appropriate terminals.There is a division of transformation mechanisms chemical signal, separation of receptors mediators into two categories - ionotropic and metabotropic. Ionotropic receptors (the so-called «channel», fast) form a single complex with the ionophore, so that the change in the conformation of the receptor caused by the mediator leads to the opening of ion channels and rapid significant shifts in the conductivity of the postsynaptic membrane. An example

is the GABA, glycine, and acetylcholine receptors during their interaction with nicotinic cholinergic receptors and part of the receptors for glutamate, aspartate, and purines.

Metabotropic receptors (the so-called slow ones) carry out the postsynaptic effect by activating specific membrane enzymes that ensure the formation of secondary messengers in the membrane or in the cytosol of the postsynaptic cell, which, in turn, specifically activate certain enzymes; at the same time, cascades of enzymatic processes are launched, ultimately leading to covalent modification (usually phosphorylation) of membrane or cytoplasmic proteins. This type of action is realized much more slowly than the ionotropic one and is accompanied by relatively small shifts in the conductance of the postsynaptic membrane. The metabotropic category includes the interaction of acetylcholine with muscarinic receptors, the postsynaptic action of catecholamines and serotonin [2].

Neuro Modulators

Neuromodulators, compared to neurotransmitters, have the following characteristics:

1) They don't have an independent physiological effect but modify their effect.

2) The action of neuromodulators has a tonic character - slow development and a long duration of action (seconds, minutes).

3) Neuromodulators do not necessarily have a synaptic or even neural origin. They can be released from glia.

4) The action is not associated in time with the effect of a neurotransmitter and is not necessarily initiated by nerve impulses.

5) The target can be not only the postsynaptic membrane and not only the membrane receptors; the neuromodulator acts on different parts of the neuron, and its action can be intracellular. Thus, the term «neuromodulator» is a much broader concept than the term «neurotransmitter». Neuropeptides are also metabotropic mediators. The discovery of peptide mediators has significantly expanded the understanding of the chemical mediation of signals in the nervous system. Quite recently, the neuromuscular junction was considered a classic example of a chemical synapse, the morphofunctional organization of which ensures fast, precisely directed signal transmission to the "anatomical" address.

In systems with a "chemical" address, the specificity of signal transmission is due not to a local anatomical connection between the pre- and postsynaptic structure, but to the presence of specialized receptors for this mediator only on target cells, and this type of signal transmission can be slow and diffuse [3]. It is in the transmission of such This type involves many neuropeptides with some classical neurotransmitters, in particular monoamines, which can also be released remotely in relation to the target cell located at a distance from the secreted cell. There are two main types of neuromodulations - presynaptic and postsynaptic.

Presynaptic Modulation

The release process of many neurotransmitters is modulated through autoregulation; the released neurotransmitter acts on its own presynaptic autoreceptors, decreasing subsequent release (presynaptic inhibition) or increasing release (presynaptic facilitation). In this situation, the neurotransmitter simultaneously performs the function of a neuromodulator. For example, presynaptic α-adrenergic receptors of sympathetic nerve endings mediate inhibition of norepinephrine secretion. Presynaptic autoreceptors are coupled to the adenylate cyclase system. According to their pharmacological characteristics, presynaptic autoreceptors differ from postsynaptic receptors of the same neurotransmitter. Presynaptic autoreceptors of glutamate, serotonin, dopamine, GABA, histamine, adrenoreceptors, muscarinic cholinergic receptors are known [4]. Modulation can occur at the level of changes in the excitability of nerve endings, biosynthesis of neurotransmitters, entry of Ca^{2+} into the nerve ending, and at the stages of exocytosis [4,5].

Postsynaptic Modulation

Postsynaptic modulation can be autoregulatory (positive or negative) when the activity of receptors is changed by modifying their affinity or quantity, as well as due to changes in receptor-coupled systems intracellular and intramembrane mediators. An example is receptor desensitization with prolonged exposure to a neurotransmitter and hypersensitization with insufficient exposure to it [5]. Postsynaptic receptors undergo heteroregulation as a result of exposure to neuromodulatory substances. Of considerable interest is the postsynaptic interreceptor interaction between accompanying mediators, primarily neuropeptides and classical neurotransmitters [1,5].

Associated Mediators

Associated, or coexisting, mediators (cotransmitters) are synaptic mediators that are characterized by co-localization and co-release. Co-localization refers to the synthesis and deposition of mediators in the same neuron, their presence in the same presynaptic endings, but not necessarily in the same synaptic vesicles. Thus, low molecular weight classical neurotransmitters are deposited mainly in small optically transparent vesicles, while peptide mediators are deposited in large optically dense vesicles, although there are data on cases of their joint localization. The difference in the systems of deposition of these types of mediators is due to differences in the places of their synthesis: classical neurotransmitters are synthesized in the cytoplasm of presynaptic endings and then enter the synaptic vesicles, while peptide mediators are synthesized in the Golgi apparatus, i.e., in the soma of the neuron, and are delivered to the nerve endings already packaged into bubbles. Co-release is understood as exocytosis of two (or more) mediators as a result of the same process of activation of the presynaptic ending in the form of a discharge of action potentials with one or another frequency. Another sign of concomitant mediators is the ability to cause functional changes in the same target cell [6].

The classification of neurotransmitters and neuromodulators is based on their chemical nature. Neurotransmitters are divided into two large groups:

1) Amino acids: γ-aminobutyric acid (GABA), glycine, glutamate and aspartate;

2) Biogenic amines: as a rule, they are derivatives of amino acids, as a result of their decarboxylation.

Further division within the group is based on the nature of the interaction of the amino group with the organic radical:

a) Acetylcholine is the only representative of choline derivatives;

b) Histamine is a histidine derivative and contains an imidazole group;

c) Monoamines in addition to the primary amino group contain derivatives of indole (serotonin) or catechol (catecholamines - dopamine, adrenaline and norepinephrine). The basis for the synthesis of indole and catecholamines are amino acids - tryptophan and tyrosine, respectively.

Neuromodulators are divided into four large groups:

1) Neuropeptides (endorphin, met-enkephalin, calcitonin, substance P) are formed from large protein precursor molecules. More than one neuropeptide can be formed from one protein. More than one neuropeptide can be present in one cell at the same time, often acting as a mediator;

2) Derivatives of fatty acids (eicosanoids and arachidonic acid) are involved in the regulation of inflammation, fever, etc.

3) Purines and pyrimidines (extracellular ATP, ADP, adenine, as well as UTP and UDP).

4) Gaseous substances (NO, CO and H_2S) are characterized by the absence of specific mechanisms of accumulation and storage inside the cell, as well as the absence of specific receptors on the postsynaptic membrane.

Acetylcholine (Ach)

The mediator acetylcholine is an ester of choline and acetic acid. It is widely represented in various parts of the central nervous system, especially in the basal ganglia, thalamus and gray matter of the cerebral hemispheres, where its content is several times higher than that in the white matter of the cerebral hemispheres. The smallest amount of ACh is found in the cerebellum [7]. Based on data on the extraction of acetylcholine from the nervous tissue, it is assumed that it is in three forms with different localization:

1. Free - 25% of the total amount of ACh;
2. Labile bound - easily extractable water;
3. Strongly associated with proteins.

Free ACh is located in the extracellular space, labile bound in the cytoplasm, and tightly bound in synaptic vesicles. The role of vehicles is in the synthesis, storage and secretion of ACh. For the synthesis of the neurotransmitter, the nervous tissue receives choline from the outside, since it is practically not synthesized in the brain and enters there from the blood through the BBB (blood-brain barrier). At the same time, part of the choline is used for the synthesis of lecithin and ubiquinone.The intracellular content of choline in the brain tissue is more than 50%, the rest of it is captured by the terminals from the synaptic cleft after hydrolysis and is reused. Choline captured by cholinergic terminals (60-70%) immediately turns into acetylcholine. The synthesis of acetylcholine is inhibited by thiol reagents, Cu^{2+}, some α-keto acids, especially α-ketoglutarate, and monoiodine acetate. The active center of the enzyme contains imidazole, a histidine residue that accepts the acetyl group of acetyl-CoA and transfers it to choline [8]. The content of acetylcholine and the activity of acetylcholine transferase in nerve endings are ≈ 100 times higher than in the nerve. This reserve is enough to carry out the transmission of several thousand pulses. However, under conditions of prolonged stimulation of cholinergic nerves, the supply of the mediator in the terminals is depleted.

It is still not completely clear where the synthesis of acetylcholine comes in the terminals - exclusively in the cytoplasm, followed by the accumulation of the mediator in synantic vesicles or partially in synaptic vesicles. Cleavage of ACh occurs under the action of acetylcholinesterase (AChE). AChE is a typical neuronal enzyme localized in synaptic membranes, where it inactivates «used» Ach [7,8]. The cholinergic system of the brain is formed by three main clusters of neurons:

1) Motor neurons of the spinal cord - form neuromuscular connections, the collaterals of these cells form excitatory synapses on small intercalary neurons of the intermediate substance;

2) Interneurons of the basal nuclei - mainly localized in the striatum (striate body);

3) Projection neurons form synapses with cells located at a considerable distance from the places of localization of the accumulation of their bodies. The processes of projection neurons are able to form both excitatory synapses and inhibitory synapses. Often in these neurons, ACh is colocalized with GABA. Small clusters of cholinergic neurons exist in the cerebral cortex, the hippocampus, and the olfactory bulb. Acetylcholine interacts with receptors on the postsynaptic membrane or with autoreceptors on presynaptic terminals.

The division of cholinergic receptors is based on the nature of their interaction with alkaloids: nicotine and muscarine. N-cholinergic receptors are activated by nicotine and blocked by curare, M-cholinergic receptors are activated by muscarine and blocked by atropine. N-cholinergic receptors are located on postganglionic neurons of the autonomic ganglia, cells of the cerebral cortex, hippocampus, thalamus, hypothalamus, and pontine nuclei. M-cholinergic receptors are located on the neurons of the

cerebral cortex, hippocampus, amygdala, striatum, olfactory bulb, postganglionic neurons of the autonomic ganglia and cardiomyocytes. Taking into account the localization of cholinergic neurons and the localization of ACh receptors, the following biological effects of ACh are distinguished:

1) Ensuring the work of internal organs. ACh reduces the frequency and strength of heart contractions, increases the secretory and motor activity of the intestine, relaxes the involuntary sphincter of the bladder, facilitating urination, reduces the smooth muscles of the bronchioles and eyes (iris sphincter), etc.;

2) Participation in the work of the neural systems of the brain - the brain is relatively richer in M-cholinergic receptors, while H-cholinergic receptors predominate in the spinal cord. Nicotine at low concentrations has a moderate excitatory effect on the neurons of the hippocampus and cerebral cortex, while at high concentrations it inhibits the work of cholinergic systems.

3) In the central nervous system, acetylcholine is involved in the control of motor activity and processes associated with learning and memory. Dysfunction of the cholinergic system is observed in neurodegenerative diseases, in particular in Alzheimer's disease. At the same time, AChE activity in the neurons of the cerebral cortex, hippocampus and amygdala decreases, ACh biosynthesis and choline reuptake decrease, destruction of cholinergic neurons in the basal nuclei and a decrease in the number of n-cholinergic receptors in hippocampal neurons are noted. In the course of the development of Parkinson's disease, hyperactivity of striatal neurons is noted, as a result, a decrease in the activity of dopaminergic structures of the midbrain, and in case of Huntington's chorea, on the contrary, the loss of corpus striatum neurons;

4) Providing neuromuscular transmission - the innervation of the striated muscles is carried out by the processes of the cholinergic neurons of the anterior horns of the spinal cord or the motor nuclei of the cranial nerves.

Biogenic Amines

Biogenic amines include:

1) Dopamine (3,4-dioxyphenylethylamine)

2) Norepinephrine

3) Adrenaline (epinephrine)

4) Serotonin (5 hydroxytryptamine)

5) Histamine.

The main neurotransmitters of the adrenergic system are norepinephrine and dopamine, and not adrenaline, as previously thought. The largest amount of norepinephrine and dopamine is concentrated in the hypothalamus, the smallest - in the cerebral cortex [9].

Norepinephrine

The biosynthesis of catecholamines mainly occurs in the body of the neuron, followed by transport with the help of axonal current to the nerve endings and entry into the vesicles. The stocks of norepinephrine (NE) in vesicles are represented by two forms: strongly bound and labile bound. Tightly bound NE is a reserve and is released from vesicles under the influence of various influences. It practically determines the total content of NE in the brain. Labile-bound NE accounts for 10–15% of the total amount of NE and is a functionally active form of NE that is involved in nerve impulse conduction. This form, unlike the first, is characterized by a high speed of metabolism. There is also a cytoplasmic form of NE, which is insignificant in volume, but intensively metabolizing. The labile-bound form of NE is replenished by the breakdown of tightly bound NE, uptake of cytoplasmic NE, and biosynthesis. The precursor of catecholamines is tyrosine, the hydroxylation of which occurs with the participation of tyrosine-3-hydroxylase. This reaction is the slowest in the biosynthesis of catecholamines, therefore it determines the flow rate of their synthesis. The next step in the biosynthesis of catecholamines, decarboxylation of dihydrooxyphenylalanine to dopamine, is catalyzed by dopa decarboxylase. In the brain, there is an excess of DOPA-decarboxylase, the highest activity of which is noted in the hypothalamus and midbrain, the lowest - in the cerebral cortex and cerebellum. A high activity of DOPA decarboxylase was also found in the capillaries of the brain, which is an obstacle to the penetration of DOPA into the brain due to the formation of dopamine, which does not pass well through the BBB [10].

The immediate precursor of NE is dopamine, which is involved in the functioning of the brain as a neurotransmitter. Hydroxylation of dopamine at the β-carbon atom to norepinephrine is carried out by the enzyme dopamine-β-hydroxylase. This enzyme is localized within vesicles that contain catecholamine and requires the presence of ATP, NAD, NADP and Ca^{2+} to be active. The final step in the biosynthesis of catecholamines, the methylation of NE to adrenaline, proceeds with the participation of the enzyme phenylethanolamine-N-methyltransferase. This reaction carries out the transition of a substance with pronounced neurotransmitter properties - NE to adrenaline, which is a typical hormone. The methyl group donor is adenosylmethionine. The activity of phenylethanolamine-N-methyltransferase in the brain is insignificant and the process of adrenaline biosynthesis proceeds here very weakly [11]. Two enzymes, Mono Amine Oxidase (MAO) and Catechol-Oxy-Methyltransferase (COMT), are involved in the catabolism of catecholamines. COMT along with MAO plays an important role in the inactivation of catecholamines. Unlike MAO, which catalyzes the oxidative deamination of catecholamines within the presynaptic space, COMT degrades catecholamines in the synaptic circuit. Projections of neurons in the locus coeruleus, containing norepinephrine neurons, are part of the ascending reticular activating system that regulates attention, arousal, and circadian rhythms. On the periphery, the adrenergic system determines the functioning of the sympathetic division of the autonomic nervous system, the effects of various

stressful effects on the body: control of the cardiovascular system, increased glycogenolysis in the liver, etc [12].

Dopamine

Dopamine is involved in the regulation of many bodily functions: modulation of blood pressure, cognitive processes, control of emotions and physical activity. The nigro-striatal dopamine system is responsible for the initiation and control of locomotor manifestations of vital activity. The loss of dopaminergic neurons in the midbrain (substantia nigra) leads to the development of Parkinson's disease, which is expressed in a violation of the inhibitory control over the contraction of striated muscles. Dopamine deficiency has been noted in Alzheimer's disease and schizophrenia. On the contrary, hyperactivity of the dopaminergic systems of the brain is observed during the development of manic states and hallucinations. Modulation of autonomic 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) [13]. Projections of locus coeruleus neurons are part of the ascending reticular activating system that regulates attention, arousal, and circadian rhythms. On the periphery, the adrenergic system determines the functioning of the sympathetic division of the autonomic nervous system, the effects of various stressful effects on the body: control of the cardiovascular system, increased glycogenolysis in the liver, etc [12].

Serotonin (5-Hydroxytryptamine)

The highest content of serotonin was found in the chromaffin granules of the cells of the gastrointestinal tract, spleen, platelets, where it performs a hormonal function, in the tissues of the brain and spinal cord it acts as a mediator. The highest concentrations of serotonin in the CNS are found in the hypothalamus and midbrain, the lowest - in the cerebellum. The concentration of serotonin in the gray matter of the brain is almost twice as high as in the white matter. The administration of serotonin to animals causes disturbances in the coordination of movements, a state of stupor and the phenomenon of catalepsy. With a decrease in the content of serotonin in the brain, aggressiveness appears. The CNS effects of catecholamines and serotonin are opposite. With a decrease in the concentration of serotonin in the brain, persistent insomnia is observed, which is removed by the introduction of the immediate precursor of serotonin, 5-hydroxytryptophan [14]. The half-life of serotonin is 10-30 minutes. Serotonin doesn't penetrate well through the BBB, but 5-hydroxytryptophan penetrates well through it. The limiting step in the synthesis of serotonin in serotonergic neurons is the formation 5-hydroxytryptophan depends on the entry of tryptophan into the brain through the BBB. The coenzyme of tryptophan-5-hydroxylase is pyridoxal phosphate.

Serotonin Metabolism

Inactivation of serotonin is carried out by its reuptake by the terminals and the action of MAO with the formation of 5-hydroxyindoleacetic acid. In nervous tissue, under conditions of increased formation of NADH·H+, serotonin can be converted into 5-hydroxytryptophol. Side pathways of serotonin metabolism are compensatory and are detected under conditions of MAO inhibition in pathology [15]. In other tissues, tryptophan and serotonin metabolism pathways exist through the formation of melatonin, tryptamine, and kynurenine.5-hydroxyindoleacetic acid.

The Melatonin Pathway: In the pineal gland, serotonin is a tissue hormone, turns into anantigonadotropic hormone - melatonin, which has a high biological activity involved in the regulation of the sleep-wake cycle.

The Kynurenine Pathway: This pathway of metabolism involves 80-90% of incoming tryptophan in the body. Occurs in the liver. Kynurenine and its metabolic products counteract the central effects of serotonin and tryptamine and inhibit the accumulation of tryptophan in the brain. The transition of tryptophan from the serotonin pathway to the kynurenine pathway may be the cause of mental depression.

The Tryptamine Pathway: When L-tryptophan is decarboxylated in the brain, tryptamine is formed, from which serotonin is not synthesized in the body. In liver microsomes, tryptamine can be hydrolyzed to form 6-hydroxytryptamine. The highest content of tryptamine was found in the cerebellum, cortex and basal ganglia. Tryptamine is an antagonist of reserpine. It is possible that the tryptamine pathway plays an important role in the genesis of schizophrenia. Confirmation of the involvement of serotonin in the activity of the central nervous system and the association with the onset of psychosis, is confirmed by the picture of poisoning by the competitive serotonin antagonist Lysergic acid Diethylamide (LSD), contained in ergot alkaloids, it is suggested that the central psychogenic effect of LSD is caused by its competition with serotonin for serotonin receptors in the brain [15].Serotonin has an effect on sleep stages. 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 movements of the eyeballs. According to the testimony of people awakened at this time, there are vivid dreams. Serotonin increases the duration of the orthodox sleep stage, and a drop in its content in the brain causes insomnia [16].

Histamine

The main source of histamine are basophilic leukocytes and mast cells in response to the action of various allergens. In the CNS, histaminergic neurons are located in the nuclei of the gray tubercle and mastoid bodies of the hypothalamic region of diencephalon. Their collaterals reach the telencephalon (cerebral cortex and hippocampus), thalamus, brainstem (central gray matter of the midbrain, nucleus of the solitary tract). In the brain, histamine is also found in mast cells in the interstitium. Histamine is formed by decarboxylation of the amino acid L-histidine by L-histidine decarboxylase [15]. Activity serves as a limiting factor in the accumulation of histamine in tissues. The half-life of synthesized neuronal histamine is about 30 minutes.

Histamine accumulates in synaptic vesicles and is released from nerve terminals by a Ca^{2+}-dependent mechanism. The mechanisms of histamine reuptake into neurons are not known. There are three subtypes of histamine receptors based on their pharmacological properties, synaptic localization, and mediated biological effects. All receptors belong to the superfamily of G protein-coupled receptors (metabotropic receptors):

1) H_1-receptors - are a glycoprotein of 490 amino acid residues located on the membrane of postsynaptic cells. The highest density of H1-receptors was noted in the thalamus, the pyramidal layer of the hippocampus, and the layer of Purkinje cells in the cerebellum. The action of histamine is realized by increasing the production of cAMP and the concentration of intracellular calcium. Antagonists of this group of receptors are used in the treatment of allergic diseases. Penetrating through the blood-brain barrier, they have an undesirable side sedative effect associated with the blockade of histamine receptors in the brain;

2) H_2-receptors - glycoproteins of 358 amino acid residues, located on the postsynaptic membrane of neurons of the caudate nucleus, putamen, amygdala and cerebral cortex, as well as glia cells. Due to the association of H_2-receptors with G proteins, their activation leads to an increase in the intracellular concentration of cAMP. Most selective H_2 -receptor antagonists are unable to cross the blood-brain barrier;

3) H_3-receptors - their selection 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. Their activation leads to inhibition of the secretion of ACh, dopamine, serotonin and norepinephrine. H_3-receptors are found in areas of the frontal cortex, basal ganglia, and substantia nigra of the midbrain. Intracellular effects are due to the activation of G-proteins.

4) Histamine is the main mediator of inflammation and allergic reactions in the body. Histamine secreted by neurons is involved in the regulation of cerebral circulation and the permeability of the walls of the blood vessels of the brain. Histamine is involved in the regulation of the sleep-wake cycle, energy balance, body temperature, food intake, various emotional states due to extensive histaminergic innervation of the components of the limbic system. A significant decrease in the number of histaminergic neurons is observed in the development of Alzheimer's disease.

Activation of H_1- and H_2-receptors of the cardiovascular system leads to pronounced changes in its work. Thus, the heart rate (H_2) increases, vasodilation occurs, and in the vessels of the microvasculature due to the contraction of actin filaments of endothelial cells, leading to an increase in the gap between the latter, an increase in their permeability (H_2) is observed. Histamine causes contraction of the smooth muscles of the intestine and bronchospasm but has no significant effect on the smooth muscles of the eye and genitourinary tract. Histamine stimulates gastric secretion by activating H_2-receptors in the parietal cells of the stomach [16].

GABA

GABA is the most important mediator of amino acid. In the brain of higher mammals, it performs inhibitory functions. Proof of its neurotransmitter role is the distribution of both GABA itself and the enzyme glutamate decarboxylase synthesizing it in the nervous structures associated with inhibition processes. In addition, there is a system of inactivation and reverse transport of GABA in the synaptic chain. The largest amount of GABA was found in the substantia nigra, globus pallidus, and hypothalamus. In terms of content in various parts of the central nervous system, GABA is many times higher than other neurotransmitters. So, in the hypothalamus, the total content of acetylcholine, norepinephrine, dopamine and serotonin is 10 μg/g, while the content of GABA in this part of the brain is 600 μg/g. The half-life of GABA in brain tissue is 10 minutes. Disturbances in the metabolism and balance of two amino acids - GABA and glutamic acid, from which the mediator is formed, is important in the genesis of seizures. A lack of vitamin B_6 in the brain leads to a decrease in the activity of pyridoxal-dependent enzymes. As a result, the content of GABA in the brain decreases and the level of glutamate increases. The consequence of this imbalance and especially the decrease in GABA is the occurrence of epileptiform seizures. In addition to postsynaptic inhibition, GABA is involved in presynaptic inhibition by reducing the secretion of acetylcholine from the presynaptic membrane. Along with this, due to the similarity of the chemical structure with acetylcholine, GABA can compete with it for receptor sites on the postsynaptic membrane [15,17].

Glycine and GABA are the main mediators mediating inhibition in the CNS due to pronounced hyperpolarization of postsynaptic cells due to the entry of negatively charged chloride ions into the cell. GABA receptors, which are widely represented on presynaptic terminals, act as heteroreceptors that control the release of the mediator from dopamine, norepinephrine, serotonin, and glutamatergic neurons. Activation of GABA receptors of the amygdala relieves anxiety, and a decrease in their number or blockade causes the development of convulsive conditions observed in epilepsy. The role of the GABAergic system of the brain in the processes of long-term memory and the development of some neurodegenerative diseases is not ruled out [18].

Glutamate and Aspartate

Glutamatergic and aspartatergic neurons within the CNS are of the greatest importance for the organism. They are especially widely represented in the cerebral cortex, from where their projections reach the hippocampus, caudate nucleus, amygdala, nucleus accumbens, superior colliculus and red nucleus of the midbrain, pontine nuclei. Another large cluster of glutamatergic neurons is found in the hippocampus. From here, their processes are sent to the cells of the hypothalamus, accessory nucleus and lateral septum. Glutamate mediates both fast (membrane depolarization) and slow (long-term

potentiation) synaptic processes. It is involved in the regulation of the secretion of pituitary hormones, the migration of neurons in the course of individual development. Increased release of glutamate and aspartate due to prolonged stimulation of glutamatergic pathways leads to the development of excitotoxic effects observed in ischemia, epileptic conditions, neurodegenerative diseases (Alzheimer's and Parkinson's diseases). These effects are due to the massive entry of Ca^{2+} into the cell and the achievement of concentrations that trigger the mechanism of cell death [19].

Receptors for Glutamate and Aspartate

They are represented by both ionotropic and metabotropic receptors, classified on the basis of pharmacological differences (the ability to be activated by specific agonists).

NMDA Receptors: N-methyl-O-aspartate acts as a specific agonist. They are widely represented in the cells of the cerebral cortex (layers II and III), the hippocampus, the basal nuclei, the olfactory bulb and the hypothalamus. They consist of five transmembrane proteins with different sites for binding (agonists, modulators of the ion channel conductivity - Mg^{2+} and a number of non-competitive antagonists, various activity regulators), forming an ion channel permeable to Na+, K+ and Ca^{2+} (ionotropic receptors). The NMDA receptor is organized into four transmembrane segments, of which the second segment is responsible for the formation of the ion channel and the formation of cytosolic sites for phosphorylation and glycosylation, including protein kinase C and calmodulin-dependent kinases. At rest, the ion channel formed by the NMDA receptor is blocked by Mg^{2+}. The blocking effect is removed during depolarization, after which positively charged ions enter the cell, causing further depolarization of the membrane. A manifestation of the activation of NMDA receptors is the entry of Ca^{2+} into the cell. In the case of prolonged activation of NMDA receptors, an excess amount of Ca^{2+}inside the cell has a toxic effect on neurons, causing their death.

AMPA Receptors: α-amino-3-hydroxy-5-isoxazolepropionic acid acts as a specific agonist. Numerous neurons of the neocortex (layer V), amygdala, caudate and accumbens nuclei, and the molecular layer of the cerebellum. They belong to ionotropic receptors, forming a transmembrane channel permeable to Na^+, K^+ ions. Under certain conditions, the ion channel can be permeable to Ca^{2+} ions. Molecular cloning methods established the presence of four types of AMPA receptors: $GluR_1(_A)$-$GluR_4(_D)$, consisting of approximately 900 amino acids. For each type of receptor, an alternative splicing variant is possible, leading to the emergence of the «flip» and «flop» isoforms, which determine the physiological properties of the formed channel. AMPA receptors can exist in both hetero- and homomeric configurations, however, in the latter case, the ion channel conductance is much lower.

Kainate Receptors: Kainic acid acts as a specific agonist. Widely represented in neurons of the cerebral cortex, hippocampus, nuclei of the reticular formation of the diencephalon. These receptors are associated with the formation of an ion channel permeable to Na^+, K^+ and Ca^{2+} ions. Presented in hetero- and homomeric forms. Kainate receptors are widely represented on the membrane of presynaptic terminals, which suggests their participation in the control of mediator release into the synaptic cleft.

Metabotropic Glutamate Receptors (mGluR): Quisqualate serves as a selective agonist. Their stimulation leads to the activation of various G-proteins, which is manifested in the inhibition of adenylate cyclase, stimulation of phospholipase and in direct action on potassium and calcium ion channels. There are eight subtypes of membranotropic glutamate receptors, formed from 854-1179 amino acids with a homology of 40%, and organized into three groups based on pharmacological properties and the second messenger used. They are widely represented among brain structures, located both on the post- (mGluR1) and presynaptic membranes (mGluR2) [20]. General characteristics of neuromodulators and neuropeptides. A significant number of peptides synthesized in neurons act as neuromodulators, i.e. substances capable of influencing the action of «classical» signaling substances (mediators). Due to their size, large protein molecules are unable to accumulate in synaptic vesicles, be released from presynaptic terminals, and interact with the receptors of the postsynaptic cell. Therefore, often in the course of normal development, a chain of no more than 30 amino acids, a neuropeptide, is randomly split off from them.

According to the "neuropeptide" postulate of D. de Wied (D. de Wied, 1987), neuropeptides include substances of a protein nature synthesized in nerve cells and realizing their action by activating receptors at the neuronal level. Depending on the ability of the representatives of the original family of neuropeptides to bind to the receptors of the postsynaptic membrane, they are divided into two groups:

1) Neuropeptides of common origin, activating various receptors - for example, substance P interacts with the NK_1 receptor, and neurokinins A interact with the NK_2 receptor;

2) Neuropeptides of common origin, activating common receptors - methenkephalin and leuenkephalin interact with the same 5-opioid receptor.

Unlike the synthesis of neurotransmitters, which occurs directly in the nerve endings, the formation of neuropeptides occurs on ribosomes in the cell body. Subsequently, the precursor molecule is transferred to the Golgi apparatus, where it is included in the composition of large electron-dense vesicles (100-200 nm) transported to the nerve terminals. Axon transport plays a special role in the transfer of neuropeptides to nerve endings. This is an active process not mediated by ordinary diffusion [21]. Depending on the speed of movement of intracellular organelles, there are:

1) Slow transport - the speed of movement is 1-2 mm / day. Through it, structural proteins, tubulin, and neurofilament proteins move;

2) Fast transport - the speed of movement reaches 400 mm

/ day. Transfer of mitochondria and various vesicles, including synaptic vesicles.

Depending on the direction of movement of the transferred components, there are:

1) Anterograde transport - movement towards the end of the axon;

2) Retrograde transport - movement towards the cell body.

The removal of an excess amount of neuropeptide occurs by its cleavage by means of membrane peptidases (metallopeptidases). The presence in one neuron of two or more neuropeptides and / or neurotransmitters creates opportunities for their interaction with each other: strengthening or weakening the postsynaptic action of each, strengthening or weakening the processes of release and capture. The relatively large size of most neuropeptides makes it difficult for them to penetrate the blood-brain barrier, limiting their action to the region of the brain and spinal cord.

Tachykinins and Substance P

This group includes neurokinin A, neurokinin B and substance P. There are three main types of tachykinin receptors: NK_1, NK_2 и NK_3, the endogenous agonists of which are substance P, tachykinins A and B. A high concentration of tachykinins and substance P was found in various parts of the central nervous system: the spinal cord, caudate and accumbens, tonsils. A high concentration in substance P is characteristic of substantia nigra neurons. Colocalization of substance P and tachykinins (neurons of the striatum, sensory neurons of the spinal cord), substance P and GABA (some interneurons of the cortex and hippocampus) were noted [22]. Tachykinins and substance P are integrated into neural networks responsible for the perception of pain sensations (nociception). They act as a transmitter of pain signals at the level of the spinal cord (neurons of small diameter of the posterior horns), mediate the course of inflammatory processes (stimulate the release of histamine by mast cells) [23].

Opioid Peptides

This group includes dynorphin, methenkephalin, leuenkephalin, endorphin, nociceptin. They have the ability to interact with receptors activated by exogenous morphine application. Neurons containing opioid peptides are widely represented in various parts of the brain and spinal cord. Their concentration is especially high in the neurons of the diencephalon (hypothalamic nuclei and tonsils). In addition to controlling pain sensitivity, the opioid system is involved in the implementation of breathing, eating behavior, stress-induced behavioral programs, etc. The action of opioids is not limited to the development of inhibitory processes in the central nervous system. In some cases, excitation is provided indirectly, for example, during release. Inhibition of the work of some inhibitory elements of the nervous system under the influence of opiates (GABAergic neurons) leads to synaptic facilitation in the neuronal networks of the hippocampus [24].

Galanin

It is known that there are three types of galanin receptors: $GAL(_R)_1$, $GAL(R)_2$ and $GAL(_R)_3$ with 40-50% homology to each other. Galanin mediates inhibitory effects in learning and memory processes, as well as in the development of pain sensations.

Neurotensin

The neuropeptide is found exclusively in the neurons of the hypothalamus and amygdala, in smaller quantities they are present among the cells of the thalamus, substantia nigra, caudate nucleus and putamen, and spinal cord. Neurotensin is often colocalized along with other neuropeptides (enkephalins, cholecystokinin) and neurotransmitters (dopamine, norepinephrine, GABA). Three types of neurotensin receptors are known to exist: NT_{R1}, NT_{R2}, and NT_{R3}. Participation of neurotensin in thermoregulation (causes hypothermia), eating behavior (reduces food intake), mediation of analgesic effects, in interaction with dopaminergic nigrostrial and mesolimbic systems of the brain is shown. It dilates peripheral blood vessels, causing a drop in blood pressure, and increases blood sugar levels (hyperglycemia) [25].

Neuropeptide Y

Neurons containing neuropeptide Y are located in the hypothalamic nuclei, amygdala and hippocampus. All receptors for neuropeptide Y (Y_1, Y_2, Y_4, Y_5, Y_6) are metabotropic receptors. Neuropeptide Y is distributed in the central nervous system, is involved in the regulation of the cardiovascular system, food intake and digestion, in the control of circadian rhythms, and regulates the release of sex hormones. It is known about the participation of neuropeptide Y in the mechanisms of learning and memory, the formation of anxiety states [26].

Neuromodulators - Derivatives of Fatty Acids

This group includes eicosanoids formed from unsaturated C_{20} fatty acids containing from three to five double bonds. The main source of eicosanoids is the essential arachidonic acid, synthesized in all cells of the body.

Eicosanoids

They are divided into two main groups:

1) Prostanoids, which include prostaglandins, prostacyclins and thromboxanes;

2) Leukotrienes.

A special group of eicosanoids is anandamide, which binds to specific (cannabinoid) receptors in the brain. The first step in the formation of eicosanoids is the release of arachidonic acid from phospholipids under the action of cytosolic phospholipase A_2. It can be activated by a specific protein, as well as due to stimulation of certain types of receptors (NMDA or 5-HT_2). Prostaglandins and thromboxanes are formed from arachidonic acid under the action

of cyclooxygenase, and leukotrienes are formed under the action of lipoxygenase. It is known about the existence of receptors for prostaglandins (PGD_2 and PGE_2) in the peripheral and central (practically in all parts of the brain) nervous system. The role of thromboxanes and leukotrienes in the CNS is not well understood. Eicosanoids are involved in the regulation of inflammation, pain, fever, and blood pressure. At the cellular level, they are able to modulate the work of ligand-gated ion channels, inhibit the activity of Na^+/K^+-ATPase and neurotransmitter reuptake systems. It is assumed that the mechanisms of long-term potentiation in hippocampal neurons involve arachidonic acid, which is released upon stimulation of NMDA receptors [27].

Anandamide

This endogenous substance has been found in the brain. It is able to activate cannabinoid receptors at very low concentrations. The exact sites of anandamide synthesis in the brain are unknown. Depolarization of neurons leads to the release of anandamide into the extracellular space, from where its excess can be removed using an unidentified transporter by the reuptake mechanism. Anandamide is further converted to 12- or 15-hydroperoxyanandamide by lipoxygenase or to arachidonic acid by hydrolase. There are two types of cannabinoid receptors: CB_1 and CB_2, the differences between which are based on pharmacological properties. CB_1 receptors have been identified in the cerebral cortex, olfactory bulb, hippocampus, basal ganglia, and cerebellum; their stimulation leads to deactivation of N-type calcium channels CB_2 receptors are characteristic of peripheral tissues (macrophages and mast cells) and are not found in the CNS. Cannabinoids are involved in the regulation of pain sensitivity (antinociceptive action), the development of hypothermia, and the inhibition of spontaneous locomotor activity.

Extracellular Purines and Pyrimidines as Neuromodulators

Purines (adenosine, ADP and ATP) and pyrimidines (UDP and UTP) are among the most important signaling molecules. We can say that only ATP is a classic neurotransmitter, other substances of purine and purinergic nature do not have the necessary properties. ATP is widely represented as a cotransmitter through oxidative phosphorylation of glucose in mitochondria. Its main share is used to maintain the work of ATPases, and the rest of ATP enters the synaptic vesicles, acting as a neurotransmitter. The extracellular concentration of adenosine is regulated by a dual mechanism: bilateral membrane transfer and enzymatic cleavage (adenosine deaminase and kinase). Despite the significant role played by the purinergic system in the regulation of the activity of internal organs, its participation in the work of the central nervous system remains the subject of intensive study. Thus, an increased extracellular concentration of ATP leads to cell hyperexcitability and enhances the perception of pain (in this case, it is ATP coming from destroyed cells that is one of the pain mediators). In the hippocampus, its involvement in the processes of memory and learning has been confirmed. Unlike ATP, adenosine has a predominantly calming effect, reducing the release of many neurotransmitters (dopamine, GABA, glutamate, acetylcholine, dopamine, serotonin, norepinephrine). The involvement of purinergic transmission in the control of the work of a number of neural rhythm generators, in particular the respiratory one, cannot be ruled out [28].

A neural impulse releases a chemical component called a neurotransmitter at the end of the nerve fiber, which then transfers the impulse to another nerve fiber. Four neurotransmitters fall within the category of biogenic amines [1]. These include adrenaline, norepinephrine, dopamine, and serotonin. According to the action (direct or neuromodulatory), function (excitation - epinephrine, norepinephrine, or inhibition - serotonin, GABA) or, more specifically, the chemical structure of NTs may be used to classify them. Biochemical monoamines include serotonin, histamine, and catecholamines (dopamine, norepinephrine, and epinephrine). Non-monoamine Examples of NTs (such as ATP and adenosine), purines, and gasotransmitters include nitric oxide, carbon monoxide, and hydrogen sulfide [2].

Conclusion

According to all evidence and based on confirmed findings, it is clear that the markers of neurotransmitters play a variety of biological roles in addition to their neurological and pathogenic effects on the human body. Additionally, the presence of neurotransmitter markers can be employed as a diagnostic tool for a variety of illnesses, not just neurodegenerative ones. Thus, the data on neurotransmitters presented in the article create a fundamental basis for further research in this area and will serve as the basis for subsequent clinical trials to prevent and correct the pathology of the nervous system.

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