REVIEWS

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MOLECULAR MECHANISMS DEFINING APPLICATION OF GLYCINE AND ZINC COMBINATION IN CORRECTION OF STRESS AND ANXIETY MAIN MANIFESTATIONS

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The aim of the work was to carry out a systematic analysis of the molecular mechanisms that determine the possibility of a combined use of amino acid glycine and zinc compounds for the treatment of patients with manifestations of stress and anxiety.

Materials and methods. Information retrieval (Scopus, PubMed) and library (eLibrary) databases were used as research tools. In some cases, the ResearchGate application was applied for a semantic search. The analysis and generalization of references was carried out on the research topic, covering the period from 2000 to the present time.

Results. It has been shown that amino acid glycine, along with gamma-aminobutyric acid (GABA), is a key neurotransmitter that regulates physiological inhibition processes in the central nervous system (CNS) by increasing transmembrane conductance in specific pentameric ligand-gated ion channels. The introduction of zinc ions can potentiate the opening of these receptors by increasing their affinity for glycine, resulting in an inhibitory processes increase in CNS neurons. The replenishment of the glycine and zinc combined deficiency is an important element in the correction of a post-stress dysfunction of the central nervous system. A balanced intake of zinc and glycine is essential for most people who experience daily effects of multiple stresses and anxiety. This combination is especially useful for the people experiencing a state of chronic psycho-emotional stress and maladaptation, including those who have a difficulty in falling asleep.

Conclusion. A balanced maintenance of the zinc and glycine concentration in the body of a healthy person leads to the development of a stable anti-anxiety effect, which is accompanied by the normalization of the sleep-wake rhythm, which makes it possible to have a good rest without any loss of working efficiency after waking up.

Keywords: glycine; zinc; anxiolytic agents; brake action; anxiety states

Abbreviations: GABA – gamma-aminobutyric acid; pLGICs – pentameric ligand-gated ion channels; CNS – central nervous system; GlyR – glycine receptor; MT – metallothioneins; ROS – reactive oxygen species; RNS – reactive nitrogen species; SHMT – serine hydroxymethyltransferase; GCS – glycine cleavage system; VIAAT – vesicular inhibitory amino acid transporter; BBB – blood-brain barrier.

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МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ, ОПРЕДЕЛЯЮЩИЕ ПРИМЕНЕНИЕ КОМБИНАЦИИ ГЛИЦИНА И ЦИНКА В КОРРЕКЦИИ ОСНОВНЫХ ПРОЯВЛЕНИЙ СТРЕССА И ТРЕВОГИ

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Цель. Работа посвящена системному анализу молекулярных механизмов, определяющих возможность комбинированного использования аминокислоты глицин и соединений цинка для лечения пациентов с проявлениями стресса и тревоги.

Материалы и методы. В качестве инструментов проведения исследования использовались информационно-поисковые (Scopus, PubMed) и библиотечные (eLibrary) базы данных. В ряде случаев для семантического поиска использовалось приложение ResearchGate. В работе осуществлялся анализ и обобщение научной литературы по теме исследования, охватывающей период с 2000 по настоящее время.

Результаты. Показано, что аминокислота глицин, наравне с гамма-аминомасляной кислотой (ГАМК) является ключевым нейромедиатором, регулирующим процессы физиологического торможения в центральной нервной системы (ЦНС) путем увеличения трансмембранной проводимости в специфических гетеропентамерных лигандзависимых хлорных каналах. Введение ионов цинка способно потенцировать открытие данных рецепторов путем увеличения их сродства к глицину, в результате чего происходит усиление процессов торможения в нейронах ЦНС. Восполнение сочетанного дефицита глицина и цинка является важным элементом коррекции постстрессорной дисфункции ЦНС. Сбалансированное потребление цинка и глицина имеет важное значение для большинства людей, ежедневно испытывающих последствия многочисленных стрессов и находящихся в тревожном состоянии. Особенно полезна данная комбинация для лиц, испытывающих состояние хронического психоэмоционального напряжения и дезадаптации, в том числе имеющих сложности с засыпанием.

Заключение. Сбалансированное поддержание концентрации цинка и глицина в организме здорового человека приводит к развитию стойкого противотревожного эффекта, который сопровождается нормализацией ритма сон-бодрствование, что дает возможность полноценного отдыха без потерь работоспособности после пробуждения.

Ключевые слова: глицин; цинк; анксиолитические средства; торможение; тревожные состояния

Список сокращений: ГАМК – гамма-аминомасляная кислота; pLGICs – гетеропентомерные лиганд-зависимые хлорные каналы; ЦНС – центральная нервная система; GlyR – глициновый рецептор; МТ – металлотионеины; ROS – реактивные формы кислорода; RNS – реактивные формы азота; SHMT – серин гидроксиметилтрансфераза; GCS – митохондриальная система расщепления глицина; VIAAT (vesicular inhibitory amino acid transporter) – везикулярный переносчик тормозных аминокислот; ГЭБ – гематоэнцефалический барьер.

INTRODUCTION

A negative impact of stress and anxiety is experienced by an increasing number of people in the modern world, regardless of age and gender [1]. It is known that stress is also called a state of acute or chronic psycho-emotional tension. It should be also notified that anxiety disorders are significant psychosocial risk factors for the development of many chronic noncommunicable diseases [2]. Taking into account the growing need for timely therapy and prevention of disorders associated with the development of stress and anxiety, the search and development of safe and effective means for their correction are becoming increasingly important.

Treatment regimens for anxiety states of various

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origins are based on the use of a number of anxiolytic psychotropic drugs [3]. The molecular mechanism of their anti-anxiety action is based on a long-term increase in the activity of subclass A gamma-aminobutyric acid (GABA) receptors [4]. This class of membrane receptors responsible for the inhibition in neurons belongs to the family of pentameric ligand-gated ion channels (pLGICs) [5, 6]. The interaction of the agonist with the receptor, leading to the opening of a selective anion channel on the surface of the excitable membrane, leads to an increase in the Cl^- flux, which causes hyperpolarization of the neuron [7]. This activation of the transmembrane anionic current through the GABA receptors makes it possible to consider GABA as the main inhibitory neurotransmitter in the central nervous system (CNS) in the classical approach to neurophysiological processes [8]. Along with this, the second most physiologically important mediator that causes inhibition in the neurons of the spinal cord and brainstem is amino acid glycine [9]. This neurotransmitter, along with GABA, is present both in specific glycinergic and mixed synapses and is widely distributed in different parts of the brain. It also activates the transmembrane conductivity of chloride ions in the glycine receptor (GlyR), which belongs to the already mentioned pLGICs family [10, 11] (Fig. 1).

It is noteworthy that the structures of transmembrane proteins are isolated together with zinc ions, which are present in the analyzed recombinant proteins [12, 13]. Zinc belongs to the group of the most significant trace elements in the body along with iron, magnesium, and iodine. A decrease in the content of this divalent cation leads to significant problems for patients in both developing and developed countries [14, 15].

Zinc is the second most common micronutrient in the body after iron. On average, the body of an adult contains 2–3 grams of zinc [16]. In the body, it is distributed according to the skeletal type – 63% in the skeletal muscles, 22% in the skeletal system. The maximum concentration of zinc is also observed in the muscles and bones, as well as in the prostate gland in men. The concentration of zinc in the brain is estimated at 150 µmol/l, which, in turn, is 10 times higher than the content of zinc in blood serum [17]. Zinc is involved in all types of metabolism: it is assumed that it binds to about 3000 enzymes *in vivo*, which corresponds to about 10% of the human proteome [18]; regulates the cell stability and permeability and participates in membrane transport [19]; it has a pronounced immunomodulatory effect on hematopoiesis, osteogenesis, respiration processes and programmed cell death (apoptosis) [16, 20]. The role of Zn^{2+} as a neurotransmitter and modulator of the neurons state has been experimentally proven, since this ion is able to accumulate in presynaptic vesicles with a subsequent release into the synaptic cleft [21]. In addition, the level of zinc affects the susceptibility to learning and memory [22]. These results show that zinc ions, along with well-known neurotransmitters, can directly affect the state of neurons and participate in the regulation processes of CNS excitation and inhibition.

THE AIM of the work was to carry out a possible combined application of glycine and zinc compounds to change the metabolism and correct the conditions of patients with anxiety disorders and manifestations of stress.

MATERIALS AND METHODS

Information retrieval (Scopus, PubMed) and library (eLibrary) databases were used as research tools. In some cases, the ResearchGate application was used for a semantic search.

The analysis and synthesis of the scientific literature on the research topic, was carried out covering the period from 2000 to September 2022.

The following keywords and word combinations were used in the search: anxiety, anxiolytic properties, neuron metabolism, a synaptic cleft, inhibitory mediators, glycine metabolism, glycine receptor, GABA, GABA receptors, glycine transporters, chloride ion properties, chloride connectivity, zinc metabolism, tissue zinc levels, zinc levels, zinc transport, zinc effects, allosteric regulation, reactive oxygen species, antioxidant effects, metabolic levels of glycine, metabolic level of zinc, blood-brain barrier, vasodilatation, cerebral blood flow, anti-anxiety effects of glycine, glycine effects on stress, clinical trials of glycine.

Visualization of membrane receptors was carried out using the data from the Protein Data Bank (PDB) (https://www.rcsb.org/). To make up chemical formulas and illustrations, the libraries of the ACD/ChemSketch 2020.2.0 software package were used.

RESULTS AND DISCUSSION

A feature of the molecular mechanisms underlying the therapeutic effect of glycine and zinc ions on patients suffering from anxiety disorders is the combined effect of these metabolites on various biochemical and signaling systems. In fact, it is necessary to discuss a complex effect touching upon several systems at once.

In the context of accumulation and transformation, in neurons and other types of human cells, there are fundamental differences between glycine and zinc due to their chemical nature. Glycine is a non-essential amino acid that is actively involved in many metabolic processes, while Zn^{2+} is a part of the trace elements, the level of which is always regulated by an influx from an external source.

Processes of zinc transport and storage in human cells and tissues

In enterocytes of the small intestine, zinc buffer proteins determine the process of this ion transfer into the bloodstream. Further, Zn^{2+} is redistributed between albumin (the main zinc carrier, binds up to 80% in blood), α-microglobulin and transferrin [22, 24]. The protein content of food, as well as the condition of the mucosal layer of the small intestine, determine the absorption of zinc. Only 10% of zinc is excreted from the body with sweat and urine, the rest – with fecal masses [25].

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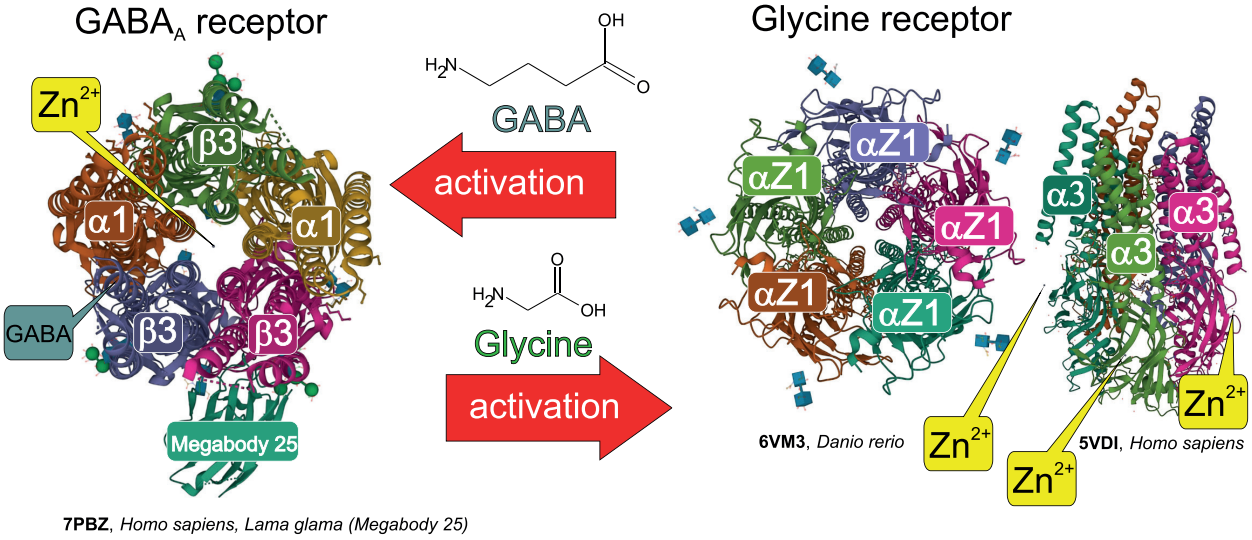

Figure 1 – Pentamers activation of pLGICs family by CNS inhibitory neurotransmitters

Note: Structural images of membrane proteins are presented based on the Protein Data Bank (PDB) (https://www.rcsb.org) in parallel planes (GABA$_A$ receptor, 7PBZ, [12]; glycine receptor, 6VM3, [23]) and perpendicular (glycine receptor, 5VDI, [13]) plane of the membrane.

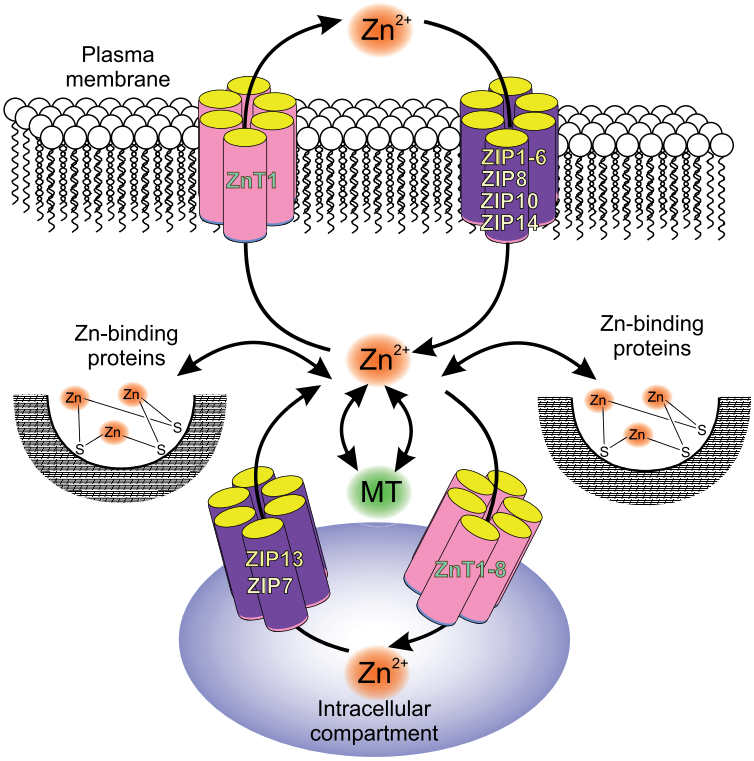

Figure 2 – Main ways of zinc ions transport and deposition in human cells

Note: Intracellular compartments are: endoplasmic reticulum (ZnT1, ZIP7), Golgi apparatus (ZnT5-7, ZIP13), endosomes (ZnT4), lysosomes (ZnT2), insulin granules (ZnT5, ZnT8) and synaptic vesicles (ZnT3).

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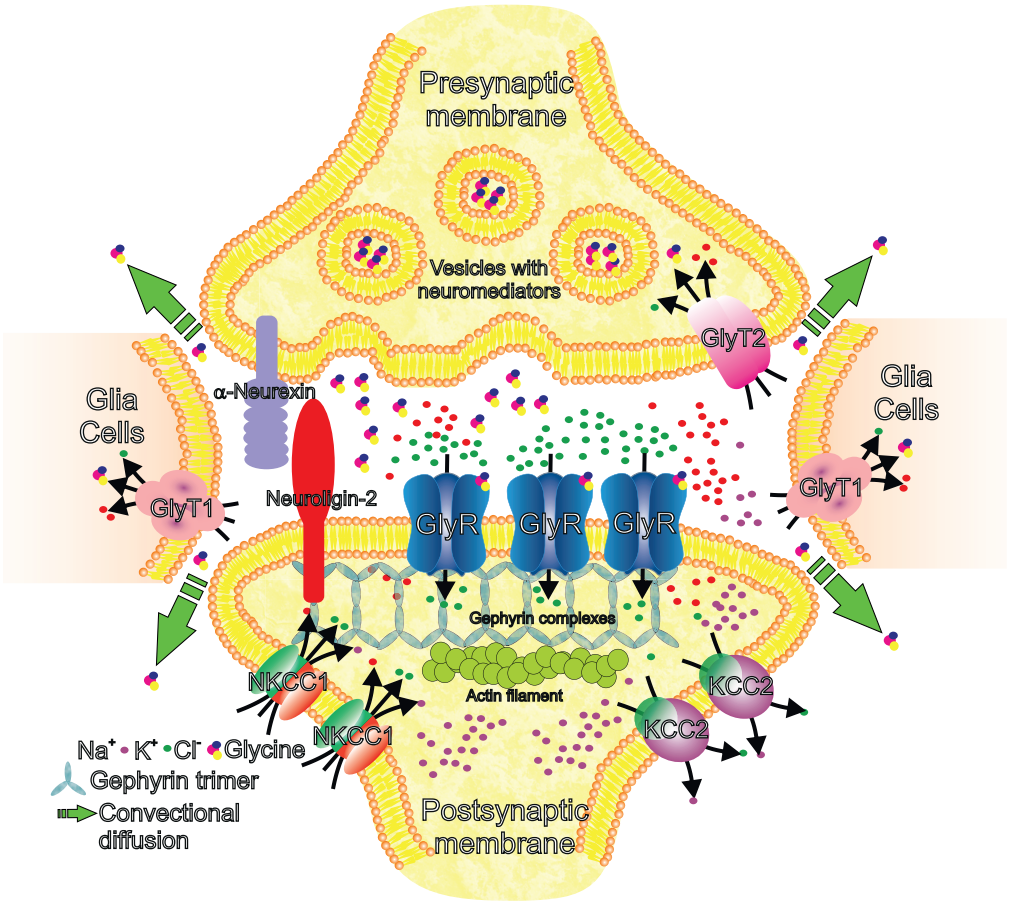

Figure 3 – Schematic representation of glycinergic synapse

Note: A neurotransmitter release from synaptic vesicles is accompanied by a subsequent diffusion into the synaptic cleft and the activation of structured GlyR and gephyrin clusters on the postsynaptic membrane. The increasing concentration of chloride ions in the postsynaptic terminal is regulated by transport through the KCC2 transporter. Structural plasticity of the synapse is mediated by the interaction of α-neurexin (presynaptic membrane) and the neuroligin-2 complex with the structural network of gephyrin trimers in the postsynaptic terminal [43].

At the cellular level, 30–40% of zinc is localized in the nucleus, 50% in the cytoplasm and organelles, and the rest – in the cell membrane. Cellular zinc homeostasis is mediated by three main mechanisms [26]. First, this is transport across the plasma membrane by importer proteins from the ZIP and ZnT families (Fig. 2). Second, this is due to the sequestration mediated by the transporter into intracellular organelles, including endoplasmic reticulum, a Golgi complex and lysosomes. To maintain the cell viability, a strict control of zinc homeostasis is necessary, since dysregulation leads to the cell death. The third mechanism for maintaining homeostasis is the metallothionein/thionein system [18]. Metallothioneins (MTs) form complexes with about 20% of intracellular zinc. MTs are ubiquitous proteins characterized by a low molecular weight, a high cysteine content and the ability to form complexes with metal ions.

One MT molecule can bind up to seven zinc ions. Due to the different affinity of metal ion binding sites, Zn can act as a powerful cellular zinc buffer. Free and weakly bound zinc ions interact with the apoprotein thionein (T_{red}) to form MTs [27]. An increase in the level of free zinc ions triggers the transcription factor-1 (MTF), thus inducing the expression of thionein [18]. In addition, oxidation of thiols by reactive oxygen species (ROS) or nitrogen (RNS) triggers the formation of oxidized protein thionine (Tox) with a concomitant zinc release [28].

Since there is no zinc storage system in the body, its level in cells must be constantly maintained. Both vegetable (mushrooms, nuts, cereals, legumes) and animal (meat, liver, seafood, cheese) products can be used as sources to maintain the normal level of this ion [25, 29].

In accordance with the norms of physiological needs for energy and nutrients for various population groups in the Russian Federation (Methodological recommendations MP 2.3.1.0253-21), the recommended daily allowance is from 3 to 12 mg of zinc for children and 12 mg for adults. In the US, the daily allowance of zinc for men is 11 mg, for women – 8 mg. In Germany, it is 10 mg for men and 7 mg for women [26].

Glycine metabolism in human cells

As mentioned above, unlike zinc, amino acid glycine, being both a substrate and a product of enzymatic reactions, is actively involved in the metabolic processes

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of human cells. In most cases, glycine is synthesized by serine hydroxymethyltransferase (SHMT), which uses serine supplied with food or obtained as a product of anabolic reactions from glucose and glutamate, as a substrate [30]. SHMT is a pyridoxal phosphate and a tetrahydrofolate dependent protein that is present in both the cytoplasm (SHMT1) and mitochondria (SHMT2), with the mitochondrial enzyme being more active [31]. Alternative metabolic pathways are the synthesis of glycine from threonine (with the participation of threonine aldolase and threonine dehydrogenase), choline (initiated by choline oxidase), and glyoxylate (catalyzed by alanine glyoxylate aminotransferase) [32, 33]. In general, the balance and dominance of these anabolic pathways is highly dependent on conditions, diet, and a body state. As catabolic reactions, one can consider the reversibility of the SHMT reaction, as well as the mitochondrial glycine cleavage system (GCS), which is a combination of four proteins (glycine decarboxylase (P-protein), aminomethyltransferase (T-protein), dihydrolipoamide dehydrogenase (L-protein) and a protein containing lipoic acid (H-protein) [34]. It should be notified that despite the complexity of the process, GCS is considered as a reversible system and its activity is unevenly distributed in human tissues: the glycine cleavage system is more represented in the liver and kidneys and, to a lesser extent, in the brain, testicles, and the small intestine [30].

Role of glycine as neurotransmitter in neurons

Synthesized glycine is pumped into vesicles *via* the vesicular inhibitory amino acid transporter (VIAAT), which is associated with the transport of chloride ions into synaptic particles [35]. Such an activity is typical for both glycinergic and GABAergic neurons, as well as for terminal endings of a mixed type [36]. Exocytosis of synaptic vesicles leads to the diffusion of glycine into the postsynaptic membrane with a subsequent activation of GlyR, which, in turn, leads to the depletion of the chloride ion gradient [37, 38]. For most mature CNS neurons, the intracellular concentration of chloride ions is maintained at a low level (about 5 mM) [39], which is achieved due to the activity of K^+/Cl^- carriers known as KCC2 [40, 41], which function along with $Na^+/K^+/Cl^-$ transporter (NKCC1), as well as glycine transporters – GlyT1 and GlyT2 [42] (Fig. 3).

It should be emphasized that a distinctive structure feature of the postsynaptic region containing glycine and GABAA receptors is their cluster organization on the membrane surface. A similar effect is achieved due to the interaction of GlyR with a specific protein, gephyrin [44], which consists of three subunits [43] and forms trimers associated with cytoskeleton (Fig. 3). This protein is a part of a multistage system that ensures the formation and development of neuroplasticity of the neurons postsynaptic membrane containing receptors activated by inhibitory neurotransmitters (glycine and GABA) [45]. This process is dynamic and can be regulated in various ways, in particular, by the level of a specific brain-derived neurotrophic factor [46]. Glycine released into the synaptic cleft is subsequently captured back into neurons and glial cells through the already mentioned GlyT carriers, and some of the neurotransmitter molecules are carried away by convection diffusion into the interstitial fluid. This process is important for the formation of spatial heterogeneity in the distribution of glycine and the explanation of the molecular mechanisms of its effects in neurons [33].

Other concomitant and metabolic effects of glycine

The considered molecular activation mechanism of chlorine ions transmembrane currents indicates the direct participation of glycine in the formation of inhibitory processes in CNS neurons and is the basis for the formation of various treatment regimens aimed at reducing anxiety and reducing the manifestation of stress. Thus, it has been experimentally shown that high doses of glycine when taken orally (3 g once before falling asleep) improve the subjective and objective assessment of the quality of sleep in the group of patients under consideration [47]. The oral intake of glycine reduces metabolic disorders in patients with cardiovascular diseases, inflammation of various origins in a number of cancers, as well as in obesity and diabetes [48]. Glycine protects against oxidative stress caused by a wide range of toxic compounds (including drugs) at the level of cells or an entire organ in the liver, kidneys, intestines, and a vascular system [49]. It is noteworthy that glycine has a direct effect on the arteriole dilatation [50, 51], which is the most important aspect of this amino acid overall effect on the CNS state [52]. The impact on the blood flow system in microvessels and capillaries leads to a theoretically substantiated [53–55] and experimentally confirmed increase in the glucose content in tissues [56].

Allosteric regulation of GlyR by zinc ions

A number of experimental works have shown the allosteric regulation of GlyR by zinc ions [57, 58]. The effect of zinc on the activity of glycine receptors depends on the level of the ion content and has a biphasic form. At low concentrations of Zn^{2+} (<10 μM), the receptor is activated, while at high concentrations (>10 μM), it is inhibited. These multidirectional processes involve different sites on the receptor and have different molecular mechanisms. Potentiation is achieved by increasing the affinity of the receptor for glycine, while inhibition is achieved by decreasing its efficiency [57]. These effects should be considered as a consequence of zinc physicochemical properties; zinc is the only ion among transition metals that does not have a biological redox activity. It is the lack of the zinc redox activity, along with its relatively strong affinity for proteins that has made zinc a suitable ion to play the role of a

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structural cofactor that modulates the activity of the glycine receptor.

Antioxidant effects of glycine and zinc

In addition to the immediate direct combined effect on the state of the neuron membrane polarization, glycine and Zn^{2+} have many effects on metabolic processes that directly affect the condition of patients with anxiety disorders. In particular, it has been experimentally shown that an increase in the concentration of glycine has a protective effect on the oxidative phosphorylation system in the mitochondria of neurons under anoxia and hypoxia conditions [59–61], which is a part of the global regulatory mechanism of the metabolism switching state depending on the level of the tissue amino acids [62]. In addition, a direct increase in the content of glycine reduces the generation level of reactive oxygen species initiated by glutamate excitotoxicity [63]. The antioxidant effect is supported by the mediated participation of glycine in the glutathione tripeptide in the system of protection against the oxidative stress, which is the basis of this amino acid protective effect in various ischemic conditions and acute cerebrovascular accidents [64]. Under normal physiological conditions, Zn^{2+} is redox-inactive; therefore, it takes part in the processes of receiving and transmitting electrons indirectly. The antioxidant properties of zinc are the result of several indirect mechanisms, i.e. the inhibition of ROS formation by transition metals and sulfhydryl stabilization [65, 66].

The above-mentioned molecular mechanisms of the glycine and zinc effect on the cellular and subcellular systems of the brain tissue indicate the need for the combined use of these metabolites to achieve a more pronounced effect in patients suffering from anxiety disorders. At the same time, both the ability to maintain the concentration of the amino acid and microelement in question, as well as their effectiveness and bioavailability, are important.

Bioavailability and maintenance of glycine and zinc levels in human body

Despite the fact that glycine is a non-essential amino acid, Melendes-Hevia E. et al. point at the need for its supply from outside as a source to meet the biological needs of the cells [67]. It should be notified that to date, the ability of glycine to penetrate the BBB with the help of nonspecific amino acid carriers when administered orally has been experimentally proven [47]. Nevertheless, the doses used in this method of administration are quite high [68] and, therefore, it is necessary to take into account the specificity of local changes in the concentration of glycine, which is achieved by an effective choice of this metabolite route of delivery.

To maintain full zinc homeostasis, a sufficient daily intake is necessary, because the systems of the intracellular zinc ions localization discussed above, are rather dynamically filled compartments and traps, which ultimately can lead to the absence of a deposition system for this microelement in the body.

Unfortunately, zinc deficiency does not show any specific symptoms. With its deficiency, such nonspecific conditions as sleep disturbances, deterioration of the skin, hair and nails, decreased appetite, increased hair loss, impaired night vision, decreased mood, increased duration of wound healing, and others can be observed [69].

Zinc deficiency is more common among people on the diet high in phytates [15]. Most often, they are residents of developing countries. Phytates are found in grains, seeds, nuts, legumes, cocoa beans and cocoa powder, and coffee beans. Phytates bind to zinc, thereby reducing its bioavailability [25, 26]. It is worth noting that zinc derived from animal products has a higher bioavailability compared to plant foods. Therefore, vegetarians are usually recommended to increase the zinc norm by 1.5 times [26].

To increase its bioavailability in vegetarian diets, legumes should be used in the sprouted form, or grains and legumes should be soaked in water for several hours before cooking.

According to the unified sanitary-epidemiological and hygienic requirements for goods subject to sanitary-epidemiological supervision (control), the recommended adequate level of the daily zinc intake for an adult is 12 mg; the upper allowable intake level is 25 mg [70]. The physiological need for children is from 3 to 12 mg/day (depending on age). Breastfeeding until at least 6 months of age provides an adequate level of zinc intake in the child's body [71].

Interestingly, some authors point at the need for sublingual zinc in the treatment of colds [14]. A slow drug dissolution in the mouth will allow zinc ions to be released, absorbed and transported to the nose – the source of infection. The chemical composition of the preparation is also important so that zinc can be ionized in the oral cavity at pH 7.4: citric acid, glycine and tartrate prevent zinc ionization [14].

In biologically active food supplements, zinc can be present in the form of compounds: acetate, sulfate, chloride, citrate, gluconate, lactate, oxide, carbonate, L-ascorbate, L-aspartate, bisglycinate, L-lysinate, malate, mono-L-methionine sulfate, picolinate, L-pyroglutamate, as well as amino acid complexes (in accordance with the Unified Sanitary-Epidemiological and Hygienic Requirements). Biological zinc supplements have a varying bioavailability. Zinc bound to amino acids such as aspartate, cysteine and histidine, has the highest absorption concentration, followed by zinc chloride, sulfate and acetate, while zinc oxide has the lowest bioavailability [14, 26, 72]. A comparison of various saccharides and their combinations effect on the zinc uptake by vesicles with brush border membranes showed that the addition of maltose and a mixture of galactose

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with glucose did not significantly reduce the level of the zinc uptake compared with the control. The addition of a glucose polymer or lactose significantly increased the bioavailability of zinc [73]. The addition of glucose to lactose or mannitol to the glucose polymer had the same effect as lactose or polymer alone, respectively. The galactose-only buffer had no effect on zinc binding. In another study, a low molecular weight lactose-zinc complex was found out to have a higher bioavailability *in vitro* [74].

The use of Zn^{2+} together with glycine will allow the formation of chelated forms of zinc, the undeniable advantages of which include a maximum bioavailability even under the conditions where the assimilation of the components is impaired (the lack of interaction with food, other minerals and gastric hydrochloric acid, the absence of adverse reactions) [75].

It has been established that zinc, as one of the most important trace elements, plays an important role in various pathological conditions. Various diseases of the gastrointestinal tract, such as malabsorption, cirrhosis of the liver, a celiac disease, Crohn's disease and chronic diarrhea, can also lead to zinc deficiency, due to the impaired absorption [19, 26].

Low zinc levels have been shown to be associated with metabolic syndrome and diabetes [76, 77], as well as decreased immunity [26, 78, 79]. Large amounts of iron from supplements can interfere with the zinc absorption. Disruption of zinc homeostasis, leading to either depletion or excess zinc, causes severe damage to neurons [80]. Zinc-induced cell death and changes in brain zinc status are associated with a wide range of diseases, including many neurodegenerative disorders, such as Alzheimer's disease, and mood disorders, including depression, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and prion diseases, as well as autism spectrum disorders. [66, 81–83].

The considered molecular mechanisms of the metabolites action are reflected in the clinical practice of the anxiety states treatment. In particular, it was shown that such anxiety symptoms as anxious mood, tension, and sleep disturbances were subjected to the greatest reverse dynamics during glycine therapy [85]. In addition, a randomized placebo-controlled study demonstrated the effectiveness of glycine in the treatment of mild anxiety in patients with an adjustment disorder with a predominance of disturbance of other emotions [86].

All major metabolic pathways are regulated by zinc metalloenzymes. The functions of these enzymes include catalytic, structural and regulatory roles. The status of zinc, whether deficient or abundant, is able of influencing each of this element's diverse roles in human biology.

CONCLUSION

Thus, deficiencies of certain essential trace elements and amino acids, such as glycine and zinc, especially their combined deficiencies, are one of the frequent causes of various adverse effects, including post-stress CNS dysfunctions. Given the accumulated experience of these micronutrients positive impact on the processes of recovery and maintenance of the central nervous system normal functioning, an adequate intake of zinc and glycine may be important for most people who experience the consequences of numerous stresses and anxiety on a daily basis. This combination can be especially useful for the people experiencing a state of chronic psycho-emotional stress and maladaptation, including those who have difficulty in falling asleep. Replenishment of zinc and glycine deficiency in the body of a healthy person is manifested by the development of a persistent anti-anxiety effect, which is accompanied by the normalization of the sleep-wake rhythm, which makes it possible to have a good rest without any loss of working efficiency after waking up.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

VNS – writing and editing the text, analyzing literary sources and interpreting the results, analyzing glycine and zinc clinical effects, approval of the text; YRN – writing and editing the text, analyzing literary sources and interpreting the results, conducting a database search in the Protein Data Bank (PDB) (https://www.rcsb.org/), selecting material on the glycine action, developing design and making illustrations using graphic tools and the library of the ACD/ChemSketch 2020.2.0 software package, approval of the article final version for publication; VYT – writing and editing the text, analyzing literary sources and interpreting the results, selecting material on the metabolic zinc action; EVS – writing and editing the text, analyzing literary sources and interpreting the results, analyzing pharmaceutically acceptable zinc compounds and bioavailability of combinations, approval of the text.

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