THE ISSUES OF CLASSIFICATION AND CHARACTERIZATION OF NEUROTROPIC AGENTS IN THE TREATMENT OF PATIENTS WITH CEREBROVASCULAR DISEASES

Fedorov VN[1] ✉, Petrovskii AK[2], Vdovichenko VP[3], Zakharova MN[2], Arshinov AV[2]

[1] Yaroslavl State Pedagogical University named after K. D. Ushinsky, Yaroslavl, Russia

[2] Yaroslavl State Medical University, Yaroslavl, Russia

[3] State Medical University of Grodno, Grodno, Republic of Belarus

In developed countries, mortality from cerebrovascular diseases (CVD) is about 12%, which is second only to mortality from cardiovascular diseases. In order to make treatment of CVD successful, a complex approach to the problem is required with compensation for cardiovascular diseases (atherosclerosis, arterial hypertension, rheological properties of blood, etc.), elimination of neurological and psychopathological syndromes, improvement of cerebral circulation and use of neurotropic agents. The use of neurotropic agents by a practicing physician is complicated due to the lack of a clear classification reflecting their position and significance in CVD treatment. It is suggested that taking into account the predominant mechanism of action targeting for a pathological process, neurotropic agents should be divided into 4 groups such as neuroprotectors, neurometabolics, nootropics and neurotrophic agents (direct activators of neutrophin synthesis in the brain). The last group is related to analogues of regulatory peptides and shares positive properties with medicinal agents from other groups: they have the properties of primary and secondary neuroprotectors, neurometabolics, and produce a positive effect on cognitive functions of a healthy and sick person. Heptapeptide Semax is a typical agent belonging to this group.

Keywords: cerebrovascular diseases, neurotropic agents, neuroprotectors, neurometabolics, nootropics, neurotrophic agents, semax.

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✉ **Correspondence should be addressed:** Vladimir N. Fedorov
ul. Technoparkovaya, 11/2, Yaroslavl, 150000, Russia; fedorv.vladimir@hotmail.com

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ПРОБЛЕМЫ КЛАССИФИКАЦИИ И ХАРАКТЕРИСТИКА НЕЙРОТРОПНЫХ СРЕДСТВ, ПРИМЕНЯЕМЫХ ДЛЯ ТЕРАПИИ НАРУШЕНИЙ МОЗГОВОГО КРОВООБРАЩЕНИЯ

В. Н. Федоров[1] ✉, А. К. Петровский[2], В. П. Вдовиченко[3], М. Н. Захарова[2], А. В. Аршинов[2]

[1] Ярославский государственный педагогический университет им. К. Д. Ушинского, Ярославль, Россия

[2] Ярославский государственный медицинский университет, Ярославль, Россия

[3] Гродненский государственный медицинский университет, Гродно, Республика Беларусь

Смертность от цереброваскулярных заболеваний (ЦВЗ) в экономически развитых странах составляет около 12%, уступая лишь смертности от заболеваний сердца. Успешное лечение ЦВЗ предполагает комплексный подход к проблеме, учитывающий компенсацию сердечно-сосудистых нарушений (атеросклероз, артериальная гипертония, реологические свойства крови и др.), устранение неврологических и психопатологических синдромов, улучшение церебральной циркуляции и применение нейротропных средств. Для практического врача использование нейротропных средств осложняется отсутствием внятной классификации, отражающей их место и значимость в лечении ЦВЗ. Предложено и обосновано разделение нейротропных средств на четыре группы, исходя из преимущественного механизма воздействия на патологический процесс: нейропротекторы, нейрометаболики, ноотропы и нейротрофические средства (прямые активаторы синтеза нейротрофинов головного мозга). Препараты последней группы относятся к классу аналогов регуляторных пептидов и во многом объединяют положительные свойства лекарственных средств из остальных групп: они обладают свойствами первичных и вторичных нейротротекторов, нейрометаболиков и положительно влияют на когнитивные функции здорового и больного человека. Типичным представителем данной группы лекарственных средств является гептапептид семакс.

Ключевые слова: цереброваскулярные заболевания, нейротропные средства, нейропротекторы, нейрометаболики, ноотропы, нейротрофические средства, семакс

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✉ **Для корреспонденции:** Владимир Николаевич Федоров
ул. Технопарковая, 11/2, Ярославль, 150000, Россия; fedorv.vladimir@hotmail.com

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The most important task of modern medicine deals with how to increase the length of a human life with simultaneous preservation of high physical and mental capacity. It is impossible to solve the task with no significant progress in treatment of nervous and primarily cerebrovascular diseases (CVD). In developed countries, CVD mortality constitutes about 12%, which is second only to mortality from cardiovascular diseases [1]. According to the National Medical Research Center for Therapy and Preventive Medicine, up to 25% of men and 39% of women in Russia die of cerebrovascular diseases

[2]. The most dangerous CVD include acute cerebrovascular diseases (ACVD): stroke is the second leading global cause of death, being the main reason for disability among adults, mental disability and age-associated decrease in cognitive capabilities [3–7]. Chronic cerebrovascular disease (CCVD) is one of the most widely spread syndromes in clinical neurology leading to structural and functional changes in white and gray matter along with neurodegenerative diseases of the brain. It is the basic cause of development of cognitive disturbances in 5–22% of the elderly [8].

Modern drug therapy of nervous diseases, including CVD, is pathogenetic. A doctor uses a medicinal agent to influence the principal links of disease pathogenesis, trying to interrupt its course. Treatment of a patient depends on dynamics of a pathological process: the used agents can be changed depending on the time from disease onset, its type and clinical picture [9,10]. In acute conditions associated with blood circulatory disturbances (stroke and TIA), the struggle against parabiotic dead-end cells (penumbra in stroke) is the most important one. A patient's life and a possible scope of neurological and cognitive deficiency depend on effectiveness of the conducted therapy [2,3,11]. The most significant activities in CCVD include support of a normal functional state of neurons, regulated activity of neuromediatory systems and decrease in apoptosis rate [10]. Insufficiently effective treatment of nervous diseases worsens the quality of life, decreases social and familial adaptation, increases mortality and reduces the length of life [13].

In order to make treatment of CVD successful, a complex approach to the problem is required with compensation for cardiovascular diseases (atherosclerosis, arterial hypertension, rheological properties of blood, etc.), elimination of neurological and psychopathological syndromes, improvement of cerebral circulation and use of neurotropic agents [14]. Neurotropic agents with at least one of three important neurotropic effects (mnestic, neuroprotective and neurometabolic) have occupied a leading position in pathogenetic pharmacotherapy of the CNS during the last two decades. They have various mechanisms of action, different points of application at the neural level and inadequate clinical effectiveness and tolerability, but, in the majority of cases, a qualitatively similar therapeutic effect (positive influence on dynamics of neurological and cognitive deficiency, general condition, working capacity, self-service, etc.) [15,16].

The issues of classification of neurotropic agents. As a rule, neurotropic agents applied in CVD therapy have not only a multicomponent but also a crossover nature of action. That's why there are so many synonyms such as neuroprotectors, neurometabolic agents, true and mixed nootropic agents, neurodynamic, neuroregulatory, neurotrophic, neuroanabolic or eutotropic agents, neurometabolic cerebroprotectors, cerebroactivators, etc. [15,17]. As the compounds have different chemical structures and mechanisms of action, a single consistent classification is difficult to compose [3,17]. The existing classifications are usually based on the structural difference between neurotropic agents (which is of theoretical interest only) or/and used by authors to reflect all more or less significant properties of the agents. That's why the classification systems are too complex to be applied in practical medicine [3,16,18].

At the same time classification signs and definitions of medicinal agent groups should be clear to a practicing physician and help the doctor treat patients and select the most suitable drug. To achieve the purpose, the classification of neurotropic agents must be based on the principle of 'the leading or determinant type of action'. The mechanism of action of any drug has a type of action determining its therapeutic effectiveness in a certain disease. It is also necessary to consider a possible presence of clinically significant additional types of action. In this case, one of the most important tasks of clinical drug classification needs to be fulfilled. It is about making the choice of agents for monotherapy and combined pharmacotherapy clearer and simpler. Working with medicinal agents from two different groups, a doctor must be sure that they are not only compatible, but also mutually increase a therapeutic activity by way of potentiation (more desirable) or combination. At the same time, just equal enumeration of different aspects of the agent mechanism of action can make a doctor take a wrong decision about the combination of drugs.

Taking into account the abovementioned requirements, we suggest that only 4 groups of medicinal agents such as neuroprotectors, neurometabolic agents, nootropics and neurotropics should be differentiated among neurotrophic agents used in clinical practice by now.

NEUROPROTECTORS

Neuroprotectors are medicinal agents that increase resistance of cerebral tissue to the damaging effects of various genesis. **The most important feature of their mechanism of action consists in interrupting a cascade of pathological reactions (primarily of hypoxic and ischemic genesis) that cause neuronal damage**; they are also used to treat neurological deficiency and cognitive disturbances [19].

A clinical and pharmacodynamic subclassification of neuroprotectors is provided. It is based on the influence of the agents on certain mechanisms of primary (ischemic cascade) and delayed death of neurons. By now, there exist four groups of medicinal agents such as glutamate antagonists and different modulatory areas of glutamate receptors; antioxidants; precursors of membrane phospholipids or membrane protectors; agents with a complex mechanism of action.

Glutamate antagonists and various modulatory areas of glutamate receptors [20,21]:

- direct NMDA-receptor agonists demonstrated a marked toxicity and their tests failed to be beyond the scope of the experiment;
- low-affinity direct NMDA-receptor agonists: remacemide;
- non-competitive NMDA-receptor antagonists: aptiganel (cerestat), acatinol memantin (memantin) is almost the only widely applied agent of this group;
- glutamate release inhibitors: lubelusol.

As glutamate and calcium excitotoxicity is one of the leading links of neuronal death pathogenesis, serious hopes were put upon the group of antiglutamate agents from the mid-1990s onwards supported by vast experimental data. However, in acute CNS pathology, clinical activity of the agents was highly modest [22].

Antioxidants: their basic function is to protect neuronal membranes from damage by free radicals [23]. From 1980s, antioxidants have been used in neurological practice. Their included ascorbic acid, vitamin E, ceruloplasmin, ubiquinone, emoxypine, olyphenum, etc. Their basic shortcoming is a weakly marked antioxidant activity requiring long-term administration in high doses.

Mexidol (INN — ethylmethylhydroxypyridine succinate; chemical rational name — 3-oxy-6-methyl-2 ethylpyridine succinate), salt of emoxypine (similar to pyridoxine) and succinic acid, is an antioxidant with a real activity. Exogenous

succinate poorly penetrates via biological membranes, whereas emoxypine makes the transport easier. Emoxypine determines an antioxidant activity of mexidol, whereas succinate defines its neurometabolic constituent [25].

Precursors of membrane phospholipids (membrane protectors): their basic therapeutic mechanism is represented by reparation of damaged membranes due to phosphatidylcholine synthesis [24,26]**:**

- citicoline (cytidine-5-diphosphocholine) is a mononucleotide, naturally occurring endogenous compound, which is an intermediate in the synthesis of phospholipids in cell membranes [24,27,28];
- choline alfoscerate (alpha-glycerylphosphorylcholine-choline, gliatilin) is precursor of acetylcholine and phosphatidylcholine. The agent contains 40.5% of metabolically protected (formed in the brain only) choline [19].

They can't become the leading agents to treat the pathology, considering the mechanism of action of antioxidants and membrane protectors (suppressed activity of free-radical oxidation and preservation of membrane functions) and pathogenesis of the main hypoxic-ischemic cerebral diseases (activation of lipid peroxidation and membrane damage occur at final stages of an ischemic cascade). They are the most effective when used in complex therapy.

Medicinal agents with a complex mechanism of action. They currently include **Gingko Biloba preparations** (Memoplant, Tanacan, Bilobil, etc.). In Europe, they use only ginkgo leaves as crude drugs to make extracts standardized by content of basic effective agents (EGb 761): ginkgolides A, B and C (6%), bilobalide A (about 3%), containing about 24% of flavone glycosides. The set of active ingredients determines polypotency of clinical effects. The mechanism of therapeutic action is associated with inhibited processes of free-radical oxidation; membrane protective action (inhibition of PLC); inhibition of cerebral edema, anti-inflammatory action and decreased intensity of apoptosis [29].

Description of neuroprotective agents often includes data on calcium channel blockers (CCB: nimodipine, cinnarizine, flunarizine, etc.) as calcium ions play an important role in pathogenesis of neuronal damage (calcium and glutamate excitotoxicity). However, all CCB used in clinical practice disturb the current of calcium ions only through L-type slow voltage-gated channels located primarily in smooth muscles (for instance, a vascular wall). Calcium and glutamate excitotoxicity is implemented in response to excitation of glutamate receptors. Then calcium is distributed inside a cell via a fast receptor-associated ion channel, not affected by CCB. A neuron also has slow calcium channels, but these are not L-type, but N- and T-type channels [30]. In CVD, anti-calcium agents prevent overload of smooth muscles with calcium ions, increasing arrival of blood to the affected area and improving neuron survival [30]. This was an indirect protective effect only.

NEUROMETABOLIC AGENTS

The leading factor preserving neuroganglian structures in ischemia and hypoxia is represented by support of stable cerebral blood flow, oxygenation and creating the conditions that activate oxygen and glucose uptake to enable the Krebs cycle. In damaged nerve cells, restitution (restorative) processes can occur only in case of proper functioning of intracellular redox processes. **The main mechanism of action of neurometabolic agents is the effect produced on the principal link of pathogenesis of nerve injury (energy deficiency).** Neurometabolic agents mainly exert an antihypoxic action.

Tissue hypoxia results in energy deficiency and lactic acidosis, thus, activating the ischemic cascade. Decreased energy deficiency prevents ischemic cascade or decreases activity of all the links [23,25,27].

Neurometabolic agents form a heterogenous group of medicinal agents with different mechanisms of action. They have a common ability to increase effectiveness of neuronal metabolism under difficult conditions (hypoxia, ischemia, oxidative stress, etc.). As glucose is almost the only energy substrate for a neuron, and stimulation of its arrival to a cell is an important component of rational pharmacotherapy of brain diseases, the majority of effective neurometabolic agents can stimulate oxygen or glucose consumption and uptake in full-scale ischemia and hypoxia.

Neurometabolic agents differ by origin and mechanism of action. Among them, the following groups of medicinal agents can be distinguished:

- Tissue hydrolysates
- Neurometabolic agents with a marked mnestic activity
- Intermediates of Krebs cycle
- Fatty acid oxidation inhibitors
- Respiratory chain natural components
- Artificial redox systems
- High-energy compounds

Tissue hydrolysates. Three tissue hydrolysates (Actovegin, Cortexin, Cerebrolysin) are used in Russian neurology practice. Other agents of the group (Cerebramin, Cerebrocurin) are not of practical importance. Actovegin is a hemoderivative derived from calf blood via dialysis and ultrafiltration. Cerebrolysine is hydrolysate extracted from porcine brain tissue. Cortexin is obtained from the cerebral cortex of cattle and pigs not elder than 12 months.

They all contain microelements, vitamins, aminoacids, various intermediates, oligopeptides (with molecular weight of no more than 10 kJ) in certain proportions and concentrations [27]. Tissue hydrolysates have multiple components, but oligopeptides are the principal active ingredients. They are responsible for the basic mechanism of action for this group such as high glucose utilization by neurons. It produces a positive effect on their survival in hypoxia and ischemia, improves effectiveness of energy metabolism and partially prevents blockage of some synthetic processes (synthesis of neurotrophins is partially preserved) [27,31].

No pharmacokinetics of Actovegin, Cortexin, Cerebrolysin has been properly examined. That's why it is not clear which components of the medicinal agents penetrate through the blood-brain barrier (BBB) and to what extent [32].

Neurometabolic agents with a marked mnestic activity. This group is not homogenous and contains as follows:

- GABA derivatives: aminalon (gammalone), picamilonum, pantogam (pantocalcin).
- Derivatives of pyridoxine: pyriditol (encephabol, enerbol, cerebol).
- Medicinal agents containing dimethylaminoethanol: meclofenoxate, acephen, deanol, centrophenoxine.

These agents have similar mechanisms of action: they accelerate penetration of glucose via the BBB and improve its uptake by cells in different brain sections, activate synthesis of ATP and creatine phosphates, increase neuronal survival in hypoxia and ischemia, and improve cerebral blood flow. This results in more intense plastic processes in neurons and improves the brain integrative and mnestic activity [33,34].

In CVD, they are indicated in case of disturbed cognitive functions in CCVD during the restorative period after stroke. Homopantothenic acid preparations have a sedative psychopharmacological action. They decrease the motor excitability producing a simultaneous activating effect on working capacity and mental activity; they also produce an anticonvulsant action [34]. Pyritinol has a marked tonic effect, whereas the agents containing dimethylaminoethanol can cause excitation [35].

Neurometabolic agents containing succinic and fumaric acids (preparations based on Krebs cycle intermediates). Medicinal agents based on succinic acid include reamberin (1.5% solution for infusions) and cytoflavin (contains succinic acid, inosine, nicotinamide and flavin mononucleotide). The neurometabolic effect of Mafusol and Confumin is largely associated with succinate exchange (15% solution of sodium fumarate for infusions) [25].

Fatty acid oxidation inhibitors. Direct (partial) fatty acid oxidation inhibitors include ranolazine, trimetazidine, mildronate, whereas indirect ones include carnitine [25].

Mildronate is an analogue of gamma- butyrobetaine, carnitine precursor: it reversibly limits the rate of carnitine biosynthesis from its precursor gamma- butyrobetaine [36,37]. Trimetazidine inhibits 3-ketoacyl coenzyme A thiolase, which is one of the key enzymes of fatty acid oxidation almost in every tissue, including myocardium and brain [25]. Carnitine is important in transfer of long-chain fatty acids via the internal membrane of mitochondria and plays a leading role in formation and regulation of azetyl-coenzyme A [25]. D, L-carnitine chloride, L-carnitine (Elcar) and acetyl-L-carnitine (Carnycetin) are used [38,39].

Natural components of the respiratory chain. Antihypoxic agents which represent natural components of mitochondrial respiratory chain and participate in electron transfer are of practical importance. They include cytochrome C and ubiquinone (ubinon). These agents fulfil a function of replacement therapy as in hypoxia mitochondria lose a part of their components due to structural disturbances. Idebenone can be considered as ubiquinone derivate. It is (5 times) smaller than Q10 coenzyme, less hydrophobic and has a greater antioxidant activity [40–42].

Artificial redox systems. Antihypoxic agents with electron-accepting properties that form artificial redox systems compensate for deficiency of a natural electron acceptor (oxygen) in hypoxia. They bypass the respiratory chain links overloaded with electrons and thus partially restore its function. Moreover, artificial electron acceptors can ensure oxidation of pyridine nucleotides (NADH) in cellular cytosol preventing inhibition of glycolysis and excessive lactate accumulation. Oliphen (hypoxen) which is a synthetic polyquinone has been implemented into medical practice. Oliphen bypasses transport of electrons in mitochondrial respiratory chain (from complexes I and II to complex III), as its redox potential has values close to those of cytochrome oxidase [25].

High-energy compounds

Preparations of creatine phosphate (neotone) are used. Unlike ATP, it can penetrate via cellular membranes well [25]. Speaking about neurometabolic agents, it should be noted that their principal point of application in medical practice is represented by acute hypoxic and ischemic conditions which are the subject of urgent neurology. Not all the groups of preparations are used in therapy of a chronic neurologic pathology. They are commonly used as a component of complex treatment only.

NOOTROPICS

Nootropics (comes from Greek 'noos' = mind and 'tropos' = changed) are medicinal agents that produce a specific influence on higher integrative functions of the brain. They improve memory, make the educational process easier, both in a healthy person, and in case of disturbances [17,18]. A nootropic action is directly associated with the effect produced on certain structures of the brain. However, higher integrative functions of the brain can be improved indirectly (as a rule, in their abnormal decrease). For instance, this can be done due to improved cerebral circulation and microcirculation or optimization of metabolic processes in a neuron.

In the second case, it would be correct to mention not a 'nootropic effect', but 'a neurocorrecting or psychoenergetizing action' of the drugs. Considering the conditions, a group of nootropics includes a few compounds, when an effect on cognitive functions is prevalent, but not additional or indirect. These are derivatives of pyrrolidine (piracetam, pramiracetam, phenylpiracetam) and regulatory neuropeptides (noopept, semax, selank).

The nootropic mechanism of action is complicated, diverse and not studied yet. There is a well-reasoned point of view, according to which nootropics penetrate through the BBB and undergo metabolism. This results in formation of compounds that have structures similar to endogenous agents that regulate the processes of intellectual footprint formation and integrative brain activity. However, effect of nootropics on synthesis and degradation of these compounds is not excluded [18,33, 43–45].

There are two generations of nootropics. Generation 1 nootropics include pyrrolidine derivatives (piracetam, pramiracetam, phenylpiracetam); they intensify initial data treatment and memory consolidation. Generation 2 nootropic agent is a synthetical analogue of Noopept (memory dipeptide) and analogue of Semax regulatory peptides. Unlike pyrrolidine derivatives, the analogue produces an effect on all 3 phases of memory trace formation (processing): initial data treatment, data consolidation and extraction.

Piracetam

Piracetam has been used in clinical practice for five decades. It entered the market in 1972 under the name of Nootropil and was intended for treatment of memory and balance disturbances. Later appeared other piracetam-like compounds primarily used to treat cognitive disturbances such as pramiracetam, phenylpiracetam, oxiracetam and aniracetam (the last two medicinal agents are not used any longer) [18,44].

A positive clinical effect of piracetam is the most pronounced in patients with mild age-related cognitive disturbances and during the restorative period of ischemic stroke. In CVD, piracetam has a number of limitations: it is not used during the acute period of cerebral damage as it intensifies energy deficiency with anaerobic energy transfer and lactate formation (with possible acidosis); requirement of a cell in oxygen is increased under hypoxia (steal syndrome). Piracetam is also contraindicated in hemorrhagic stroke [45].

Phenylpiracetam (N–carbamoyl–methyl-4-phenyl-2--pyrrolidone) was implemented in medical practice in 2003 as Phenotropil. It is significantly superior to similar doses of piracetam by a nootropic activity and produces additional psychostimulating and anxiolytic effects [18].

Pramiracetam is piracetam derivative, where the amide group was substituted by 2-aminoethyl dipropan. Its bioavailability is similar to that of piracetam. However,

it has a greater activity and, thus, is used in smaller doses. Pramirocetam effectiveness was more pronounced in younger patients than in the elderly [18,44].

Noopept (memory dipeptide analogue — N-Phenylacetyl-L-prolylglycine ethyl ester) belongs to II generation nootropics, exhibits a marked mnestic and antiamnestic activity in significantly lower doses and much earlier than piracetam [18].

NEUTROTROPHIC AGENTS (NEUROTROPHIN SYNTHESIS MODULATORS)

The group includes medicinal agents that produce a direct effect on the synthesis of cerebral neurotrophic factors. As a high level of neurotrophins produces a neuroprotective (primary and secondary) and neurometabolic effect, neurotrophic agents are neuroprotectors and neurometabolics with equal effectiveness.

Availability of additional mechanisms of effect on the nervous tissue expands their therapeutic capabilities.

It is expressly asserted by now that **analogues of regulatory peptides** produce a direct effect on neurotrophin synthesis. Regulatory peptides (RP) are represented by universal endogenous bioregulators of cellular functions in human beings and animals. Structurally, they belong to oligopeptides being a part of the complex system of specialized signalling molecules that transfer information between cells of an organism. Their principal function is to integrate the nervous, endocrine and immune systems into a single functional continuum [46–49]. The system of regulatory peptides participates in regulation of almost any physiological responses by supporting essential balance (homeostasis) of all its systems. The specific feature of the regulatory peptide system is represented by multifunctionality in the majority of them, i. e. every compound can produce an effect on several physiological functions. Over 10,000 of various RP are known by now [48].

In a cerebral tissue, RP make the level of neurotrophic factors normal. The factors inhibit different mechanisms of a pathological cascade, on the one hand, and promote a better restoration of lost functions, on the other hand. This improves the functional plasticity of the cerebral tissue (a number and quality of connectivity is increased) and enables better restoration of lost functions [46–48].

As far as the group of regulatory peptide analogues goes, Semax is used in neurology, and Selank is applied in psychoneurology. Semax is a synthetic peptide made on the basis of $ACTH_{4–7}$ (Met-Glu-His-Phe) fragment with a marked physiological activity towards the CNS in the lack of hormonal activity. Pro-Gly-Pro tripeptide with a neuroprotective activity was attached hereto to protect from hydrolysis by peptidases [46].

The therapeutic action of Semax in CVD is based on normalization of neurotrophic factors in the brain tissue: it stimulates gene expression of many neurotrophins (neurotrophins –3, –4, –5, nerve growth factor (NGF) and brain growth differentiation factor (BDNF), m-RNA synthesis of neurotrophins and their receptors, increases the level of neurotrophins in the brain tissue [50–53]. Being a regulator of the brain neurotrophin synthesis, Semax is already an equally effective neuroprotector (decreases the possibility of primary and delayed neuronal death) and a neurometabolic agent [54].

Apart from the mechanism of neuroprotective action, Semax reduces the level of glutamate excitotoxicity accelerating transport of glutamate and aspartate from the synaptic gap to the astroglia; it possesses antioxidative activity associated with the increased activity of superoxide dismutase and a direct membrane protective action implemented due to altered physicochemical properties of plasma membranes [46,48].

Semax has a marked nootropic action, the mechanism of which is associated with an increased level of neuronal-based CREB (cyclic AMP response element-binding protein) phosphorylation [55]. An important pharmacodynamic property of Semax is its ability to regulate the functional activity of basic neuromediatory systems of the brain: cholinergic, serotonergic and dopaminergic [46].

Owing to the effect produced on the synthesis of neurotrophins and own direct effects, Semax prevents the death of penumbral neurons, inhibits abnormal apoptosis, enables restoration of connectivity and functions of glial cells, promotes rapid formation and/or restoration of an intellectual footprint; and improves higher cortical functions (attention, coordination of movements, speech, thinking) [46,48,55]. Overall, mortality and disability of patients with CVD, and disease progression rate are decreased; recovery of patients is accelerated (or remission time is increased), their socialization is improved [56–60].

CONCLUSION

The considered groups of neurotropic agents are components of neuroprotective therapy in neurology, which can be defined as a timely adequate effect produced on all pathogenesis factors that inhibit neuronal homeostasis at the systemic and neuronal level. Neuroprotection can be effective only in simultaneous use of activities that preserve neuronal vitality [61]. In particular, this is about support of arterial pressure at the levels ensuring adequate cerebral perfusion and corrected homeostasis of intracranial liquids.

The cornerstone of neuroprotective therapy is activation of protection mechanisms of neurons, endothelial and glial cells from the damaging effect of hypoxia by neurotropic agents [11].

Early use of neuroprotectors in acute CVD enables to do as follows [19]: 1) increase the rate of transient ischemic attacks and minor strokes among acute ischemic cerebrovascular disturbances; 2) significantly decrease the size of cerebral infarction; 3) prolong a therapeutic window expanding the possibilities for reperfusion therapy (thrombolysis); 4) protect from additional reperfusion (hyperosmolar and oxidant) damage in ischemic stroke.

The majority of the considered agents are the most effective in primary neuroprotection. It is aimed to interrupt the sequence of reactions (primarily of glutamate calcium cascade) that damaged neurons. It was the most effective within the therapeutic window when the nervous tissue damage hadn't become irreversible yet [11].

Secondary neuroprotection interrupts delayed neuronal death such as blockade of proinflammatory cytokine biosynthesis, molecules of cellular adhesion, autoimmune aggression, decreased intensity of oxidative stress, apoptosis inhibition, upregulation of neurotrophic factors. Nootropic agents are primarily used to treat cognitive disturbances.

Neurotrophic agents are the most universal ones. Thus, Semax has a remarkable primary and secondary neuroprotective activity, it is a neuroprotector and neurometabolic agent with equal effectiveness, it also has a marked nootropic action. In some cases, polypotency of Semax effects enables to carry out monotherapy reducing the patient's drug load.

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