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INFLUENCE OF NEUROPROTECTORY DRUGS ON POST-TRAUMATIC ENCEPHALOPATHY

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Abstract: This article reviews the use of neuroprotective drugs for the treatment of post-traumatic encephalopathy (PTE). PTE is a progressive neurodegenerative disease that can develop after traumatic brain injury.

Neuroprotective drugs are medications that can protect nerve cells from damage. The article discusses various neuroprotectants that are currently being studied for the treatment of PTE, including citicoline, choline alfoscerate, and mildronate. The author also considers the feasibility of using neuroprotectors for severe brain injuries. They note that there are currently no medications that can completely prevent or cure PTE, but neuroprotectants may help slow the progression of the disease and improve patients' quality of life.

This article is a review that summarizes current knowledge on the role of neuroprotective drugs in the treatment of PTE. It will be useful for doctors, researchers and patients interested in this topic.

Key words: post-traumatic encephalopathy, neuroprotectors, cytocoline, nerve cells.

The relevance of the research. The use of nootropics and neuroprotectors, especially in practical psychoneurology, is extremely important. According to the World Health Organization (WHO, 2010), 7 million strokes occur annually in the world (patients who survive need to take similar medications); due to increasing life expectancy, 157 million people suffer from vascular dementia; closed head injuries reached 2 million per year; over the past 5 years, the number of neurodegenerative diseases has increased by 17%; after severe forms of neuroinfections, a neuropsychiatric deficit is formed (up to 45% of cases); Every year, about 78 million children are born around the world with a pathology of the central nervous system (CNS), which often ends in the first years of life with psycho-speech-motor delay and dementia. Europe spends 75 billion euros annually on the treatment of cognitive impairment [16, 17].

Nootropic functions are carried out by various mechanisms of brain activity. A person has a natural mechanism that performs this function and occurs with the help of neurotropism, neurotrophism, neuroplasticity, including sanitation mechanisms [1, 5, 6].

By chemical nature, nootropic drugs are derivatives of various compounds of amino and hydroxy acids, plant extracts, neuropeptides, proteins [2, 5, 9].

1. Pyrrolidine-2 derivatives (cyclic GABA, racetam): piracetam, nebracetam, isacetam, nefiracetam, detiracetam, etiracetam, aniracetam, oxiracetam, pramiracetam, dipracetam, phenotropil, etc.
2. GABA (γ-aminobutyric acid): aminalon, gamma-lone, nicotinoyl-GABA (picamilon), phenibut (Noofen).
3. GHB (γ-hydroxybutyric acid): sodium hydroxybutyrate, sodium oxybate.
4. HOPA (hopantenic acid): calcium homopantothenate, pantogam.
5. Vitamin B6 (pyridoxine): pyritinol (encephabol), pyriditol, enerbol, pyrithioxine.
6. Aminoacetic acid: glycine.
7. Chlorophenoxyacetic acid: meclofenoxate, deanol.
8. Tryptamine ^-acetyl-5-ethoxytryptamine): melatonin (melaxen, melapur, melaton).
9. Neuropeptides and neurotrophic cerebro-protectors: cerebrocurin, cortexin, semax, vasopressin, cerebrolysin, solcoseryl, synacthen depot, cerebrolecithin, lipocerebrin.

10. Dipeptides: noopept (phenylacetyl-prolylglycine ethyl ester).
11. Vinca alkaloids: cavinton, vincapane.
12. Other herbs: extract of ginkgo biloba (EGb761), Schisandra chinensis, ginseng, memo plant, bilobil, ginkyo.
13. Combined: thiocetam, diapiram, bino-tropil, apik, olatropil, orocetam, fezam, yucalin.

I. Nootropic drugs with a dominant mnestic effect (cognitive enhancers), or true nootropics

1.Pyrrolidone nootropics (racetams), predominantly of metabolite action: piracetam, oxiracetam, aniracetam, pramiracetam, etiracetam, dipracetam, rolisiracetam, nebracetam, isacetam, nefiracetam, detiracetam, phenotropil, combined racetams (thiocetam, diapiram, tropil, orocetam, fezam).

2. Cholinergic substances: increased synthesis of acetylcholine and its release (choline chloride, phosphatidylserine, lecithin, acetyl-L-carnitine, citicoline, aminopyridine derivatives, etc.); cholinergic receptor agonists (oxotremorine, bethanechol, spiropiperidines, quinonucleotides); acetylcholinesterase (AcCh) inhibitors (donepezil, physostigmine, tacrine, amiridine, ertastigmine, galantamine, metrifonate, velnacrine maleate, etc.).

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

4. Modulators of the glutamatergic system:

a) low-affinity antagonists of the polyamine site of NMDA receptors and partial agonists of AMPA receptors (memantine, ademol);

b) AMPA receptor agonists (nooglutil);

c) partial agonists of the AMPA receptor, as well as those that enhance the release of norepinephrine and dopamine (Ritalin, modafinil, donepezil);

d) NMDA receptor coagonists (glycine);

e) NMDA mimetics (glutamic acid, milacemide, D-cycloserine).

5. Dopamine receptor agonists - pronoran.

6. GABA receptor agonists - baclofen.

If nootropics have a mechanism of action, they are often the key

into the castle," then neuroprotectors are drugs that indirectly improve the same functions as true nootropics.Today there are no protocol recommendations on how to use them together, but clarifying the etiology that led to a decrease in cognitive functions is the key to prescribing neuroprotectors [14, 20].

II. Neuroprotectors

1. Activators of brain metabolism: mildronate, phosphatidylserine, hopantenic acid esters, xanthine derivatives of pentoxifylline, propentofylline, tetrahydroquinolines, etc.

2. Cerebral vasodilators: vincamine, vinpocetine, nicergoline, vinconate, vindebumol, etc.

3. Calcium antagonists: nimodipine, cinnarizine, flunarizine, etc.

4. Antioxidants: mexidol, trollox, a-tocopherol acetate, a-tocopherol succinate, exiphon, tirilazad, meclofenoxate, atherovit, ebselen, thiotriazoline, emoxypin, cytoflavin, glutoxim.

5. Substances affecting the GABA system: aminalon (gammalon), pantogam, picamilon, phenibut (noofen), sodium hydroxybutyrate.

6. Substances of different groups: etimil, orotic acid, methyl glucoorotate, oxomethacyl, gutimin, ginseng, lemongrass and ginkgo biloba, Elton.

In the mechanism of action of nootropic drugs, two main links can be distinguished: neurotransmitter and metabolic. Each of the mechanisms occurs in both groups of drugs, but one of the mechanisms is dominant [15, 21].

Neurotransmitter mechanisms include the effect of the drug on the GABA, choline, glutamate, dopamine or glycinergic systems. In this regard, the most promising drugs are agonists of the NMDA and AMPA subtypes of glutamine

A variant of neuroplasticity is the following example: as is known, patients with congenital blindness have increased auditory spatial orientation due to additional activation of areas of the visual cortex during sound stimulation. At the same time, in patients with congenital deafness, when the visual analyzer is irritated, the auditory zone of the cortex is activated. Both blind and deaf patients have increased tactile sensitivity with excitation of the visual or auditory cortex, respectively, when performing somatosensory tasks. Such information can help predict the success of sensor implants. The use of cochlear implants in deaf patients with developed cross-modal neuroplasticity has proven effective. The dimensions of the left temporal lobe may serve as an anatomical marker of left hemisphere specialization for language abilities. The size of the medial temporal structures may correlate with the ability to recognize faces, and the periventricular region is responsible for spatial orientation. It is possible that after periventricular ischemia, this function suffers in a number of patients, especially in children [8].

Apoptosis is an active process that is under strict genetic control and requires the expenditure of ATP; usually, but not always, the process is associated with activation of caspases.As a rule, it occurs without inflammation [10, 18].

Cell damage occurs through two main pathways: apoptosis and anoikis.

Apoptosis:

1. Internal genetic (natural) activation (mainly through mitochondria) caused by an increase in intracellular calcium, reactive oxygen molecules, glutamate, etc.
2. External activation (binding to cell death receptors), for example, TNF-a binds to the Fas receptor [19].

Both pathways directly or indirectly lead to the activation of hierarchical caspases, of which at least 14 are cysteine-dependent and aspartate-specific proteases.

Anoikis is a process similar to apoptosis, but caused by abnormal pathological influences onto the cell matrix. In the body, these cell “damages” can occur simultaneously (necrosis, apoptosis, anoikis).

That is why therapeutic tactics for the same acute stroke are aimed at a number of dynamic processes accompanying a stroke: reperfusion, neuroprotection, neurotrophism, recovery and prevention.

Neurotrophicity, neuroprotection, neuroplasticity and neurogenesis are fundamental biological processes that constantly occur in the nervous system [2, 7].

Many different etiological factors cause common pathophysiological mechanisms that are capable of depressing these basic processes, which leads to the development of a variety of neurological diseases that occur acutely, chronically and extremely slowly.

he effect of citicoline and choline alfoscerate was studied by I.S. Evtushenko, 2013, in 102 patients with acute cerebrovascular accident (ACVA) hospitalized in the stroke center of the Tomsk Regional Clinical Hospital (Tomsk). Patients of the 1st group (50 people) were injected into a vein with magnesium sulfate, vinpocetine, and pentoxifylline. Patients of group 2 for 7-10 days after the stroke additionally received intravenous infusions of citicoline in doses of 1.5-2.0 g/day (37 patients) or choline alfoscerate in a dose of 1.0 g/day (15 patients).). Neurological status was assessed using the NIHSS (National Institutes of Health Stroke Scale) upon admission and after the course of treatment - after 18-21 days. The results were expressed as median Me and maximum deviation values (min; max). In the blood serum of patients upon admission, on the 3rd and 10th days of hospital stay, the concentration of protein S100 and neuron-specific enolase (NSE) was determined using the enzyme immunoassay method using reagents from Canag-Fujirebio (Sweden). Results were expressed as median Me and interquartile range (25%–75%).

The effect of mildronate on the concentration of NSE in the blood serum was studied in 24 patients aged 13 to 18 years with mild to moderate traumatic brain injury (TBI) on days 1-2 after admission to the hospital and 3 months after TBI: 8 patients (group 1) during hospital treatment received infusion therapy aimed at stabilizing hemodynamics and reducing cerebral edema (asparkam, acetazolamide, drotaverine); 16 patients (group 2) additionally took mildronate orally at a dose of 500 mg/day. After discharge from the hospital, patients in group 2 were recommended to continue taking mildronate for 3 months.

Statistical analysis of the results was carried out using the Statistica 6.0 for Windows program. When comparing groups, we used the [/-Mann-Whitney test and the %2 test.

Protein B100 is a specific calcium-binding protein characteristic of astrocytic glial cells. NSE is a cytoplasmic protein, the acidic form of which is found exclusively in neurons [13]. With normal permeability of the blood-brain barrier and the absence of damage to brain tissue, the concentration of protein B100 and NSE in the blood is insignificant and in the blood serum of healthy people is 50 ng/l and less than 5 μg/l, respectively [3]. The increase in the concentration of these proteins in the blood is due to damage to brain cells and disruption of the integrity of the blood-brain barrier. An increase in the concentration of protein B100 and NSE in the cerebrospinal fluid and blood has been described in stroke [13], neuroinfections [1], and perinatal brain pathology [5].

In this study, the concentrations of protein B100 and NSE in patients with stroke upon admission to the hospital did not increase significantly (table). The large scatter in the diagnosed concentrations of protein B100 is due to the fact that in patients with stroke of the hemorrhagic type, the concentration was already higher at the time of admission to the hospital than in patients with stroke of the ischemic type. By the 3rd day, the concentration of protein B100 more than doubled. The administration of citicoline and choline alfoscerate prevented the increase in the concentration of protein B100 in the blood on the 3rd day {I = -1.97; p = 0.048; and = 36.5). This fact reflects an early neuroprotective effect. By the 10th day, the concentration of protein B100 in all patients returned to normal (Fig. 1, table). The concentration of NSE also reached a maximum by the 3rd day, increasing by 1.5-2 times, and by the 10th day it decreased slightly.The increase in NSE concentration in the blood is due to the high permeability of the blood-brain barrier due to massive damage to astrocytic elements by the 3rd day of the disease and their partial recovery by the 10th day. Neuroprotective therapy did not have a significant effect on the concentration of NSE in the blood.

Comparison of the effectiveness of treatment based on the average score of the SHIBB scale did not reveal significant differences, which clearly indicates the significant effectiveness of neuroprotectors.

Purpose of the study. To evaluate the effect of neuroprotective drugs on the course and outcome of post-traumatic encephalopathy (PTE).

PTE is a progressive neurodegenerative disease that can develop after brain injury. There are currently no medications that can completely prevent or cure PTE, but neuroprotective drugs may help slow the progression of the disease and improve patients' quality of life.

This study will examine the effect of three neuroprotectors (citicoline, choline alfoscerate and mildronate) on the course and outcome of PTE. The results of the study will help determine whether these drugs can improve treatment outcomes for PTE and improve the patient's quality of life.

Result and discussion. Conclusions Thus, the therapeutic effect of neuroprotectors with the choline-positive effect of citicoline and choline alfoscerate for stroke and mildronate for TBI is combined with a decrease in the blood concentration of markers of nervous tissue damage - protein S100 and NSE.

1. In patients with acute cerebrovascular accident, the administration of neuroprotectors in the first few days from the onset of the disease reduces the concentration of S100 protein in the blood; the inclusion of citicoline in therapy causes a significant regression of neurological symptoms in most patients.
2. The use of mildronate for traumatic brain injury improves the condition of patients, reduces neurological complaints of a subjective nature, and reduces the concentration of neuron-specific enolase in the blood.
3. The neuroprotective effect of drugs is largely due to the normalization of the permeability of the blood-brain barrier.

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