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The role of copper compounds in neurological disorders due to their excessive or insufficient supply to the brain tissue

Abstract: This literature review covers the topic of nervous system disorders caused by defects in copper metabolism in brain tissue. The role and participation of this element in many physiological functions of the central nervous system in normal and pathological conditions are identified and described. Neurodegenerative disorders in which there is an accumulation of "free" copper in the brain tissue are considered (Alzheimer's, Wilson, Menkes). Genetic diseases caused by excessive or insufficient copper intake in the brain tissue, which manifest as neurological disorders, are described. Particular attention is paid to the features of copper metabolism in brain tissue with neurological disorders. This direction is also complemented by a description of pathological changes during the deposition of copper in the nervous system. The article reveals the mechanisms of toxicological effects in case of excessive intake of copper in the nervous tissue of experimental animals.

Keywords: copper, brain tissue, central nervous system, excess and deficiency of copper, neurodegenerative disorders, Wilson's disease.

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Copper is a trace element that can be found in every cell of the human body. Copper plays an important role in the health of the central nervous system, especially brain tissue. The concentration of copper in the brain is relatively high compared with other organs of mammals, and the distribution of copper depends on the brain area, subcellular position, age, environmental and genetic factors [1]. Interest in the study of the effect of copper on the nervous system is not accidental, it is due to the fact that the subclinical neurobehavioral effects of copper, both from excessive dietary input and from the environment, are rarely described and not studied systemically. At the same time, in industrial regions where copper ore processing plants and copper smelting plants operate, an excessive supply of copper in the body is not uncommon and requires studying [2].

As an essential element, copper is part of more than 30 different body enzymes, including ceruloplasmin, cytochrome C-oxidase, superoxide dismutase, necessary for the development of the immune and central nervous system.

Many enzymatic reactions that are necessary for the normal functioning of the brain and nervous system are catalyzed by copper enzymes. Thus, dopamine-monooxidase catalyzes the conversion of the neurotransmitter dopamine to noradrenaline [3]. Monoamine oxidase plays a role in the metabolism of the neurotransmitters noradrenaline, adrenaline and dopamine [4, 5]. Copper-dependent enzymes are involved in the regulation of gene expression, enhancing or inhibiting the transcription of certain genes [6].

It has been established that a decrease or absence of ceruloplasmin activity disrupts the supply of sufficient amounts of copper to tissue respiration enzymes, while free copper accumulating in tissues blocks the SH-groups of many enzymes. The consequence of insufficient use of copper is its deposition in the tissues of the liver, brain, kidneys, cornea, and other organs. A paradoxical situation arises: the disruption of biological processes due to an insufficient amount of copper and the accumulation of copper in tissues with symptoms of intoxication [3].

Copper is involved in many physiological functions of the central nervous system, including modulating the excitability of neurons, as a result, intoxication with copper compounds can lead to functional disorders of the nervous system [7]. Since copper is involved in many functions necessary for such fundamental processes as phospholipid synthesis of cell membranes, regulation of

neurotransmitters, energy synthesis, maturation of the extracellular matrix of neuropeptides, neuroendocrine signaling, elimination of free radicals [8, 9], its role in the functioning of the nervous system is extremely large.

As a rule, copper does not act as an independent element of metabolism, it is always in the composition of certain active compounds, therefore, excess copper, not bound to protein compounds, becomes toxic and is able to settle in various organs. Excess copper in the body can result from its presence in prostheses, pesticides, contacts with copper cookware, in pools with water treatment with copper sulphate, hemodialysis, use of hormonal contraceptives, overdose of copper-containing drugs, etc [8]. In addition, the concentration of copper in the blood increases with acute and chronic inflammatory processes, diseases of the liver, kidneys, alcoholism, myocardial infarction, certain types of anemia, malignant tumors, after extensive surgical interventions [7].

The need for copper for the normal course of embryogenesis has been proven. It was established experimentally that perinatal copper deficiency in animals leads not only to long-term neurochemical changes, but also to behavioral disturbances. With prolonged copper deficiency in the body, nerve fibers, like heart muscle fibers, die irreversibly [10].

In the case of chronic poisoning with copper and its salts, functional disorders of the nervous system are possible. In particular, this pathology occurs in swimmers (due to water colouring using copper sulfate), which is accompanied by functional disorders of the nervous system, ulceration and perforation of the nasal septum, dry skin and other injuries [11, 12].

It is noted that the accumulation in the brain tissue of "free" copper (not associated with ceruloplasmin) is characteristic of such neurodegenerative diseases as Alzheimer's disease, Wilson's disease, Parkinson's disease, Menkes disease, amyotrophic lateral sclerosis, prion diseases, etc. Although these diseases are multifactorial, their unifying factor is the accumulation of copper, which is believed to initiate oxidative stress, disrupting the production of cytochrome C oxidase and SOD 1, which contributes to the accumulation of proinflammatory cytokines (IL-l?, IL-6, IL-12 and others), and subsequently, induced mitochondrial apoptosis and nervous degeneration [13-17].

Genetic diseases of excessive copper retention are well described. One of the diseases that is accompanied by an increase in the concentration of copper in organs and tissues and well demonstrates significant neurological complications is Wilson- Konovalov disease. This disease has an autosomal recessive mode of inheritance and occurs with a frequency of 1: 30000 [7].

The main enzymes that provide copper transport in the body are ATPases ATP7A and ATP7B. In enterocytes and the choroid plexus of the brain, mRNA belonging to ATP7A was detected. This enzyme is involved in the process of absorption of copper in the intestine and its penetration into the brain. The pathogenesis of the Wilson-Konovalov disease is based on the mutation of the ATP7B gene in chromosome 13, which encodes the synthesis of another Cu-ATPase, or Wilson's protein. ATP7B has 6 copper-binding motifs. It transports copper ions from the cell due to the energy of ATP splitting, and also participates in the formation of functionally active ceruloplasmin from apoceruloplasmin, which is then released into the blood. The absence of ATP7B disrupts the release of copper from the brain into the bloodstream, from the blood to the bile, and further from the body. Normally, this gene is significantly expressed in the liver, kidney and placenta, and weakly in the brain, heart, muscles and pancreas. Its mutation prevents the removal of copper from the bile and the formation of ceruloplasmin from apocероloplasmin, which causes the accumulation of copper in the liver and a decrease in the concentration of ceruloplasmin in the blood. Although the excretion of copper in the urine increases in this case, there is a delay of copper in the body during its normal absorption. As a result of a mutation in the blood, the concentration of plasma proteins, ceruloplasmins, which are responsible for the transport of copper in the body, sharply decreases. Neuronal ATP7A is concentrated in the perinuclear region and can be found in neurites in vitro [18] and in vivo [19].

At the age of 6 years and older, neuromuscular disorders occur: limb tremor, dysarthria (scanning speech) and dystonia (muscle tone disorder). Later neuropsychiatric complications prevail: changes in personality and behavior, reduced learning ability [5]. Free, non-ceruloplasmin toxic copper is deposited in the liver, brain and eye structures, kidneys and other organs. Clinical manifestations depend on the accumulated amount of free toxic copper in various organs [20-22].

According to its manifestations, Wilson-Konovalov's disease can have two leading clinical forms: mainly liver pathology and mainly nervous system pathology [23].

As shown in some studies [24, 25], the brain is most actively depositing free toxic copper, which causes varying degrees of severity of pathological changes in its structures. Moreover, all pathological changes in the brain are divided into angiotoxic and cytotoxic. Atony of small vessels and capillaries of the brain, stasis, minor hemorrhages and perivascular edema are manifestations of angiotoxic brain damage during copper intoxication. Such disorders lead to ischemia of the nervous tissue and its subsequent death. Circulation disorders are found predominantly in areas of the gray matter of the brain with a developed vascular system, while the content of copper in the cerebrospinal fluid is increased [26-30]. The accumulation of free toxic copper in the brain, mainly in the subcortical nodes, leads to dystrophic changes in nerve cells and their death.

Among the mental disorders that develop in 20In patients with cerebral dystrophy, caused by an excess of copper in the brain tissue, it can be detected by neuroimaging. According to various studies, structural focal changes occur in the form of bilateral symmetrical areas in the region of the basal ganglia. Similar foci are found in the thalamus, trunk and cerebellum [31-34].

Dynamic studies of patients with hepatocerebral dystrophy using MRI, performed by S. Sinha et al, revealed the presence of diffuse atrophy in the cortex and cerebellum [35], which was confirmed by A. Shanmugiah et al. [36], which MR-spectroscopically revealed a deficiency of dopaminergic (D2) receptors in the subcortical ganglia. Kaladjian et al. [24, 36, 37] suggest that bipolar mental disorders are likely due to disorders in the limbic structures of the brain.

According to some reports, the distribution of copper varies in different areas of the brain. In experimental modeling of Wilson's disease in rats, it was shown that there is more copper in the gray matter of the brain than in the white matter [37]. According to Rajan et al. [36], the highest concentration of copper is found in the rat hypothalamus. High levels of copper were observed in the medial cranial nucleus, in the central gray matter near the cerebral aqueduct in adult rats [38].

In animals with chronic copper intoxication, histopathological changes in the cerebral cortex were detected, such as degenerative changes of neurons with pyknotic nuclei and dense eosinophilic cytoplasm, accompanied by astrogliosis. However, according to some assumptions [35], the observed impairments of motor behavior and memory were associated with the deposition of copper in the striatum and hippocampus, which is apparently due to the deterioration of synaptic transmission [39, 40].

In vitro, it has been shown that synaptosomes can absorb copper, and membrane depolarization stimulates the release of copper [41]. The most characteristic morphological sign of brain damage in Wilson-Konovalov disease is a progressive change in the subcortical ganglia, primarily lenticular nuclei (n. Lenticularis), mainly the putamen, as well as the caudate nucleus, the outer segment of the globus pallidus, and the dentate nucleus of the cerebellar cortex, which affects the motor function of the body. Thus, the pathological process is very common [2, 42]. During the pathological-anatomical study of the brain, macroscopic and microscopic changes in the brain substance were detected, wrinkling of the brain substance and the formation of cavities were observed. Microscopically, peculiar changes of glia can be observed, called Alzheimer type I and II glia. Type I is characterized by a sharp increase in the size of the entire cell and a large nucleus rich in chromatin. Type II is characterized by an almost complete absence of cytoplasm and a giant nucleus, which is very poor in chromatin and therefore has the appearance of a "bare" nucleus [42].

Wilson-Konovalov disease, as previously mentioned, is a genetic disease and this ailment is very rare, and an excess of copper as a whole, according to statistical information, is much less common than the lack of this element.

Another well-known hereditary disease - Menkes syndrome - a congenital disorder of copper metabolism. The symptom complex is caused by mutations in the ATP7A gene, which encodes the copper-transporting ATP-ase, alpha polypeptide (ATP7A; MIM * 300011), which is involved in the absorption of copper from food and the transfer of ions of this metal to other cells [43].

In Menkes syndrome, there is a defect in the absorption of copper, its excessive accumulation in the kidneys, while the liver and brain suffer from its deficiency. This leads to changes in blood vessels and deterioration of the brain. Menkes disease is characterized as a recessive disorder with growth

retardation, brittle hair and focal degeneration of the brain and cerebellum [44]. Neurodegenerative processes alter the gray matter of brain-damaged twisted cerebral arteries [43].

Decreased supply of copper reduces the activity of copper enzymes (for example, lysine oxidase), which are necessary for the structuring and functioning of bones, skin, hair, blood vessels and the nervous system [45].

Menkes syndrome is quite rare, about 1: 50,000 - 1: 200,000 births. Most often it affects men. Most children born with Menkes syndrome have a life expectancy of 3 to 5 years. By three months, growth retardation becomes evident, psychomotor retardation and its progressive disorders with the loss of previously acquired skills, convulsions appear. From now on, degenerative processes in the central nervous system become dominant in the clinical picture. When conducting angiography in the brain, internal organs and limbs, elongated, crimped arteries of various sizes with alternating areas of expansion and contraction are detected [46].

Along with the above, modern research confirms the excess of the copper content in brain tissue in the case of an acquired neurodegenerative disease, such as Alzheimer's disease [47], which also indicates the involvement of copper in the pathogenesis of neuro-damage.

As is known from literary sources, in Alzheimer's disease, the hippocampal neurons responsible for memorization are primarily affected. Therefore, memory loss, and especially difficulty remembering recently learned information, is usually the first sign of illness [47].

In the brain tissue, there is a strict regulation of metals, preventing damage that can potentially be caused by oxidative damage by the base metals. In fact, oxidative damage found in neurodegenerative diseases is probably due to higher levels of these metals. The involvement of intracellular transporters for copper has been shown in animal models of Alzheimer's disease [48], which increased the likelihood of higher levels of metals being associated with impaired transporter activity. Consequently, the potential effects of toxicants that affect the activity of transporters may contribute to the emergence and progression of neurodegenerative diseases [48].

There is an assumption that copper-induced hydroxyl radical formation contributes to the development of Alzheimer's disease. An excess of copper leads to retention in the brain tissue of beta-amyloid whites, which later form into amyloid plaques characteristic of Alzheimer's disease [1].

Beta amyloid proteins are a byproduct of the activity of brain neurons. Under normal conditions, a purification system is functioning - a protein related to the lipoprotein receptor-related protein 1 (LRP1), which binds amyloid beta-cells and "forwards" them from the cells to the blood vessels through which toxic proteins leave the brain. With excessive admission to the nervous system, copper impedes this process [49]. Research has found that copper contributes to the oxidation of LRP1; in its oxidized form, it does not function and does not purify nerve cells from beta-amyloids. However, experiments with human endothelial cell culture of the human brain have shown that small doses of copper reduce the level of LRP1 and its ability to bind and excrete beta amyloid [50].

Different parts of the brain accumulate copper compounds to varying degrees, apparently due to age, blood flow intensity, damage to the blood-brain barrier, and the activity of copper-transporting proteins [50].

ith age, copper has been found to accumulate in the cells of the walls of the brain capillaries (endothelial cells), which provide a protective role for the blood-brain barrier and limit the penetration of harmful substances into the brain. The accumulation of metal in the brain tissue with age causes a toxic effect, which has been proven in experiments with animals. Thus, in experiments with mice, which for three months were given water with low copper content (0.13 mg / l) (10 times less than the MPC of copper ions in water, but 52 times more than usually happens in water which animals drink), by the end of the experiment, the copper content in the walls of the brain capillaries increased almost 2.6 times, and the concentration of the protective protein LRP1 was halved. Such changes usually occur with 25-28-month-old mice, that is, the brains of young animals that received copper are similar to the brains of venerable mouse elders [51].

There are observations of sheep when insufficient intake of copper during pregnancy caused enzootic ataxia in lambs due to degenerative disorders in the form of diffuse symmetric demyelination of the central nervous system. This disease is also known as the "saddle back" or "sagging back",

since the main symptom is spinal curvature. The characteristic neurological symptoms of this disease are spastic paresis of the lower part of the body, severe impairments in motor coordination [47]. Disorders of the central nervous system are also confirmed in experiments on guinea pigs with a lack of copper in food [52].

In experiments with impaired blood-brain barrier in mice, unobstructed passage of copper into the brain and its influence on the activity of neurons was observed. In addition, the formation of beta-amyloid proteins and their complexes was stimulated. In addition, copper has been shown to cause inflammation of brain tissue, which also contributes to the disruption of the blood-brain barrier and the accumulation of toxins [53].

In ultrastructural studies on sheep with chronic copper sulfate poisoning, changes in brain tissue were detected in the form of an increase in the volume of astrocytic nuclei, vacuolization of white matter. At the same time, astrocytes contained more glycogen, mitochondria and the endoplasmic reticulum than usual [54]. The authors suggest that the changes found are associated with impaired metabolic processes in glial transport mechanisms.

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The introduction of copper sulfate to mice of the SFLP during pregnancy has a damaging effect, which is determined by the stage of embryonic development. Introduction on the 7th day of pregnancy caused resorption of all embryos, with the introduction on the 8th day, anomalies of the neural tube and the heart were detected, when exposed on the 9th day - weak embryotoxic and teratogenic effects. A significant number of fetuses examined on the 12th day of gestation had exencephaly [55].

In an experiment using CT scans or MRI, atrophy of brain tissue and cerebellum, decrease in the density of white matter areas of the brain, presence of subdural hematomas, expansion of the salvian sulcus, pachygyria are found [55].

A morphological study of the brain reveals areas of gray matter degeneration with neuron loss and gliosis, especially in the cerebellum. When electron microscopy detects an increase in the number of mitochondria, a change in their size, electron-dense little bodies inside them. In the white matter - axonal degeneration [55].

When conducting the experiment with the use of acute induction with heavy metal salts, changes in the behavior of rats were very pronounced, which shows more significant disturbances in higher nervous activity. This indicates the onset of a phase of short-term adaptation of higher nervous activity to the toxic effects of metal salts during chronic intoxication. The behavioral data of rats with copper ion poisoning are consistent with the accumulation of metal ions in brain cells and cytomorphological studies, where malignant tumors were observed in brain cells, which resulted in changes in animal behavior, manifested in a decrease in motor and emotional activity. When poisoning with zinc and iron salts, accumulation of these metals in the brain cells was less, cytomorphological results showed atypical cells without malignancy, changes in behavioral reactions of rats were less pronounced [55].

Thus, the foregoing indicates the important role of copper and its compounds both during the embryonic phase of the central nervous system and during the functioning of the mature brain. At the same time, both inadequate entry into the brain tissue and its excess can cause serious disturbances in the morphological structure of various brain regions, and, consequently, in the functioning of the latter. The above confirms the need for further study of the metabolism of copper in brain tissue.

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Роль соединений меди в неврологических нарушениях при избыточном или недостаточном поступлении в мозговую ткань

Аннотация: В данном литературном обзоре затрагивается тема расстройств нервной системы, вызванных нарушением метаболизма меди в мозговой ткани. Выделяются и описываются роль и участие элемента во многих физиологических функциях центральной нервной системы в норме и при патологических состояниях. Рассматриваются нейродегенеративные нарушения, при которых отмечается накопление в мозговой ткани "свободной" меди (болезни Альцгеймера, Вильсона, Менкеса). Описаны генетические заболевания, вызванные избыточным или недостаточным поступлением меди в мозговую ткань, которые проявляются выраженными неврологическими нарушениями. Особое внимание уделено особенностям метаболизма меди в мозговой ткани при неврологических нарушениях. Данное направление дополняется также описанием патоморфологических изменений при депонировании меди в нервной системе. В статье раскрываются механизмы токсикологического воздействия при избыточном поступлении меди в нервную ткань экспериментальных животных.

Ключевые слова: медь, мозговая ткань, центральная нервная система, избыток и недостаток меди, нейродегенеративные нарушения, болезнь Вильсона.

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Мыс қосылыстарының ми ұлпасына артық немесе жеткіліксіз түскен кездегі неврологиялық бұзылулардағы рөлі

Аңдатпа Бұл әдеби шолуда ми ұлпасындағы мыс метаболизмінің бұзылуынан туындаған жүйке жүйесінің бұзылыстары тақырыбы қозғалады. Қалыпты және патологиялық жағдайларда орталық жүйке жүйесінің көптеген физиологиялық функцияларында элементтің рөлі мен қатысуы ерекшеленеді және сипатталады. Нейродегенеративті бұзылулар қарастырылады, онда ми ұлпасындағы "бос" мыстың (Альцгеймер, Вильсон, Менкес аурулары) жиналуы байқалады. Мыстың ми ўлпасына артық немесе жеткіліксіз түсуінен туындаған генетикалық аурулар сипатталған. Неврологиялық бұзылулар кезінде ми ұлпасындағы мыстың метаболизмінің артықшылықтарына ерекше көңіл бөлінген. Бұл бағыт мысты нерв жүйесінде депонирлеу кезінде патоморфологиялық өзгерістердің сипаттамасымен толықтырылады. Мақалада тәжірибиелік жануарлардың жүйке ұлпасына мыстың артық түсуі кезіндегі токсикологиялық әсер ету механизмдері ашылады.

Түйін сөздер: мыс, ми ұлпасы, орталық нерв жүйесі, мыстың артықшылығы мен жетіспеушілігі, нейродегенеративті бұзылыстар, Вильсон ауруы.

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