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NOOTROPICS IN COMLEX THERAPY OF CHRONIC CEREBRAL ISCHEMIA

The clinical and pharmacological characteristics of nootropics as one of the most effective groups of neuropsychotropic drugs have been considered. The nootropics has been classified by the principal mechanism of action. The examples of clinical use of drugs on patients with chronic cerebral ischemia have been given.

Key words: cerebrovascular diseases, cognitive disorders, neuroprotection, and nootropics.

Today, cerebrovascular disease (CVD) is one of the most important problems of modern medicine in the view of its widespread occurrence, high mortality or disability caused by it, and significant financial costs for its treatment and prevention [1, 2]. In advanced economies, mortality from cardiovascular diseases continues to range from 12 to 15% of the overall mortality [3]. According to the statistical forecast, in 2020, it will reach 25 million cases annually [4]. In Ukraine, CVDs are ranked the second or the third by incidence and by mortality among this class of diseases [2]. In 2000—2010, in Ukraine, the number of stroke cases increased 1.6 times, while the total number of all CVDs grew from 3.4 to 4.5% [5]. This implies the relevance of pharmacological correction of cerebral blood circulation failure, as well as the importance of means of prevention or treatment of brain vascular pathology, somatovegetative and psychopathologic failures, and personal reactions to the disease [6].

Chronic cerebral blood circulation failure that in the Soviet literature and clinical practice is referred to «discirculatory encephalopathy» (DE) has a significant share in the structure of brain vascular diseases [7]. Discirculatory encephalopathy is a syndrome of multiple-lesion brain affection as a result of chronic cerebral vascular failure and/or repeated episodes of acute cerebrovascular accidents (venous insufficiency, transient ischemic attack, and stroke). The disease is characterized by a slow progressive course and progressive brain function disorder [8].

The most common causes of brain circulatory disorders are hypertension, atherosclerosis, cerebral arteries, diabetes, and heart disease with a high risk of thromboembolism into the brain. In more seldom cases the cerebral circulation disorders develop as a result of inflammatory changes in blood vessels (vasculitis), blood coagulation disorders, abnormalities of vascular development, etc. In most cases, the cerebral vascular insufficiency develops in the elderly [7, 9]. Stroke and DE can be considered to be two cerebrovascular syndromes which can be a manifestation of the same disease [10]. However, it should be noted that in

most cases, stroke is a result of affection of large cerebral arteries (especially, their atherosclerosis), while DE is often caused affection of small cerebral vessels (cerebral microangiopathy) [11, 12].

Along with focal neurological symptoms the clinical course of chronic cerebrovascular insufficiency includes cognitive impairment to which attention has been paid in the last decade because of its widespread occurrence [13, 14, 15, and 16]. In the case of CVS, cognitive impairment has a progressive character and at some point reaches the severity of dementia [13, 17]. Vascular dementia is one of the most serious complications of unfavorable course of cerebral vascular insufficiency. According to statistics, vascular etiology underlies, at least, 10—15% of dementia cases in the elderly [18]. However, in recent years, on both domestic and foreign publications the emphasis in clinical research increasingly shifts from identifying and studying the existing dementia towards the pre-dementia stages of neurogeriatric diseases when the therapeutic cure can be more effective and able to prevent or significantly defer the social maladjustment [19].

Impaired cognitive and associative functions under the conditions of cerebral pathologies occur against the background of severe structural changes of brain cells as a result of inhibition of bioenergetic processes, development of glutamate excitotoxicity, overproduction of reactive oxygen species (ROS), deactivation of antioxidant systems, and activation of apoptosis [20]. The energy deficit initiating a glutamate-calcium cascade, i.e. the release of aminoacidergic excitatory neurotransmitters, aspartate and glutamate, and the intracellular accumulation of Ca^{2+} is a trigger link of ischemic death of neuronal cell. The processes beginning at the early hours of hemorrhage and underlying the glutamate-calcium cascade (changes in the metabolism of glutamate and calcium, oxidative stress, and overproduction of NO•) induce long-term effects of ischemia. This is a reaction of genome with the launch of genetically programmed molecular mechanisms, dysfunction of astrocytic and microglial pools, development of immune changes, and initiation of neuroapoptosis as a consequence of formation of persistent cognitive deficit [21].

The DE morphological substrate is characterized by small focal and diffuse changes in the white matter of brain, hippocampal sclerosis, as well as by phenomena of secondary cerebral atrophy [11, 14, 22, and 23].

The modern medical science advances thanks to the use of new highly effective pharmacological agents having a pronounced therapeutic effect of CVD. The introduction of new classes of pharmacological agents acting at different stages of pathogenesis and optimizing cerebral metabolism makes it possible to suspend CVD progression [6, 24, 25, and 26]. Therefore, the application of neuroprotective agents which combines antioxidant, anti-ischemic, and nootropic properties are very relevant [20, 27].

The concept of pharmacotherapeutic neuroprotection makes it possible to distinguish two main trends. *The primary neuroprotection* is for interrupting fast mechanisms of cell necrotic death, i.e. the reactions of calcium glutamate cascade (antagonists of NMDA- and AMPA-receptors and calcium channel blockers: Remacemide, Rilutek, Nimotop, etc.) [28]. *The secondary neuroprotection* is aimed at reducing the severity of late ischemia effects: the blockade of pro-inflammatory cytokines, adhesion of cell molecules, inhibition of oxidative stress, normalization of neurometabolic process, inhibition of apoptosis, and reduction of cognitive deficit (antioxidants, antihypoxants, metabolitotropic drugs, nootropics: Emoxipin, Thiotriazoline, Glycine, Piracetam, Thiocetam, Citicoline, Cerebrolysin, Cortexin, Cerebrocurin, etc.) [29, 30]. Nootropics are the most important means of secondary neuroprotection.

Nootropics formed a separate group in the early 1980s, when after successful application of the first drug in this class, piracetam (nootropil), other pyrrolidone derivatives appeared. Previously, in the late 1960s, gamma amino butyric acid GABA (Gammalon, Aminalon) was used as a means of improving mnemonic processes. According to

WHO, the group of nootropics includes medicines that directly activate the cognitive processes, improve the memory and mental activity, as well as raise the brain resistance to aggressive factors.

Three decades hence the introduction of neurotropic drugs into clinical practice for regulation of memory processes they have become the most commonly used medical drugs. Moreover, nootropics gained a wide popularity not only in neurology and psychiatry, but also in other areas of the hospital and ambulatory pharmacotherapy. Nootropics regulate higher mental processes in humans, such as cognitive functions and cognitive abilities (education) due to modulating the memory rate and reliability of storage of information received (introduced). At the same time, they change the ability to improve the reproduction of already existing, i.e. stored information, or, conversely, to worsen the extraction of data from memory and to forget unnecessary information (e.g., memories of pain during the surgery, stressful experiences in disasters, etc.). The modulation of these processes or, in other words, the possibility of using pharmacological agents, if necessary, to stimulate or to inhibit the mechanisms of extraction of information from short-term and/or long-term memory (reproduction of memory engrams) is one of the most important problems of modern neuropharmacology. A distinctive feature of nootropics is their ability not to affect the higher nervous activity and the human psyche in its normal (healthy) condition and to improve the processes in the case of functional disease or morphological impairment. Using the present-day analytical pharmacological methods it is very difficult to establish any significant change in behavior of healthy people and animals, as well as in shifts in the conditioned reflex reactions, brain activity, or in biochemical processes in the nerve tissues under the influence of neuroprotective drugs. They have a therapeutic effect of cognition enhancers only in the case of mnemonic dysfunctions, if administered, at least, 3—4 months.

The range of modern neuroprotective drugs is large and diversified. In pharmacology, there are several classifications of nootropics. Below, the classification by the principal mechanism of action is given.

CLASSIFICATION OF NOOTROPICS

In clinical practice, these drugs are classified into two major groups: nootropics of direct action (cognitive enhancers) and neuroprotective agents [31, 32]:

I. **Cognitive enhancers or «true» nootropics**:

1. *Pyrrolidone nootropics* (*racetams*) with predominant metabolite action: Piracetam, Fenotropil combined racetams (Thiocetam, Olatropil, and Phezam).

2. *Cholinergic agents*: enhancers of synthesis and release of acetylcholine (Phosphatidylserine, lecithin, Citicoline); cholinergic receptor agonists (Oxotremorine, Bethanechol); and acetylcholinesterase inhibitors (Physostigmine, Galanthamine, etc.)

3. *Neuropeptides and neurotrophic cerebroprotectors*: Semax, Cerebrolysin, Cortexin, Cerebrocurin.

4. *Modulators of glutamatergic system*: a) low-affinity NMDA receptor polyamine site antagonists and partial agonists of AMPA receptors: Memantine, Ademol);

b) *AMPA receptor agonists*: Nooglutyl;

c) *AMPA receptor partial agonists, as well as enhancers of noradrenaline and dopamine release*: (Ritalin, Donepezil);

d) *NMDA receptor co-agonists*: glycine;

e) *NMDA mimetics*: glutamic acid, D-cycloserine.

5. *Dopamine receptor agonists*: Pronoran;

6 *GABA receptor agonists:* Baclofen.

II. **Neuroprotective agents**:

1. *Activators of brain metabolism*: Mildronat, Phosphatidylserine, xanthine derivatives of Pentoxifylline, etc.

2. *Cerebral vasodilators*: Vincamine, Vinpocetine, Nicergoline, etc.

3. *Calcium channel blockers*: Nimodipine, Cinnarizine, Flunarizine, etc.

4. *Antioxidants*: Mexidol, a-tocopheryl acetate, Thiotriazoline, Emoxipin, Cytoflavin, Glutoxim.

5. *Substances affecting the GABA system*: Aminalon (Gammalon), Pathogen, Picamilon, Fenibut (Noofen), sodium hydroxybutyrate.

6. *Different groups of substances*: orotic acid, Naftidrofuryl, ginseng, lemongrass, Ginkgo biloba, and Siberian ginseng.

For the direct nootropics the effect on memory is the main action, although they have other pharmacological properties (anticonvulsant, antihypoxic, circulatory, antioxidant, etc.) as well. The direct nootropics include substances with very different structure, from the relatively simple racetams to the complex peptide formations. The neuroprotective agents comprise brain metabolism activators, cerebral vasodilators, calcium antagonists, antioxidants, and substances affecting GABA system.

MECHANISMS OF ACTION OF NOOTROPICS

Two main links can be distinguished in the mechanism of action of nootropic drugs: the neurotransmitter and the metabolic ones. Both mechanisms occur in both groups of products, but one of them is the dominant mechanism.

Neurotransmitter mechanisms include the effect of the drug on GABA, choline, glutamate, dopamine, or glycinergic systems. In this respect, the most promising are the agonists of NMDA and AMPA subtypes of glutamine receptors and the agonists of GABA receptors (*Nooglutyl, Memantine,* and *Modafinil*) which have larger strength that the classical racetams (Piracetam, Pramiracetam, Aniracetam), but these drugs can cause a number of severe side effects. The substances that can be bound to the AMPA receptors have attracted the attention of researchers who deal with developing new drugs for the treatment of Alzheimer's and Parkinson's diseases, schizophrenia, depression, epilepsy, amyotrophic lateral sclerosis, Huntington's chorea, NPD disease, multiple sclerosis, mild cognitive impairment, and age cognitive impairment. Among the various types of ligands of AMPA receptors the positive modulators (or potentiators) that improve memory and cognitive functions in humans and animals are of particular interest, insofar as the intense ion current caused by the action of these modulators on AMPA receptors with subsequent depolarization of postsynaptic membrane has been established to trigger a gene expression mechanism responsible for the synthesis of neurotrophins, the nerve growth factor (NGF) and the brain derived neurotrophic factor (BDNF). For this reason, the drugs acting on AMPA receptors can be effective as neuroprotective agents. *Piracetam, Oxiracetam,* and *Aniracetam* have been established to activate AMPA type of glutamate receptor (the endogenous ligand is amino-3-hydroxy-5-methylisoxazole-4-propionate). However, they do not affect NMDA receptor neurons. This leads to an increase in the yield of calcium from the cell, as a result of which the concentration of intracellular calcium decreases. Pramiracetam increases the rate of choline sodium-dependent absorption in the hippocampus. It affects the cognitive functions through acceleration of flow of impulses from cholinergic neurons in the septum of hippocampus. Phenylpiracetam has been established to have an affinity with H-cholinoreceptors, not with NMDA-subtype of glutamate receptors.

The introduction of the drug increases the number of both H-cholinoreceptors and NMDA-receptors, but decreases the amount of serotonin and dopamine receptors in the brain. Unlike other piracetam-like drugs, *Levetiracetam* has a pronounced anticonvulsant effect, in connection with which it is used as a cure for epilepsy. Its mechanism of action has not been fully understood, but it is assumed not to have a direct effect on such «classic» antiepileptic processes / target as GABA-ergic transmission and sodium channels. The most probable site of action of Levetiracetam is SV2A protein. This protein is assumed is to be involved in the process of exocytosis. As a result of structural similarity with membrane transporters it can play a role in maintaining synaptic homeostasis of such components as ATP and calcium. The effect on calcium homeostasis is supported by the data according to which SV2A interacts with synaptotagmin that is a sort of calcium sensor, as well as by the inhibition, under the action of Levetiracetam, of calcium release by PC-12 cells containing SV2A and by the lack of this ef-

fect in SV2A-free 3T3-fibroblasts. According to the available data, within the therapeutic dosage range, Levetiracetam reduces the ion fluxes into neurons, which are induced by AMPA receptor activation. This effect is likely caused by inhibition of calcium channels. Levetiracetam and *Nefiracetam* activate NMDA receptors through the activation of protein kinase C and the phosphorylation of one of subunits of this receptor. Consequently, this increases the binding of glycine with NMDA receptors. *Fasoracetam* modulates the glutamate receptors, which leads to adenylate cyclase activation and enhances the formation of cyclic adenosine monophosphate (cAMP) involved in various «signalling» processes, including education and memory.

Due to the normalization of energy metabolism the racetams enhance the release and reuptake of neurotransmitters (glutamate, norepinephrine, dopamine, etc.). The racetams reduce the intensity of lipid oxidative modification reactions and formation of free radicals, as well as contribute to their elimination. Also, they can create the conditions for facilitating the synaptic neurotransmitter mechanisms and for activating the synthesis of proteins, in particular, S-100 memory protein and RNA. The racetams increase the intensity of incorporation of labeled phosphatidylcholine into protein and uridine into RNA, as well as the incorporation of P^{32} into the brain phospholipids, which enhances the synthesis of macromolecules required for the memory processes. Along with this, racetams activate adenylate cyclase which catalyzes ADP transformation into ATP as well as regulate the glucose utilization in nervous tissue and the Na/K-ATPase activity.

Recently, the use of nootropics whose dominant mechanism of action is the activation of glutamine AMPA receptors (ampakines): *Nooglutyl, Memantine, Ademol, Modafinil*, and *Ritalin,* has been intensively discussed. This group of drugs acts primarily on two processes developing in the neurons during memory consolidation: membrane depolarization and CREB protein activation. The depolarization occurs after the release of glutamate excitatory neurotransmitter into synapse, which stimulates the AMPA receptors on the neuron surface receiving the nerve signals. The other surface protein, NMDA receptor, reacts to glutamate under the action of depolarization. As a result, a complex chain of molecular interactions involving the formation of cyclic AMP and, consequently, the CREB protein activation, is activated inside the cell. The CREB activation is crucial for memory consolidation: the activated CREB helps to «turn on» genes, in particular c-fos, responsible for the synthesis of protein enhancers of specific synapses [33]. The AMPA mimetics accelerate the processes of memory by enhancing the reaction of AMPA receptors to glutamate, i.e. by facilitating the depolarization. These drugs cause an increase in the level of active CREB in cells, for example, by suppressing the phosphodiesterase destroying the cyclic AMP.

The formation of memory trace in the cell is accompanied by the formation of a mediator molecule, the cyclic AMP (cAMP). This molecule stimulates the synthesis of protein binding to the nerve cell DNA. As a result, a whole set of genes responsible for the synthesis of proteins completing the synapses is activated. Thereby these proteins increase the synapse effectiveness. This process underlies the consolidation of memory trace. The triggering protein is *cAMP response element binding protein* (CREB). The higher is the CREB level in neuron, the faster is the memory consolidation. Usually, cyclic AMP in the cell is destroyed by phosphodiesterase (PDE). Theoretically, the PDE inhibition increases the time of CREB activity and the effectiveness and rate of memory formation. During preliminary tests, PDE inhibitors have proved themselves to be an effective memory enhancer. Therefore, the pharmaceutical companies are actively developing PDE-based drugs (known as PDE-4).

Among the positive modulators of AMPA receptors there *Modafinil* and *Ritalin*, drugs that not only intensify the glutamate transmission, but also increase the concentration of noradrenaline and dopamine in the brain tissue. Modafinil

has not only mnemotropic, but also anti-depressive, adaptogenic, and narcoleptic effects. Ritalin has similar effects.

Among the «true» nootropics there are the drugs that activate cholinergic transmission, *Citicoline* (Ceraxon) and *Donepezil*. Citicoline (also known as cytidine 5'-diphosphocholine, CDP-choline) is a mononucleotide consisting of ribose, cytosine, pyrophosphate, and choline. Citicoline acts as a donor of choline for the biosynthesis of acetylcholine and increases its release in cholinergic nerve endings. It enhances attention, capacity to education, and memory. Citicoline intensifies dopamine synthesis, probably due to enhanced activity of tyrosine hydroxylase retarding the dopamine reuptake in the nerve endings. Both the receptor and the metabotropic mechanisms with nootropic and neuroprotective effect are typical for citicoline. Citicoline enhances the rapid regeneration of damaged cell surface and mitochondrial membranes while maintaining the cell integrity and bioenergetic capacity. Citicoline reduces the phospholipase content, which prevents apoptotic and necrotic death of neurocytes. The Citicoline metabolites: choline, methionine, betaine, and nucleotides derived from cytidine are involved in many metabolic processes and regulate the thiol-disulfide equilibrium of nervous tissue system. Citicoline stabilizes lipid rafts carrying the glutamate transport proteins thereby speeding up the removal of glutamate excitotoxic neurotransmitter from the synaptic cleft. Citicoline enhances phospholipid synthesis and neuron repair. The preclinical studies demonstrated the efficacy of Citicoline in reducing the severity of ischemic brain affection. Citicoline reduces the severity of apoptosis and degeneration of hippocampal neurons. It improves memory in experimental animals [34, 35]: the animals who administered Citicoline in the subacute phase of hemorrhage showed better motor recovery. In the structure of motor neurons, there are observed an enhancement of branching of dendrites and an increase in the spine density. These data indicate that Citicoline increases neuroplasticity in intact areas thereby facilitating functional recovery.

Clinical trials of Citicoline in acute phase of ischemic hemorrhage in Spain, Italy, France, Japan, and the United States have demonstrated that it facilitates the recovery of neurological function, as well as reduces the cerebral infarction in patients with ischemic stroke [35, 36, 37, 38, 39, and 40].

The ability of Citicoline to enhance cognitive function in patients with vascular pathology of the brain has been showed in a number of placebo-controlled studies. One of early tests showed a significant enhancement of cognitive functions, primarily attention, accompanied by improving affective status in 33 patients with vascular dementia treated with Citicoline at a dose of 1 g/day intravenously for 28 days [41]. A double-blind placebo-controlled study involving 100 patients with chronic cerebrovascular insufficiency demonstrated that being administered at a dose of 1 g/day intravenously Citicoline caused an improvement of cognitive, affective, and behavioral functions [42]. A double-blind placebo-controlled trial involving 146 patients with multi-infarct dementia proved that the administration of Citicoline at a dose of 750 mg/day intravenously for 2 months led to a significant improvement of Mini-Mental State Examination (MMSE) indicators, whereas in the placebo group a slight deterioration is reported [43]. Interestingly, that the repeated study conducted in 10 months demonstrated the sustainability of obtained results: the state of patients who administered Citicoline was stable, whereas the patients receiving placebo continued to deteriorate. The ability of Citicoline administered at a dose of 1000 mg/day intramuscularly by two courses of 4 weeks to enhance the cognitive and affective functions has been confirmed in placebo-controlled studies [44].

Using PET it has been showed that the improvement of cognitive function due to administration of Citicoline in patients with vascular dementia correlates with increased cerebral perfusion [45]. In patients with multi-infarct demen-

tia Citicoline not only improves Mini-Mental State Examination results, but also reduces the severity of depression symptoms assessed using the Hamilton scale [46]. The last conclusion is extremely important, given the common post-stroke depression and its adverse impact on the outcome. The drug can be effective also at the stage of mild cognitive impairment and cognitive deficit related to chronic deteriorative vascular process [47]. Fioravanti and Yanagi [52] in their survey published by the Cochrane Library in 2009, proceeding from the analysis of 14 double-blind placebo-controlled clinical studies conducted since 1978 concluded that Citicoline ensured a statistically significant moderate mitigation of the severity of cognitive function disorders in patients with cerebrovascular disease, at least, in short-term and medium-term horizons [48]. In patients with post-stroke cognitive impairment the long-term treatment with Citicoline (within 12 months) effectively improves functional and neurological recovery and facilitates recovery of cognitive functions, especially, orientation in time and attention [49].

The Citicoline favorable effect on cognitive function can be associated with enhanced activity of cholinergic system, enhanced synthesis and release of dopamine and norepinephrine in certain brain regions, enhanced phospholipid synthesis and stabilization of cell membranes, and enhanced glucose uptake by neurons [50]. Using the magnetic resonance spectroscopy it has been showed that the improvement of cognitive abilities of patients during treatment with Citicoline correlates with the accumulation of phosphatidylcholine in the brain [51].

The Cochrane survey [52] covers 14 studies involving older patients with a variety of disorders, from memory disorders to moderate vascular cognitive impairment, diabetes or senile dementia. The authors concluded that the effect of Citicoline on cognitive function was clearly evident at the behavioral level and it could be easily assessed clinically regardless of paradigm used for the assessment. Citicoline is well tolerated, with the placebo group having showed more side effects than the active treatment group [53].

Donepezil (Aricept) is central acetylcholinesterase inhibitor modulating dopamine and glutamate transmission. It is currently approved in the United States and indicated for suspending the progressive memory loss in Alzheimer's disease, as well as for the treatment of narcolepsy [54].

Donepezil is a specific reversible inhibitor of acetylcholinesterase: it increases the density of n-cholinergic receptors in cortex and hippocampus, is an agonist of D_2-receptors in cerebral cortex and a positive modulator of AMPA receptors, improves the brain cognitive and integrative activity, facilitates the learning process, enhances metal alertness and attentiveness, stimulates the short- and long-term memory. It is regarded as a promising means of secondary neuroprotection for reducing post-shock dysfunction.

The discovery of neurotrophic peptide factors led to the formation of a new strategy for pharmacotherapy, the peptidergic or neurotrophic treatment of diseases of the central nervous system. A complex of medical drugs called *neurotrophic cerebroprotectors* was developed to be used in the treatment of neurological disorders. *Cerebrolysin*, *Cerebrocurin*, and *Cortexin* are the most successfully used drugs for the treatment of neurological and psychiatric diseases. The recent studies showed the ability of these drugs to interact with receptors via G-protein and to increase the gene expression. The «biologically active conformations» have been proposed for them to ensure the drug preferable interaction with receptor.

Neurotrophic cerebroprotectors (Cortexin, Cerebrocurin, and Cerebrolysin) reduce the transmitter dysfunction by increasing the affinity of GABA receptors and limiting the hyper-excitability of NMDA receptors. Cerebrocurin and Cortexin enhance the affinity of BDNF binding to its receptors. The effect of drugs on trkB receptors of neurotrophins can indicate that they are involved in the regulation of natural growth factors. The cure of CNS pathologies (cerebral ischemia, hypertension, alcoholism, and fetal alcohol syndrome) in animals with neurotrophic cerebroprotector (Cerebrocurin and Cortexin) re-

sulted in an enhanced expression of c-fos early response gene in the hippocampus and sensorimotor cortex, against the background of cognitive functions recovery. Cerebrocurin shows mitoprotective properties in the case of CNS pathology (cerebral ischemia, hypertension, alcoholism, fetal alcohol syndrome) as it mitigates the mitochondrial dysfunction and regulates (via HIF-1) the activity of cytosolic-mitochondrial compensatory energy shunts. In author's opinion, the Cerebrocurin ability to influence the concentration of HSP 70 proteins is a key aspect of the mechanism of its neuroprotective and nootropic effect. HSPs are involved in the regulation of CNS cognitive and mnemonic functions through the chaperone activity, i.e. the ability to recognize damaged or newly synthesized memory proteins and to make ATP-mediated repair of their structure.

Numerous experimental and clinical studies have demonstrated the feasibility of an integrated drug based on a fixed combination of Piracetam and Thiotriazoline and called *Thiocetam* [55].

Thiocetam as a nootropic drug reduces the cognitive deficits caused by hypoxia, cerebral ischemia, neurotoxins, and alcohol. Thiocetam alleviates the mnemonic deficit caused by deprivation of paradoxical phase of sleep and by «conflict situation». It significantly surpasses Piracetam by the mnemonic strength.

Thiocetam has a positive effect on the primary processing of information, its fixation and consolidation, eliminates the mnemonic deficit not only before the training of animals, but also after it. Piracetam is effective only at the early stages of memory formation. Thus, Thiocetam is characterized by a wider range of nootropic effects as compared with Piracetam [20, 25, 27, 32, 55, 56, and 57].

The Thiocetam efficacy data are of particular interest for modeling various forms of cerebral ischemia. Thiocetam administered after modeling acute stroke significantly reduces the inhibition of unconditioned reflexes to noxious, photic, and sound stimuli. It significantly alleviates neurological disorders and improves motor activity, orientation, and capacity for training in the animals.

For the patients who administered Thiocetam, a decrease in the amount of ischemia-modified neurons and slept capillaries and a mitigation of perivascular and pericellular edema were reported. Decreasing number of slept capillaries is an important pathogenetic factor for the prevention of neuronal death. Thiocetam significantly activated the proliferation of glial cells and their function and caused enhanced satellitosis, which was a major factor in ensuring the livelihoods of neurons during the development of ischemic brain damage of any etiology.

As compared with Piracetam, Thiocetam better corrects the brain bioenergy deficit in acute cerebrovascular disorders (stroke), mainly due to the recovery of aerobic energy generation. It raises the RNA level in the brain tissues of animals with stroke, which reflects the activation of protein synthesis and is an adaptive response to hypoxia, which provides restructuring of brain metabolism without increasing oxygen demand. Thiocetam's ability to effect the DNA and RNA level, as well as the nuclease activity in the cerebrospinal fluid and in the blood has been reported for the patients with initial manifestations of cerebrovascular disease [56, 58].

Thiocetam inhibits the activity of free radical reactions in the ischemic brain, significantly reduces the accumulation of bio-toxic products (aldehydes, ketones) thereby minimizing their neurodestructive effect on neurons.

The researches have shown that Thiocetam being administered at a dose of 20—30 ml intravenously, by drop infusion, in 100 ml of saline solution 1 time per day facilitates the effective improvement of neuropsychological status, indicators of brain bio electrical activity of in patients with circulatory encephalopathy (stage II) complicated with atherosclerosis.

Thiocetam has a strong antioxidant effect. It causes reducing the markers of oxidative and nitrosating stress (aldehyde phenylhydrazone, carboxyphenylhydrazone, and nitrotyrosine) and the endothelial dysfunction markers (homocysteine and endothelin-1) in parallel with increasing con-

tent of recovered equivalents of thiol-disulfide system in patients with chronic cerebral ischemia. Having been treated, the patients showed signs of improved hemodynamics and alleviated pyramidal insufficiency, as well as sensitive and coordination disorders. Among the positive effects of treatment with Thiocetam there was also enhanced reproduction of visual, auditory, and verbal stimuli and raised mental capacity.

CEREBROPROTECTORS

Numerous experimental studies have established that the neuroprotective and nootropic effects of Cerebrocurin and Cortexin are based on their ability to mitigate mitochondrial dysfunction and neuroapoptosis of complex pathological processes leading to persistent cognitive impairment. In author's opinion, the mechanism of antiapoptotic effect of Cerebrocurin is related to its ability to influence the neuron genome in extreme condition, namely: Cerebrocurin enhances the expression of global transcription factor AP-1 and antiapoptotic protein Bcl-2, as well as intensifies the synthesis of key antioxidant enzymes, Zn-Cu-SOD and Mn-SOD, and the expression of glutathione enzymes. In addition, according to the results of several researches, which are in good agreement with the previous studies of author's team, Cerebrocurin modulates the activity of mitochondrial NO-synthase thereby alleviating the intensity of nitrosating stress and, consequently, resulting in inhibited neuroapoptosis. Cerebrocurin suppresses all manifestations of apoptosis (ROS production, fragmentation of CA-1 neuron nucleus in the hippocampus area, and decrease in the number of apoptotic modified cells) and enhances the expression of bc1-2. It surpasses Cortexin, Cerebrolysin, Semax, Noopent, and Piracetam by the strength of antiapoptotic effect.

The experimental studies have showed that the simulation of CNS pathology followed by cognitive deficit leads to a significant change in the genome response, which manifests itself by violation of the pattern of *c-fos* early response gene expression (a significant decrease in the number of *c-fos*-positive neurons in the hippocampus and

The mechanism of action of Thiocetam [55]

Properties	Pharmacological effects
1. Antioxidant	1. Inhibition of pathways for the formation of reactive oxygen intermediates by neuron bioenergy systems 2. Increased activity of AO enzymes, especially SOD 3. Reduced production of reactive oxygen intermediates in the Fenton and the Haber-Weiss reactions 4. Inhibition of nitrosating stress reactions 5. Increased activity of glutathione component of thiol-disulfide system
2. Anti-ischemic	1. Mitoprotective effect (alleviation of mitochondrial dysfunction) 2. Increase in high-energy phosphates due to ATP synthesis in aerobic reactions 3. Activation of mitochondrial respiratory chain 4. Stimulation of RNA and protein synthesis in ribosomes 5. Enhancement of satellitosis of glial cells 6. Improvement of cerebral hemodynamics
3. Nootropic	1. Inhibition of protein oxidative modification in the brain 2. Improvement of neurocyte trophics 3. Activating effect on GABA shunt 4. Increase in concentration of S-100
4. Antiapoptotic	1. Increase in concentration of antiapoptotic proteins bcl-2 2. Inhibition of NO-dependent mechanisms of apoptosis

sensorimotor cortex). The changes in the expression pattern in the early response gene nucleus, «tertiary messengers» (*c-fos* gene, *c-jun* gene, *krox-20* gene, *zif / 268* gene, etc.) can be considered a genome non-specific response to any noci-influence, including ischemia. The proteins of fos-, jun-, and krox-gene families are known to play a crucial role in controlling the cell cycle: development, growth, and differentiation of cells, as well as to determine the fate of differentiated neurons and CNS cognitive and mnemonic functions. Cerebrocurin normalizes the *c-fos* gene expression. It modulates the activity of mitochondrial NO-synthase by mitigating the nitrosating stress and regulating the opening of mitochondrial pore and, as a consequence, alleviates the mitochondrial dysfunction. Probably, it influences the activity of mitochondrial nitroreductase through limiting the formation of peroxynitrite. In author's opinion, the Cerebrocurin property to activate the synthesis of HSP-proteins is explained, *firstly*, by its ability to modulate the genome response under conditions of hypoxia thereby activating the global transcription factors that trigger the HSP synthesis. *Secondly*, several studies have demonstrated the ability of neurotrophic cerebroprotector (Cerebrocurin, Cortexin, and Cerebrolysin) to communicate directly with HSP-proteins, and to present them as such to dendritic cells. The experimental data have allowed the author to suggest that the energotropic effect of Cerebrocurin and Cortexin can be realized indirectly via the expression of HSP-proteins and the activation of enzymes involved in the operation of malate-aspartate shuttle. However, it is necessary to take into account also the direct ergotropic effect of these drugs related to their ability to influence the processes of mitochondrial dysfunction by inhibiting the opening of mitochondrial pore and the release of cytochrome C into the cytoplasm, as well as their antioxidant activity caused by their influence on the expression of genes encoding the synthesis of antioxidant system enzymes, catalase and superoxide dismutase, and in the case of Cerebrocurin, by its influence on the expression of c-fos gene [4].

Currently, Cerebrocurin is widely used in clinical practice. *Cerebrocurin* has been established:

- To be an effective therapeutic agent for the treatment of patients with residual effects of stroke (including those who underwent a reconstructive surgery on the great vessels as a result of stroke), as well as of patients with early and moderate chronic DE;
- To cause a subject improvement (improvement of general condition, enhancement of general motor activity, alleviation and disappearance of headaches and dizziness, pain relief and increase in range of motion in the paretic limb, mitigation of emotional distress) in the patients with various severity of cerebral vascular disease, if administered in the course of protracted treatment;
- To cause a restitution of pathological neurological symptoms (vasodepression and reduced spasticity, increased muscle strength and range of motion in the paretic limb, reduced anisocoria, improvement of coordination), if administered in the course of protracted treatment;
- To improve memory, attention, emotional and volitional attitude (according to neuropsychological studies, for the patients with aphasic disorders there were reported an improvement in spontaneous, interactive, automatic, and repetitive speech, ability to paraphrase the text, and capacity of auditory-verbal memory);
- To have a positive effect on cerebral hemodynamics (according to ultrasonography data, the patients with residual effects of stroke and DE reported a vasodepression, adequate changes in pulse volume, a slight intensification in blood circulation through the main (external and internal carotid) arteries, a mitigation of asymmetry of blood circulation and venous circulatory distress);
- To cause a complex restructuring of functional systems generating alpha, beta, delta, and theta rhythms, which is different for the patients with different types of EEG abnormalities (increase in the brain energy, mitigation of pathological activity, the regulating effect on brain

rhythm pacemakers at all levels (cortical, cortical-subcortical, and hemodynamic), to create a favorable basis for the physical, psychological, and social rehabilitation of patients with cerebral vascular pathology, especially, those who have suffered stroke);

- Not to have side effects; to effect favorably the cerebral hemodynamics and neurometabolism (due to Cerebrocurin's neuropsychological functions combined with a normalizing effect on liver, lipid and lipoprotein metabolism it is recommended to be used for the treatment of various forms of cerebral vascular disease).

The initial dose of Cerebrocurin shall be, at least, 20 ml (10 injections). Intensification of therapy in the form of extension of the initial course to 15—20 injections and repeated courses are highly recommended in the case of severe organic brain pathology, particularly, for the patients who have suffered stroke.

CONCLUSIONS

This paper summarizes the published data on the clinical and pharmacological properties of neuro-psychotropic drugs, the nootropics. Every year, the wide range of nootropics expands with new drugs. This requires that the modern clinician knows of the molecular and biochemical mechanisms and the individual characteristics of the clinical use of drugs.

The current strategy of the treatment of chronic cerebral ischemia involving nootropics allows for quick and delayed mechanisms of neurodegeneration and subsequent cognitive impairment and identifies several metabolically achievable goals in the struggle for the survival of neurons and enhancement of their functional activity: to normalize the balance of excitatory/inhibitory transmitters, to mitigate the mitochondrial dysfunction, and to enhance the expression of protective proteins.

Therefore, it is necessary to include nootropics, on the differentiated basis, at each subsequent stage of complex therapy of chronic cerebral ischemia allowing for their mechanisms of action in the view of the normalization of «target» links of neurometabolism and the inhibition of ischemic cascade reactions, and at the systemic level, for the mitigation of neurological symptoms and the improvement of CNS cognitive functions.

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НООТРОПИ У КОМПЛЕКСНІЙ ТЕРАПІЇ ХРОНІЧНОЇ ІШЕМІЇ МОЗКУ

Викладено клініко-фармакологічну характеристику ноотропів — однієї з найбільш продуктивних груп нейропсихотропних лікарських препаратів. Побудовано класифікацію ноотропних засобів за основним механізмом дії. Наведено приклади клінічного застосування препаратів при хронічній ішемії мозку.

Ключові слова: цереброваскулярні захворювання, когнітивні порушення, нейропротекція, ноотропи.

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НООТРОПЫ В КОМПЛЕКСНОЙ ТЕРАПИИ ХРОНИЧЕСКОЙ ИШЕМИИ МОЗГА

Изложена клинико-фармакологическая характеристика ноотропов – одной из наиболее продуктивных групп нейропсихотропных лекарственных препаратов. Построена классификация ноотропных средств по основному механизму действия. Приведены примеры клинического применения препаратов при хронической ишемии мозга.

Ключевые слова: цереброваскулярные заболевания, когнитивные нарушения, нейропротекция, ноотропы.

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