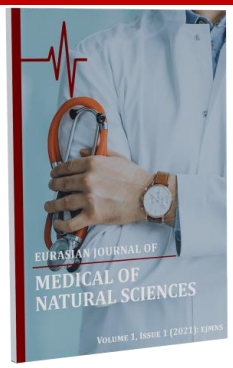
EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 7.921 www.in-academy.uz



RIVASTIGMINE'S ABILITY TO PREVENT NEURONAL DEATH AND DAMAGE

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https://doi.org/10.5281/zenodo.14850920

ARTICLE INFO

Received: 05th February 2025
Accepted: 10th February 2025
Online: 11st February 2025

KEYWORDS

Rivastigmine, neuroprotection, cholinesterase inhibitor, neurodegeneration, cognitive functions, neuroprotective effect, neuron protection, acetylcholinesterase, butyrylcholinesterase, neurotransmitters.

ABSTRACT

In modern neurology, special attention is paid to the search for effective methods of protecting nervous tissue from damaging factors and slowing down the processes of neurodegeneration. Rivastigmine, as a representative of the class of cholinesterase inhibitors, occupies a special place among drugs with neuroprotective properties due to its dual mechanism of action.

Introduction. The relevance of the study of the neuroprotective effects of rivastigmine is due to the steady increase in the prevalence of neurodegenerative diseases in the world, which is associated with both an increase in the life expectancy of the population and the impact of various adverse factors on the nervous system. According to WHO, the number of patients with cognitive impairments of varying severity increases by 7-9% annually.

Rivastigmine is a second-generation cholinesterase inhibitor drug with the ability to simultaneously inhibit both acetylcholinesterase and butyrylcholinesterase. This dual mechanism of action provides a wider range of therapeutic effects compared to selective inhibitors. The drug helps to increase the concentration of acetylcholine in the synaptic cleft, which improves the transmission of nerve impulses and helps preserve cognitive functions.

Of particular interest is the ability of rivastigmine to exert a neuroprotective effect, which is realized through several mechanisms:

- reduction of oxidative stress
- reduction of neuroinflammation
- regulation of apoptosis processes
- stimulation of neuroplasticity
- improvement of cerebral microcirculation

Modern studies show that the neuroprotective properties of rivastigmine are not limited to cholinergic effects only. The drug also affects other neurotransmitter systems, which expands the range of its therapeutic use. The accumulated data indicate a positive effect of the drug on cognitive functions, behavioral disorders and daily activity of patients.

In clinical practice, the long-term protective effect of rivastigmine on nerve cells is particularly important, which makes it possible to slow down the progression of neurodegenerative processes and improve the quality of life of patients. The results of numerous clinical studies confirm the efficacy and safety of long-term use of the drug.

The study of the neuroprotective effects of rivastigmine continues to be an urgent area of modern research, due to the need for a deeper understanding of the mechanisms of its action and the search for new therapeutic possibilities. Of particular interest is the study of potential synergistic effects when rivastigmine is combined with other neuroprotective agents.

The results of the conducted studies indicate an improvement in therapy with central acetylcholinesterase inhibitors, including rivastigmine, not only in mild and moderate, but also in severe dementia. However, the need for the earliest possible prescription of this group of drugs is emphasized, which presumably makes it possible to delay the progression of the disease. According to some authors, the positive dynamics in the condition of patients on the background of therapy with acetylcholinesterase inhibitors is manifested not only in improving the results of neuropsychological tests, but also in a slower progression of the disease.

There was no significant data on the protective effect of this group of drugs in asthma until recently, which could largely be due to the design of the studies, which in most cases were short-lived. The situation has changed somewhat recently. It has been shown that even after the withdrawal of acetylcholinesterase inhibitors, the degree of progression of the pathological process decreases, and clinically this is manifested by a slower increase in cognitive and behavioral disorders. The assumption of a protective effect of acetylcholinesterase inhibitors, in particular rivastigmine, is supported by the results of monitoring patients with moderate cognitive impairment (MCI) who have been receiving this therapy for a long time — for 3-4 years. It should be noted that OCD is often considered as the prodromal stage of asthma, and the risk of developing this disease is significantly higher in women with OCD than in men.

The UKR concept was proposed to denote pre-dementational disorders of higher brain functions caused mainly by asthma. AD goes through a number of stages in its development, characterized by a consistent increase in symptoms, ranging from mild cognitive disorders, mainly in the field of memory, to severe disorders reaching the degree of dementia. The duration of the prodromal (preclinical) stage of this disease remains unknown, but there is no doubt that it is years. To denote this prodromal period, the term UKR was proposed. At the same time, there is no clear boundary between normal aging and OCD, as well as between OCD and BA (its initial stages). UKR patients are an important group from a theoretical and practical standpoint. From a theoretical point of view, the study of these disorders allows us to get closer to understanding the clinical features of the earliest manifestations of dementia (mainly ASTHMA), and is also important in the context of the "neurology of normal aging." From a practical point of view, the identification of individuals with mild cognitive impairment at the time of examination, but who are at risk of developing dementia, allows the use of certain therapeutic programs at the earliest stages of the disease. It is in this category of patients that they can be expected to be more effective. In addition, the effectiveness of

neuroprotective therapy, which is currently being actively developed, seems to be more reasonable and promising.

The prevalence of OCD reaches 10% among people over 65 years of age, and 10-15% of them develop a detailed clinical picture of asthma within a year. UKR should be interpreted with some caution as an exceptionally early stage of asthma, since they may be based on other causes, including depression, cerebrovascular lesions, frontotemporal dementia, diffuse Lewy body disease, etc. Currently, some cases of OCD are considered as a preclinical stage of vascular dementia. At the same time, there are at least 2 variants of vascular disorders. In the first of them, with pronounced diffuse changes in the white matter of the cerebral hemispheres, the clinical picture is dominated by executive function disorders, and the second is associated with heart attacks and repeated episodes of acute cerebral circulatory disorders and is manifested by more polymorphic symptoms, the nature of which is determined by the localization of the ischemic focus (foci).

The appointment of rivastigmine in UKR is accompanied not only by a positive clinical effect, but also reduces the risk of developing ASTHMA in this category of patients, although it was previously reported that there was no such effect. It should be noted that the positive effect is related to the gender of the patients — a significant reduction in the risk of developing in patients with AD was noted specifically in women, in men such an effect was not statistically significant. In addition, women with the amnesic type of UKR who received rivastigmine for a long time showed a decrease in the degree of increase in cerebral atrophy and ventricular volume of the brain compared with patients receiving placebo. Currently, it has been shown that the effectiveness of the drug is to some extent determined by the available genotype of butyrylcholinesterase. Considering the results obtained, indicating differences in the effectiveness of rivastigmine in men and women, it is necessary to take into account certain features of the structure of white matter depending on gender, in any case, this is evidenced by the data of magnetic resonance imaging.

Patients with asthma treated with rivastigmine have a less significant increase in cortical atrophy in the parietotemporal regions compared with the group of patients treated with placebo or other selective acetylcholinesterase inhibitors. Against the background of rivastigmine therapy, less significantly than with other acetylcholinesterase inhibitors, there is a decrease in the volume of white matter, including in the deep parts of the hemispheres and the brain stem. Many researchers believe that the protective effect of rivastigmine, the ability of this drug to reduce the progressive atrophy of the white matter of the brain and, consequently, to keep cortical-cortical connections intact, is primarily due to the inhibition of butyrylcholinesterase. It is emphasized that the neuroprotective effect is based on the blocking of rivastigmine butyrylcholinesterase outside synapses, in glial tissue, in deep sections of cortical structures and subcortical sections, which, in particular, leads to a decrease in the pro-inflammatory effect of this enzyme.

Recently, it has been shown that one of the mechanisms of action of this drug, leading to a decrease in amyloid deposition, is the anti-inflammatory effect. In particular, rivastigmine's ability to reduce the severity of demyelination, activation of microglia, formation of proinflammatory cytokines, and axonal damage was demonstrated on the model of experimental autoimmune encephalomyelitis. Currently, the role of inflammatory processes

in the pathogenesis of asthma is emphasized. The data obtained indicate the importance of the non-synaptic mechanism of action of acetylcholinesterase inhibitors on the progression of asthma associated with the effect of this group of drugs on myelination processes in the central nervous system.

Prospects for the use of rivastigmine in other dementias

The effectiveness of acetylcholinesterase inhibitors, in particular rivastigmine, has been noted not only in asthma and vascular dementia, but also in other forms of dementia — dementia with Lewy bodies, dementia with Parkinson's disease and dementia due to traumatic brain injury (TBI).

It is important to note that in addition to the direct restoration of the acetylcholinergic defect, central acetylcholinesterase inhibitors are also able to affect the cerebral blood flow. In AD, according to functional neuroimaging methods, there is a decrease in regional cerebral blood flow and metabolism, which is most pronounced in the temporoparietal and frontal regions. At the same time, the localization of hypometabolism zones does not always coincide with areas in which there is an acetylcholinergic defect characteristic of this disease. However, a low level of regional blood flow in the temporal lobes is one of the predictors of the rapid progression of a cognitive defect.

It is suggested that central acetylcholinesterase inhibitors can improve cerebral perfusion, and thus this group of drugs may be effective in cases of both vascular and primary degenerative dementia [18]. Indeed, against the background of therapy with central acetylcholinesterase inhibitors, an increase in regional cerebral blood flow is noted in patients with asthma.

In particular, rivastigmine not only increases the level of acetylcholine in the brain, which is reduced due to the disease, but also increases cerebral blood flow in the frontal, parietal and temporal regions, which is accompanied by an improvement in the cognitive sphere of patients. However, it is possible that these changes in blood flow are related not so much to the effect of rivastigmine directly on blood vessels, but rather to increased metabolism in areas of the brain where acetylcholine-responsive neurons have been preserved (stimulation of neuronal activity at the postsynaptic level).

Currently, acetylcholinesterase inhibitors (galantamine, rivastigmine, donepezil) have been shown to be effective not only in asthma, but also in vascular dementia. Cognitive and behavioral improvements were noted in patients with subcortical vascular dementia who received rivastigmine for 52 weeks. It is possible that in some cases, these studies included patients with mixed dementia rather than "pure" vascular dementia. It should be noted that there is very little evidence that for "pure" vascular dementia (i.e. without coexisting Alzheimer's changes), a cholinergic defect is not characteristic. However, the concept of an acetylcholinergic defect in vascular dementia is supported not only by clinical, but also by experimental and pathomorphological data. In particular, in a specially bred line of rats with a hereditary predisposition to hypertension and strokes (an experimental model of vascular dementia), there is a significant decrease in acetylcholine and choline in the cerebral cortex, hippocampus and cerebrospinal fluid. According to autopsy data, patients with vascular dementia show cholinergic deficiency in the cortex, hippocampus and striatum, as well as a

decrease in acetylcholine concentration during postmortem examination of cerebrospinal fluid.

It is important to emphasize that subcortical vascular foci can lead to a central acetylcholinergic defect even in the absence of concomitant Alzheimer's changes. Central cholinergic structures, the preservation of which is extremely important in the exercise of cognitive functions, are very susceptible to damage in conditions of ischemia, while hippocampal atrophy can be detected in patients with vascular dementia in the absence of concomitant asthma.

It should be noted that "pure" vascular dementia is rare in practice. Elderly and senile people usually have a combination of vascular and primary degenerative (Alzheimer's) changes. It is more correct to consider such cases as mixed dementia. Currently, it is emphasized that the use of central acetylcholinesterase inhibitors in mixed dementia is no less effective than in asthma.

Traumatic brain injuries are the 3rd most common cause of dementia in people under 50 years of age (after infectious diseases and alcoholism). In developed countries, car accidents are the cause of TBI in about 50% of cases, but in the elderly and senile, TBI is more often caused by falls. Men are more susceptible to TBI than women. The severity of cognitive impairment after TBI depends on a number of factors, including the nature and severity of the injury, the age of the patients, the location of the lesion, and the premorbid cognitive level. In general, dementia can occur in about 3-10% of patients who survive severe TBI.

The progression of cognitive impairment after TBI may be based on disorders of the acetylcholinergic system, similar to those observed in asthma, disorders of the blood-brain barrier, autoimmune and vascular disorders caused by trauma, as well as the development of hydrocephalus. It should be noted that trauma increases the risk of asthma, and pathomorphological examination of the brain of people who have suffered a TBI often reveals changes characteristic of asthma. In this regard, the data indicating the similarity of cerebral inflammatory reactions in asthma and TBI are very interesting. The brain is protected from the action of the body's immune system by the blood-brain barrier, normally only activated peripheral T cells can penetrate through it. In TBI, proinflammatory cytokines, interleukin-1b and tumor necrosis factor increase the formation of beta-amyloid. All of this can eventually lead to the characteristic neuronal degeneration of asthma. Since cognitive deficits in all types of dementia are often associated with impaired executive functions and are caused by the separation of the anterior brain regions from cortical and subcortical structures, rivastigmine has certain advantages due to its dual mechanism of action. This is due to the fact that butyrylcholinesterase activity is most significant in the area of the thalamus, the projection pathways from which to the frontal lobes ensure the implementation of executive functions, attention and behavioral reactions, as well as in the white matter of the cerebral hemispheres. A defect in executive functions is clinically manifested by a violation of the ability to set a goal(s), a violation of the ability to plan one's actions (the ability to build a program to achieve a goal, identify and structure a number of stages and steps necessary to achieve a goal), a violation of the performance of purposeful actions (difficulties in starting an action and executing it, difficulties switching from one action to another other), difficulties in "effective execution" (impaired ability to control and regulate one's own activity, notice and correct

one's own mistakes), and also apathy. It is possible that one of the reasons for rivastigmine's effectiveness in dementia associated with Parkinson's disease, as well as in some types of vascular dementia, is that it selectively affects the frontal brain regions.

The effectiveness of rivastigmine in the treatment of dementia in Parkinson's disease was convincingly proven in a large EXPRESS study, which revealed the positive effects of rivastigmine on cognitive functions (in particular, attention), activity in daily life, and behavioral disorders. Currently, rivastigmine is the only officially registered cholinesterase inhibitor indicated for use in Parkinson's disease. Rivastigmine reduces the incidence of visual hallucinations in patients with dementia with Parkinson's disease. They showed a statistically significant improvement in attention after a 6-month course of therapy. In a multicenter, double-blind, placebo-controlled study that included dementia patients with Lewy bodies, improvements in cognitive and emotional areas were noted with rivastigmine therapy. Against the background of therapy, such characteristic diseases and severe psychotic disorders occurred less frequently. It should be noted that the cognitive defect in this disease is similar to the defect in asthma. In addition, most patients with diffuse Lewy body disease have extrapyramidal disorders (often in the absence of resting tremor), severe mental disorders (including depression and psychosis) and fluctuating disturbances of consciousness.

The data obtained are of great practical importance, since both in dementia with Lewy bodies and in psychotic phenomena in patients with dementia with Parkinson's disease, the use of neuroleptics is very problematic. In Parkinson's disease, they can enhance the main manifestations of the disease, and in some cases lead to the development of neuroleptic malignant syndrome, and in dementia with Lewy bodies, they are contraindicated.

Conclusions: Thus, the current data indicate the importance of correcting the central acetylcholinergic defect in patients with dementia, both in asthma and due to other causes (cerebrovascular insufficiency, Parkinson's disease, dementia with Lewy bodies, etc.). One of the drugs that carry out such correction is rivastigmine (exelon), which inhibits acetylcholinesterase and butyrylcholinesterase. Currently, the drug's ability to act not only symptomatically, improving cognitive and behavioral functions in patients with asthma, but also to influence the mechanisms of development of this disease. In addition to the tablet form of rivastigmine, a new form has been developed that is more convenient for use — a transdermal therapeutic system (patch).

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