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Synergistic Application of Zinc and Vitamin C to Support Memory and Attention and to Decrease the Risk of Developing Nervous System Diseases

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Provision of the body with zinc and vitamin C is important for CNS functioning. Zinc ions take part in neurotransmission (transmission of signals from acetylcholine, catecholamine, serotonin, and prostaglandin receptors) and in ubiquitin-dependent protein degradation. Zinc deficiency is associated with the development of Alzheimer's disease and depression. Zinc supplementation (10–30 mg/day) improves neurological recovery in patients with stroke and closed craniocerebral injury and also improves measures of attention; it decreases hyperactivity in children. Vitamin C is a synergist of zinc which supports the antioxidant resources of the brain, synaptic activity, and detoxification. Vitamin C supplements at a dose of 130–500 mg/day are recommended for the prophylaxis of dementia and neurodegenerative pathology.

Keywords: zinc, vitamin C, dementia, neurodegenerative, hyperactivity.

Neuroprotective functions have been identified not only for B group vitamins (a widely known fact), but also for other micronutrients. Zinc and vitamin C are among the micronutrients which have been "overlooked" in neurological practice.

Provision of the body with zinc is extremely important for the functioning of the central nervous system (CNS) at all stages of life. Systematic analysis of the molecular genetic mechanisms of the actions of zinc has demonstrated more than 1200 zinc-binding proteins and enzymes whose activities are significantly decreased in zinc deficiency. These proteins act on intracellular signal cascades, support ubiquitin-dependent proteolysis, take part in regulating embryonic growth processes, and mediate the biological effects of numerous hormones.

Experimental studies have demonstrated that zinc deficiency during intrauterine development is accompanied by the formation of anomalies of the brain and impairment to neuron functioning. In particular, zinc deficiency impairs the control of inflammation in neurons and stimulates the oxidation of cysteine in tubulin, the main protein of neuron microtubules [1].

Impairments to the activity of zinc-dependent signal pathways due to single-gene diseases leads to severe innate CNS developmental defects. Impairments to the activity of zinc-dependent proteins are associated with such diseases as Duchenne's muscular dystrophy (OMIM 310200), Charcot–Marie–Tooth disease (OMIM 614436), limb-girdle muscular dystrophy type 2H (OMIM 254110), spinocerebral ataxia type 14 (OMIM 605361), cerebellar ataxia and hypogonadism (OMIM 212840), progressive myoclonic epilepsy (OMIM 254780), Parkinson's disease (OMIM 168600), autistic spectrum disorders, structural anomalies of the brain, holoprosencephaly (OMIM 610829), macrocephaly, macrosomia, facial dysmorphism (OMIM 614192), progressive cerebral angiopathy, moyamoya disease (OMIM 607151), and others [2].

Apart from its widely known antiscorbutic function, vitamin C (ascorbic acid) is an important endogenous antioxidant, which protects neurons from glutamate toxicity. Diets containing adequate levels of vitamin C decrease the

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TABLE 1. Main Intracellular Signal Pathways Involving Zn-Binding Proteins [2]

Pathway	Number of known Zn-binding proteins	Biological role
NFκB	27	Expression of immune response genes, apoptosis, and neuron division
Wnt	19	Regulation of neurogenesis and neuron viability
ERK	10	Regulation of neuron growth, division, and viability
JNK	8	Stress responses (radiation, heat and osmotic shock)
Notch	8	Regulation of neurogenesis
PKB	8	Glucose metabolism, apoptosis, neuron division and migration
HIF	5	Response to hypoxia
PKC	5	Signal transmission from acetylcholine, catecholamine, and serotonin receptors

TABLE 2. Neuromuscular Developmental Anomalies Associated with Impairments to Zn-Dependent Activity of the Ubiquitin Degradation of Protein Structures [2]

Gene	Protein	Pathology
RNF216	Ub-ligase F216	Cerebellar ataxia and hypogonadism (OMIM 212840)
LRSAM1	Ub-ligase SAM1	Charcot–Marie–Tooth disease (OMIM 614436) – a progressive muscle atrophy
HERC2	Ub-ligase RCC1	Autistic spectrum disorders
NHLRC1	Ub-ligase LRC1	Progressive myoclonic epilepsy type 2 (OMIM 254780)
TRIM32	Ub-ligase TRIM32	Limb girdle muscular dystrophy type 2H (OMIM 254110)
RNF135	Ub-ligase NF135	Macrocephaly, macrosomia, facial dysmorphism (OMIM 614192)
RNF213	Ub-ligase NF213	Moyamoya disease (OMIM 607151) – a progressive cerebral angiopathy
PARK2	Ub-ligase "parkin"	Parkinson's disease (OMIM 168600) – a neurodegenerative disease
TOPORS	Ub-ligase Topors	Retinitis pigmentosa type 31 (OMIM 609923)

risk of cognitive impairments and Alzheimer's disease [3]. Significant impairments to the oxidative-reductive balance and compartmentalization of vitamin C in neurons and astrocytes and in the intercellular space have been demonstrated in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic sclerosis, and others [4].

Zinc and Neuroprotection: Molecular Mechanisms. Zinc ions are required for such processes important for neuron functioning as gene transcription, supporting hormone activity (including neurosteroids), ubiquitin-dependent proteolysis (degradation and processing of proteins, which is important for inhibiting neurodegenerative processes), genome stabilization (histone methylation, histone acetylation, DNA methylation, binding of cadmium ions), and immunomodulation (particularly for synthesis of interferon-1) [2].

Systematic biological analysis of zinc-dependent proteins showed that their functions can be grouped into the main rubrics: 1) gene transcription (transcription, the "zinc finger" domain, nuclear protein, DNA); 2) genome stability (DNA, N-methyltransferase, helicase, histone); 3) connective tissue structure; 4) growth and development of the CNS (biogenesis, development); 5) mediation of the effects of hormones and neurotransmitters by means of transcription and intracellular signal cascades [2].

The physiological effects of zinc are due primarily to the involvement of zinc ions in supporting the basic zinc-dependent processes of gene transcription. A significant proportion of zinc-binding proteins are transcription factors containing a structural motif (domain) known as a zinc finger. Zinc fingers in zinc-binding proteins recognize particular regions of genomic DNA, bind with them, and promote activation of the transcription of many thousands of genes [5]. For example, all steroid receptors contain zinc fingers and are unable to be active in the absence of Zn^{2+} ions.

Domains of the zinc finger type are absolutely required, particularly for signal transmission from neurotransmitter receptors via the intracellular signal pathways of neurons. In most cases, transmission of the signal from one receptor or another within the cell involves a chain of sequential bio-

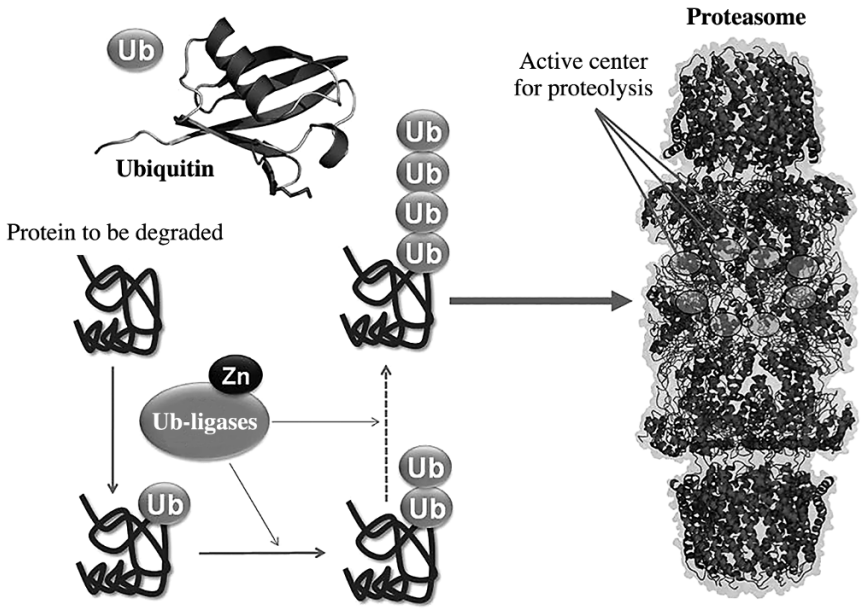

Fig. 1. The process of ubiquitin-dependent protein degradation.

chemical reactions mediated by enzymes, some of which are activated by so-called second messengers (calcium, cAMP, inositol phosphates, diacylglycerol, nitric oxide, etc.). Any part of the intracellular signal transmission system involves essentially the following sequence of events: 1) specific interaction of the external signal (a hormone, neurotransmitter, etc.) with a cellular receptor; 2) activation of receptor by the effector molecule responsible for generating/secreting second messenger molecules (calcium, cAMP, etc.); 3) activation by second messengers of the subsequent proteins of the signal cascade concerned; 4) changes in the expression of particular genes. More than 50 signal pathways have been proposed to involve zinc fingers and other Zn-binding proteins [2]. Zinc deficiency will have adverse influences on the activity of all these signal pathways. The main signal pathways directly related to neuron functioning are listed in Table 1. The data in this table are based on the results of functional interaction analysis of the human genome [2].

Another no less important mechanism of the neuroprotective action of zinc is its involvement in the ubiquitin-dependent degradation of proteins in proteasomes. Impairments to protein degradation lead to the accumulation of protein plaques in neurodegenerative pathology (particularly Alzheimer's disease). Zinc, as a cofactor of many proteases, is of fundamental importance for controlled protein degradation (proteolysis) involving the special signal protein ubiquitin.

Controlled proteolysis of processed intracellular proteins is mediated by a specific intracellular molecular machine - the proteasome. Proteasomal proteolysis clears the cell of damaged, abnormally folded proteins, with release of amino acids for the synthesis of new proteins. Proteolysis of signal proteins is required for timely "termination" of the biological signal and preparation of the neuron's signaling system to receive the next signal [6].

Proteasomes mediate controlled, multicenter, and rapid degradation of proteins previously labeled with ubiquitin. Zinc-dependent ubiquitin ligase enzymes recognize specific sites in protein sequences and attach ubiquitin molecules to these sites. Zinc is needed for attachment of the ubiquitin molecule to the target protein. Attachment of four ubiquitin molecules to a protein molecule guarantees delivery of the protein-ubiquitin complex to a proteasome for degradation (Fig. 1).

Bioinformatics analysis of the human proteome [2] demonstrated the existence of 238 Zn-containing proteins whose activity is directly linked to ubiquitin-dependent protein degradation. Table 2 shows examples of how deficiency of the activity of various ubiquitin ligases due to congenital genetic defects leads to inherited neuromuscular impairments.

For example, lack of Zn-binding TGFβ-activated kinase 1 (the *TAB2* gene), is associated with the formation of a whole set of impairments to CNS structure. This enzyme is an adaptor protein, transmitting the signal from mitogen-associated kinases to the signal pathways for neuron viability, growth, and differentiation (the ERK and TGFβ pathways) [7]. Zinc ions are of great importance for activation of the adapter protein TAB2, as zinc is involved in stabilizing the zinc finger structure of the TAB2 protein by ubiquitin molecules.

Thus, the existence of more than 1200 zinc-binding proteins in the human proteome produces the extremely wide spectrum of actions of zinc ions on the functioning of individual neurons and the CNS as a whole. The main molecular

TABLE 3. Mean Vitamin C Contents in Human Tissues and Organs [21]

Tissues and organs	Content, μM
Lymphocytes	3800
Monocytes	3100
Thrombocytes	2790
Hypophysis	2500
Adrenals	2000
Neutrophils	1350
Brain	850
Spleen	750
Liver	750
Pancreas	750
Kidneys	600
Lungs	400
Skeletal muscle	250
Cerebrospinal fluid	200
Urine	200
Gastric juice	136
Thyroid	100
Plasma	50
Red blood cells	45

mechanisms mediating the biological effects of zinc are its involvement in neurotransmission (transmission of signals from acetylcholine, catecholamine, serotonin, and prostaglandin receptors) and ubiquitin-dependent protein degradation.

Clinical Studies of the Interaction Between Zinc Supply and Neurological Diseases. The results of studies of the basic mechanisms of the molecular actions of zinc presented above are supported by results from clinical studies, pointing to the potential of using zinc formulations for the prophylaxis and treatment of neurological diseases.

A meta-analysis of five clinical trials addressed the link between the prevalence of Alzheimer's disease and the provision of vitamins B_9 (folate), B_{12}, A, C, D, and E and trace elements (copper, iron, and zinc) to participants [8]. This meta-analysis showed that patients with Alzheimer's disease had significantly lower plasma levels of vitamin C ($p < 0.001$) and zinc ($p = 0.050$). Thus, the mean plasma ascorbate level in Alzheimer's patients was 18% lower (95% CI –25% to –5%) than that in controls. Mean plasma zinc levels in Alzheimer's patients were 7% lower (95% CI –12% to +1%) than those in controls [8].

A meta-analysis of 17 studies in which zinc levels were measured in the peripheral blood of 2447 patients confirmed that zinc deficiency is associated with a higher risk of developing depression. Zinc concentrations were 1.85 μM lower in patients with depression than in the control group (95% CI 1.19–2.51 μM; $p < 0.00001$), more severe depression being associated with lower peripheral blood zinc levels ($p = 0.026$) [9].

Normalization of zinc intake improved neurological recovery in 26 patients with subacute stroke. At the beginning of the study, patients were characterized by adequate calorie intake (24 kCal/kg/day or more) and total protein intake (0.8 g/kg/day or more), while daily zinc intake was less than 10 mg/day, as compared with the recommended 15 mg/day. Patients' neurological status was assessed on the NIHSS on admission and at 30 days of receiving zinc formulations. On day 30, the increase in the NIHSS score was significantly greater in the group taking zinc than in the placebo group (4.7 ± 1.3 and $–3.3 \pm 1.1$ points, respectively; $p < 0.02$). Lower zinc intake corresponded to lower scores on the NIHSS ($r = –0.46$, $p < 0.02$) [10].

Zinc intake was associated with increased survival and faster neurological recovery in 68 patients with severe closed craniocerebral trauma. Zinc supplementation was started immediately after trauma. At one month, the death rate in the control group was 26%, compared with 12% among patients receiving zinc. The mean Glasgow Coma Score was significantly higher in the zinc treatment group on days 15 ($p = 0.005$), 21 ($p = 0.02$), and 30 ($p = 0.03$) as compared with the control group. The mean serum albumin concentration ($p = 0.003$) and the mean retinol-binding protein concentration ($p = 0.01$) were significantly higher in patients receiving zinc [11].

A number of clinical trials have demonstrated the importance of adequate provision of zinc from birth. Zinc formulations for premature babies aged up to three months during breast feeding ($n = 100$) improved measures of concentration and decreased signs of hyperactivity. Assessment of neurological development was performed using the Amiel–Tison scale. By age 40 weeks from conception, a significantly larger number of infants showed improvements in attention, gradually reaching the age-normal level ($p = 0.02$). In the control group of premature babies not receiving zinc, measures of attention were, conversely, reduced and hyperactivity symptoms were significantly more frequent ($p = 0.001$) [12].

A double-blind, randomized clinical trial showed that ingestion of zinc during the first two years of life supported active attention and cognitive capacities. At age six months, the group of babies was randomized for daily oral zinc (sulfate) solution at a dose of 10 mg/day and iron (sulfate) at a dose of 10 mg/day or placebo (iron 10 mg/day only). Only babies receiving zinc showed the normal decreases in the duration of gaze from age 6 months to age 12 months and the normal decreases in the time of distraction of attention from one object to another in games from age 12 months to age 18 months [13].

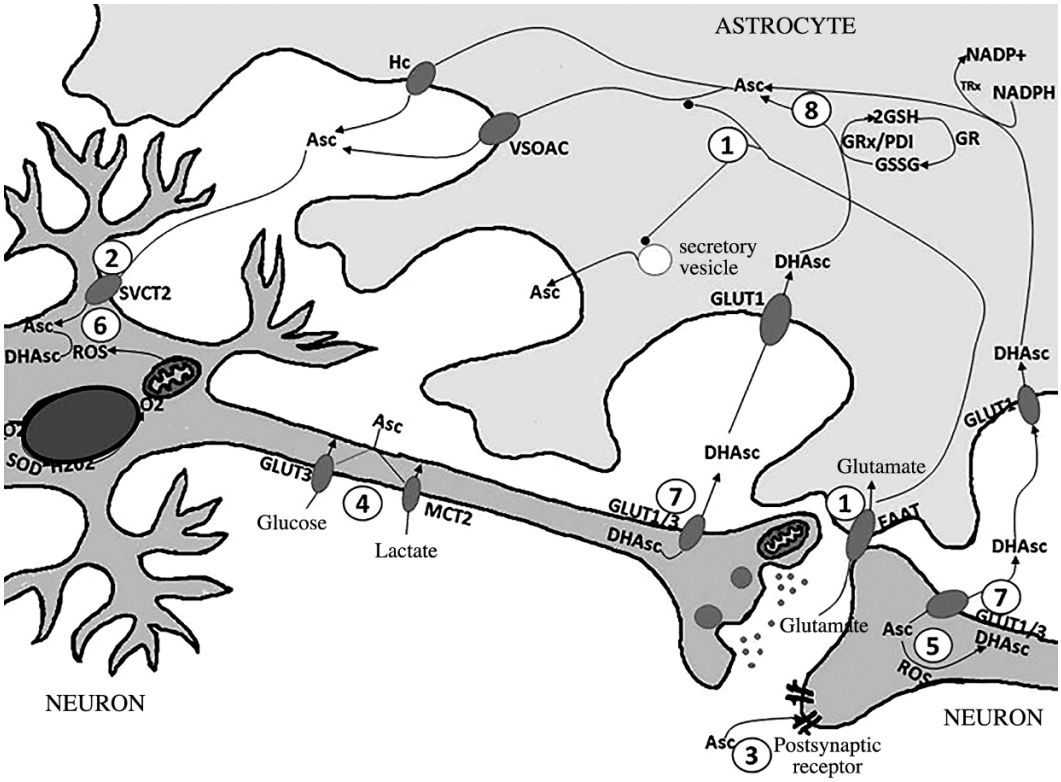

Fig. 2. Transport of ascorbic acid in the CNS and synapse function: 1) after release of glutamate into the synaptic cleft, glutamate is transferred by the EAAT transporter across the astrocyte cell membrane; within astrocytes, glutamate stimulates the release of the ascorbate anion or ascorbic acid (Asc) by exocytosis of secretory vesicles using the glutamate-aspartate transporter GLAST, the VSOAC channel, and using the transmembrane protein connexin; 2) ascorbic acid is taken up by neurons using the Na-dependent vitamin C transporter (SVCT2) and operates as a neuromodulator in glutamatergic and GABAergic synapses; 3) ascorbic acid operates as a neuromodulator in glutamatergic and GABAergic synapses; 4) ascorbic acid promotes switching of the preferred energy substrate for neuron metabolism from glucose to lactate during synaptic activity; 5) reactive oxygen species (ROS) form during synaptic activity and neuron metabolism; 6) ROS oxidize ascorbic acid to dehydroascorbic acid (DHAsc); 7) dehydroascorbic acid is released from neurons and taken up by astrocytes using the glucose transporter (GLUT-1); 8) in astrocytes, dehydroascorbic acid is reduced by glutathione (GSH – reduced glutathione; GSSG – oxidized glutathione) by glutathione-dependent reductases/disulfide isomerases (GRx/PDI) and thioredoxin TRx (with the involvement of nicotinamide adenine dinucleotide phosphate (NADP).

Use of zinc formulations for the prophylaxis and treatment of attention deficit hyperactivity disorder (ADHD) – a neurological and behavioral disorder – has potential. Zinc, supporting the functioning of a multitude of signal proteins and transcription factors, is important for supporting the balance of neurotransmitters and, thus, the prophylaxis and treatment of ADHD. In a controlled double-blind study, children and adolescents aged 7–14 years with confirmed ADHD (DSM-IV criteria) were randomized to receive methylphenidate 0.3 mg/kg/day and placebo (sucrose) or methylphenidate and zinc sulfate (10 mg/day) for six weeks. Intake of zinc promoted improvements in the children's state as measured on the global Conners rating scale [14].

Vitamin C and Neuroprotection: Basic and Clinical Studies. Neuroprotective treatment with zinc can be significantly optimized by vitamin C. Ascorbic acid is an important antioxidant with many cellular functions. It plays an important role in detoxification processes and operates as an enzyme cofactor in modulating synaptic activity [15, 16] and neuron metabolism [17]. It also functions as an enzyme cofactor involved in the biosynthesis of collagen [18], carnitine [19], tyrosine, and peptide hormones [20]. Ascorbic acid concentrates in the CNS (Table 3).

Ascorbic acid has important neuroprotective properties [22], supporting superoxide dismutase and catalase activities [23] and protecting neurons from glutamate toxicity stimulating the progression of neurodegenerative processes [24]. Transfer of ascorbic acid from intracellular reservoirs in glial cells and neurons induced by synaptic activity maintains the antioxidant resources of neurons. Increased absorption of ascorbic acid by neurons includes increases in the expression of the SVCT2 transporter on the neuron cell surface, thus leading to increased absorption of the ascorbic acid required for synapse functioning and neurotransmission [25] (Fig. 2).

Clinical studies have confirmed the interaction between the provision of vitamin C and cognitive capacities. Firstly, it should be noted that higher dietary fruit consumption (which corresponds to greater vitamin C intake) has significant influences on cognitive function in the elderly.

Study groups whose members ate fruit 1–3 times a day demonstrated a significant reduction in the risk of cognitive impairments by 50% compared with the other participants [26, 27]. Assessment of cognitive functions in nonsmoking participants aged 45–102 years showed that dietary consumption of fruit and vegetables more than four times a day has positive influences on cognitive functions [28].

Cross-sectional studies have identified a positive link between the dietary consumption of vitamin C and verbal fluency [29], abstract thinking, problem-solving, and cognitive status in general on assessment using the Mini Mental State Examination (MMSE). A number of studies have identified a link between ingestion of vitamins C and E and cognitive capacities in healthy people aged over 60 years [30].

Provision of vitamins, particularly vitamin C, as measured by nutrition diaries, correlates with cognitive functions in patients aged over 65 years. Maintenance of a normal plasma vitamin C level is a potential approach to slowing cognitive decline in the elderly [31]. A study of a group of people aged 65–94 years identified a significant correlation between the plasma vitamin C level and cognitive functions, particularly in terms of results from vocabulary and comprehension tests [32].

Studies of a cohort of 3000 subjects over seven years showed that the rate of decline of cognitive functions on the MMSE was significantly lower in those people who took larger quantities of vitamin C, especially in combination with vitamin E. A dose of vitamin C of 500 mg/day led to a significant improvement in cognitive capacities, while greater doses did not produce greater effects [33].

In addition, clinical studies have shown that inadequate provision of vitamin C promotes neurodegeneration. As noted above, recirculation of ascorbic acid to neurons by astrocytes and uptake of ascorbic acid by neurons via specific transporters (SVCT2 and others) are important mechanisms in maintaining the antioxidant defense of the brain. Neurodegenerative diseases involve an imbalance due to increased production of ROS on the one hand and decreases in antioxidant resources in neurons and glial cells on the other [34].

For example, accumulation of abnormally folded protein in Huntington's disease alters mitochondrial biogenesis and the expression of antioxidant defense genes, further increasing oxidative damage to neurons. The accumulation of amyloid in Alzheimer's disease and Parkinson's disease also stimulates ROS generation and neuron death. Recirculation of ascorbic acid in the neuron–astrocyte–intercellular space–neuron system is also slowed in lateral amyotrophic sclerosis.

Vitamin C levels were lower in patients with Alzheimer's disease than in a control group [35]. Ascorbic acid was therefore tested as a neuroprotective agent in patients for the treatment of Alzheimer's disease and lateral amyotrophic sclerosis [36]. Consumption of combined supplements containing vitamins C and E had protective influences on cognitive functions (including on assessment of attention, memory, and language), particularly in cases of vascular dementia [37]. Vitamin C at doses of over 130 mg/day for six weeks led to a decrease in the risk of Alzheimer's disease [38].

Lateral amyotrophic sclerosis is a neurodegenerative disease accompanied by damage to long motor neurons [39]. Systemic oxidative stress has been demonstrated in patients with lateral amyotrophic sclerosis, along with lower ascorbic levels in the cerebrospinal fluid. Consumption of antioxidant-rich food protects against development of this disease [40].

Huntington's disease is also an inherited neurodegenerative disease. Animal models of Huntington's disease show impairments to ascorbic acid homeostasis [41]. In particular, analysis of experimental models expressing mutant huntingtin protein (mHtt) showed reductions in the extracellular ascorbic acid pool in striatum neurons [42].

Studies of a group of 62 patients with Parkinson's disease (aged 71 ± 8.8 years) showed that vitamin C levels in lymphocytes in patients with severe forms of the disease were significantly lower than those in patients with milder forms [43]. It should be noted that ascorbate improves the bioavailability of levodopa in the treatment of Parkinson's disease [44].

Thus, existing results from clinical studies indicate that neuroprotection using vitamin C is effective and safe using doses of 130–500 mg/day. It is also important to ensure high bioavailability for vitamin C by not taking it while eating, but taking vitamin C solution or sublingual tablets. The bioavailability of ascorbic acid from the small intestine is known to decrease markedly with age. There is therefore potential for elderly patients to use sublingual formulations as tablets for absorption and soluble films. This route of administration ensures high bioavailability of ascorbic acid for the CNS.

Conclusions. Physiological provision of the body with zinc and vitamin C is extremely important for the prophylaxis of a wide range of neurological diseases and increases the survival of patients with craniocerebral trauma and stroke. The combination of zinc and vitamin C decreases the severity of such conditions as craniocerebral trauma, stroke, ADHD, Alzheimer's disease, Huntington's disease, and Parkinson's disease; it helps support memory, verbal fluency, and concentration of attention. Both zinc and vitamin C play important roles not only in supporting the antioxidant resources of the brain, but also in controlling synaptic activity and in supporting neurotransmission and ubiquitin-dependent protein degradation. These effects are obtained by supplementation with zinc at doses of 10–30 mg/day and vitamin C at doses of 130–500 mg/day. Excessive doses of micronutrients, conversely, do not decrease the efficacy of neuroprotection.

An optimum combination of zinc with vitamin C in the form of effervescent tablets "Zinc 10 + C" (Wörwag Pharma, Germany) for preparation of solution to drink is registered in Russia; this is suitable for patients from age 18 years (ac-

cording to the instructions) to support zinc and vitamin C metabolism. Each tablet contains 120 mg of vitamin C (200% of the RDA) and 10 mg of zinc (67% of the RDA). Tablets placed in water (200 ml, i.e., one glass) form an organic salt with high zinc bioavailability and excellent water solubility characteristics (up to 100%), i.e., zinc citrate; aqueous solutions of Zinc 10 + C have good organoleptic properties and do not induce nausea or vomiting. Treatment with zinc and vitamin C can also be used as adjuvant therapy, supplementing basal neuroprotective therapy.

The authors have no conflicts of interests.

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