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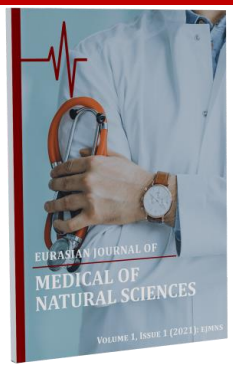

RIVASTIGMINE IN DEMENTIA THERAPY: EXPANDING THERAPEUTIC POTENTIAL FROM COGNITIVE CORRECTION TO NEURON PROTECTION

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ABSTRACT

Dementia is one of the most significant medical and social problems of modern society, which is caused by a steady increase in morbidity associated with an increase in the life expectancy of the population. According to the World Health Organization, there are more than 55 million people with dementia worldwide, and that number could triple by 2050. In these conditions, the search for effective therapies that can not only alleviate the symptoms of the disease, but also influence its pathogenetic mechanisms, becomes particularly relevant.

Introduction. Rivastigmine, a representative of the class of cholinesterase inhibitors, has traditionally been considered as a drug of symptomatic therapy aimed at correcting cholinergic deficiency in various forms of dementia. Initially, its application was focused on improving cognitive functions and daily activity of patients by increasing the availability of acetylcholine in the synaptic cleft.

However, the data accumulated in recent years have significantly expanded the understanding of the mechanisms of action of rivastigmine. Modern studies demonstrate that the drug has a wider range of pharmacological effects, including potential neuroprotective effects. Of particular interest is rivastigmine's ability to influence key pathogenetic mechanisms of neurodegeneration, such as oxidative stress, neuroinflammation, and mitochondrial dysfunction.

The dual inhibition of acetyl- and butyrylcholinesterase, characteristic of rivastigmine, provides not only a more pronounced symptomatic effect, but can also help slow the progression of the disease. Experimental and clinical studies in recent years show that the drug is able to modulate the processes of amyloidogenesis, affect the phosphorylation of tau protein and improve synaptic plasticity.

The data on the effect of rivastigmine on the processes of neuroplasticity and neurogenesis are of particular importance. It has been established that the drug can stimulate the formation of new synaptic connections and promote the survival of neurons under

pathological stress. These effects are especially important in the context of long-term therapy of neurodegenerative diseases.

Clinical observations confirm that long-term use of rivastigmine can lead to more stable treatment results compared with a short-term symptomatic effect. This may be due to the realization of the neuroprotective potential of the drug, which opens up new prospects for its use in clinical practice.

Current research also indicates the possibility of a synergistic effect of rivastigmine with other neuroprotective agents, which creates prerequisites for the development of new therapeutic strategies. Of particular interest is the study of combination therapy aimed at simultaneous effects on various links in the pathogenesis of dementia.

Thus, the evolution of ideas about the mechanisms of action of rivastigmine from a simple symptomatic agent to a drug with a potential neuroprotective effect opens up new prospects in the treatment of dementia. Understanding the molecular mechanisms of rivastigmine's neuroprotective action may help optimize therapeutic approaches and improve long-term treatment outcomes for patients with various forms of dementia.

The problem of dementia is currently very relevant, which is largely determined by the current trend towards aging of the population. One of the most common causes of dementia is Alzheimer's disease (AD). This disease, which belongs to primary degenerative dementia, is characterized by a progressive decrease in cognitive functions, primarily memory, and the development of behavioral disorders.

It is estimated that there are about 24 million patients with asthma worldwide and their number will triple over the next 3-4 decades. However, dementia is not only an important medical problem, but also a heavy socio—economic burden for both the patient himself and his caregivers, family members and society as a whole. In particular, asthma is one of the leading causes of disability in highly developed countries, and caring for a patient with asthma dramatically reduces the quality of life of the caregivers themselves.

Correction of cholinergic deficiency in the treatment of dementia

Currently, central acetylcholinesterase inhibitors are widely used for the treatment of asthma, which are considered as first-line therapies. Improvement in the condition of patients on the background of prescribing drugs of this group is noted in 40-80% of cases. The reason for their use in asthma is the presence of central acetylcholinergic deficiency, which is one of the key pathogenetic mechanisms of this disease. At the same time, there is a correlation between the severity of dementia and central cholinergic deficiency. The degree of cholinergic deficiency in the cortical regions is closely related to a decrease in the number of neurons in the basal regions of the brain, especially in the area of the basal nucleus of Meinert, where acetylcholine-producing neurons are located. In addition, the number of cholinergic receptors in the cerebral cortex decreases.

Acetylcholine is formed in presynaptic terminals under the action of acetylcholintransferase, then accumulates in vesicles, in which it is transported to the presynaptic membrane. After acetylcholine is released into the synaptic cleft, it acts on postsynaptic cholinergic receptors. The destruction of acetylcholine occurs under the action of the enzyme acetylcholinesterase, which is present in both the presynaptic and postsynaptic membranes.

Currently, it has been shown that in addition to acetylcholinesterase, the regulation of acetylcholine levels in the brain is carried out by another enzyme, butyrylcholinesterase. Therefore, a greater effect should be expected from drugs with dual effects, i.e., those capable of inhibiting both acetylcholinesterase and butyrylcholinesterase. Butyrylcholinesterase was detected in senile plaques, fibrillar glomeruli, and in the vascular wall (in amyloid angiopathy). It is believed that this enzyme is involved in the formation of senile plaques. It is assumed that the activity of butyrylcholinesterase is most pronounced in the subcortical white matter of the brain, and an increase in the activity of this enzyme in these areas explains the increase in the severity of cerebral atrophy and the size of the ventricular system of the brain with the progression of cognitive impairment in patients with dementia. It should be noted that the most significant increase in butyrylcholinesterase activity during aging is observed in those areas of the white matter, the myelination of which occurs later in the normal development of the child, in particular in the entorhinal regions.

The results of experimental and clinical studies indicate that inhibition of butyrylcholinesterase is accompanied by improved learning ability, memory, and visual-spatial functions. It has been shown that as asthma progresses, acetylcholinesterase activity decreases in certain areas of the brain, while butyrylcholinesterase activity increaseThe results of experimental and clinical studies indicate that inhibition of butyrylcholinesterase is accompanied by improved learning ability, memory, and visual-spatial functions. It has been shown that as asthma progresses, acetylcholinesterase activity decreases in certain areas of the brain, while butyrylchon.

Rivastigmine (exelon, Novartis Pharma, Switzerland) is a slow-acting inhibitor of acetylcholinesterase and butyrylcholinesterase, mainly acting at the central level. The drug is used to treat mild to moderate dementia in asthma and Parkinson's disease. Against the background of its administration in the cerebrospinal fluid in patients with ASTHMA, a dose-dependent inhibition of the level of these enzymes occurs rapidly. At the same time, significant inhibition of acetylcholinesterase activity is noted after a single dose of 3 mg of rivastigmine. The drug acts mainly on the structures of the hippocampus, temporal and frontal regions; its effect on cerebral structures persists for up to 10 hours.

The effectiveness of rivastigmine has been evaluated in a large number of studies conducted in different countries. Against the background of therapy, the most significant clinical improvement is observed from the 12th week after the start of taking the drug, while its effectiveness is dose-dependent. Against the background of therapy, in addition to improving cognitive function, patients experience a decrease in the severity of disorders associated with self-care, which is of great importance for relatives and relatives of patients. Currently, rivastigmine has been shown to be highly effective in patients whose asthma is complicated by hallucinations. It is important to note that the effectiveness of rivastigmine persists for a long time.

The drug is characterized by selectivity of action, since it predominantly inhibits the G1 isoform of acetylcholinesterase (it is more expressed in the hippocampus and cortex, i.e. in areas primarily affected by asthma) and to a lesser extent the G4 isoform, which significantly reduces the likelihood of peripheral adverse events. The selective effect of rivastigmine on the G1 isoform of acetylcholinesterase is believed to explain the rarity of extrapyramidal adverse

reactions. The same property of rivastigmine explains the rare occurrence of muscle cramps, which is typical for other acetylcholinesterase inhibitors. It should be noted that the genesis of crampi during therapy with acetylcholinesterase inhibitors is associated with an effect on the G2 isoform of the enzyme, located mainly in the area of neuromuscular terminals. The selectivity of rivastigmine, as well as the dual effect of action, make it preferable to prescribe it not only in the early stages, but also in the advanced stages of asthma.

It should be noted that the use of acetylcholinesterase inhibitors in clinical practice is often associated with the development of typical adverse events for this class — headache, nausea, dizziness and diarrhea due to cholinergic activity. As a rule, they are mild or moderate in severity, limited in duration and are not life-threatening.

This necessitates the development of new approaches, in particular the introduction of new delivery vehicles for acetylcholinesterase inhibitors, characterized by the absence of concentration peaks, a decrease in the frequency of adverse events and, as a result, increased efficacy due to a greater likelihood of achieving the optimal dose.

More recently, a new form of rivastigmine has been introduced into clinical practice — in the form of a patch (transdermal therapeutic system). This form of rivastigmine has undoubted advantages over the conventional oral form of the drug due to the possibility of constant rivastigmine intake into the bloodstream for 24 hours. This is mainly due to the absence of fluctuations in the concentration of the drug in the blood serum when it is used as a patch, which leads to a decrease in the frequency of side effects (by 3 times) — with high clinical efficacy and a greater susceptibility of patients to treatment. In the vast majority of cases, there is no local irritant effect when using the patch.

The literature notes that rivastigmine is characterized by a successful combination of good efficacy and tolerability. The studies conducted to date have included patients mainly of elderly and senile age, who, as a rule, have concomitant somatic pathology. In this regard, it should be noted that polymorbidity is very characteristic of elderly and senile patients — people over 65 years of age have on average more than 3 diseases, and therefore elderly patients take more than 3 medications (especially often — cardiovascular, painkillers and hypnotics).

Studies have shown that rivastigmine is well tolerated by this category of patients. It can be prescribed in conjunction with a wide range of medications that are often used in neurogeriatric practice, including antipsychotics. There was no negative effect of therapy on electrocardiographic parameters.

Conclusions: In practice, it is often necessary to switch from one acetylcholinesterase inhibitor to another. Similar problems associated with either insufficient efficacy of the drug or the development of side effects of therapy are noted in mild to moderate asthma in almost 50% of cases. It has been shown that patients who have not had a positive effect from other central acetylcholinesterase inhibitors may show improvement on the background of rivastigmine administration. In addition, unlike other acetylcholinesterase inhibitors, rivastigmine has a low potential for interaction with drugs prescribed for other indications, which is especially important for elderly and senile patients.

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