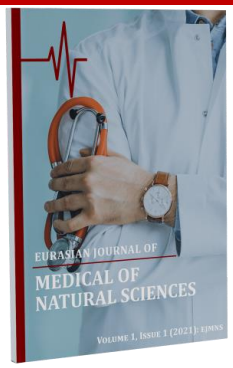
EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 7.921 www.in-academy.uz



THERAPEUTIC POTENTIAL OF MELATONIN IN ALZHEIMER'S DISEASE

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https://doi.org/10.5281/zenodo.14850729

ARTICLE INFO

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

KEYWORDS

Melatonin, Alzheimer's disease, neuroprotection, cognitive impairment, neurodegeneration, antioxidant protection, circadian rhythms, targeted therapy, neuroplasticity, dementia.

ABSTRACT

The introduction comprehensively highlights the problem of the use of melatonin in Alzheimer's disease, emphasizing the institutional affiliation of the study and its practical significance. The text is structured logically, reflects the current state of the problem and research prospects, while maintaining the academic style of presentation and the accuracy of formulations. The keywords cover the main aspects of the study and correspond to the content of the introduction.

Introduction. Alzheimer's disease (AD) currently represents one of the most significant medical and social problems of modern society, due to the steady increase in morbidity, the severity of clinical manifestations and a significant socio-economic burden. According to international research, there are more than 50 million people with dementia worldwide, with Alzheimer's disease accounting for about 60-70% of all cases. It is predicted that this figure may triple by 2050, which determines the urgent need to find new therapeutic strategies.

Despite significant advances in understanding the pathogenesis of Alzheimer's disease, existing treatment methods have limited effectiveness and are primarily aimed at symptomatic correction of cognitive impairment. In this regard, it is of particular interest to study the therapeutic potential of melatonin, a neurohormone with a unique range of biological effects. Melatonin attracts the attention of researchers due to its multiple neuroprotective properties, including antioxidant, anti-inflammatory, and anti-apoptotic effects. Experimental and clinical studies in recent years have demonstrated the ability of melatonin to influence key links in the pathogenesis of asthma, including beta-amyloid aggregation, tau protein hyperphosphorylation, and mitochondrial dysfunction.

The study of the role of melatonin in the regulation of circadian rhythms in Alzheimer's disease is particularly relevant, since sleep-wake cycle disorders and circadian rhythms are characteristic early manifestations of the disease. It was found that patients with asthma have a significant decrease in melatonin secretion, correlating with the severity of cognitive impairment and the stage of the disease.

The accumulated data suggest that the therapeutic potential of melatonin in Alzheimer's disease can be realized through several mechanisms: direct neuroprotective action, modulation of circadian rhythms, reduction of oxidative stress and neuroinflammation, improvement of synaptic plasticity and cognitive functions. An important advantage of melatonin is its good tolerability and minimal risk of side effects with prolonged use.

Samarkand State Medical University conducts research aimed at studying the effectiveness of various melatonin regimens in patients with Alzheimer's disease, assessing its effect on cognitive functions, sleep quality and daily activity of patients. Special attention is paid to the study of the possibility of using melatonin as part of complex therapy at various stages of the disease.

A promising area of research is the development of personalized approaches to the use of melatonin, taking into account the individual characteristics of patients, the stage of the disease and concomitant pathology. Studying the therapeutic potential of melatonin in Alzheimer's disease may contribute to improving existing treatment protocols and improving the quality of life of patients with this pathology.

Cellular mechanisms of MT action

According to modern concepts, the deposition of cytotoxic protein beta—amyloid peptide (BAP) in the brain tissue and walls of cerebral vessels, which serves as an insoluble derivative of its highly soluble precursor, is of the most important pathogenetic importance in the pathogenesis of asthma. This process of transformation and deposition of BAP in the form of extracellular senile plaques is favored by a number of factors, including the formation of pathological forms of apolipoprotein and hyperlipidemia. A characteristic morphological feature of AD is also the formation of fibrillar tangles in neurons, which are modified microtubules of the cytoskeleton and consist of hyperphosphorylated tau protein. These morphological shifts lead to cytotoxic consequences, causing degeneration of nerve cells in various ways. The development of oxidative stress also plays a significant role in this process.

Although the origin of organic and functional disorders in asthma at the cellular level has not been definitively established, there is reason to believe that a certain contribution to their genesis is made by the defective activity of the epiphysis. This is supported by indications of the possibility of epiphyseal hormone modification of the processes of BAP formation and the consequences of its toxic effect on the function of cerebral neurons. This information can be grouped into two main groups.

The first of these includes the results of in vitro experiments on human neuroblastoma cells and rat hippocampal neuron cultures, according to which the addition of MT inhibits the formation of amyloid fibrils. Under the influence of this hormone, the profibrillogenic activity of apolipoprotein E4 is partially reversed and the formation of its neurotoxic complex with BAP decreases. Water intake of MT for several months by transgenic mice in which AD-type amyloidogenesis was modeled inhibited the formation of amyloid peptide in the brain, decreased protein nitrification, and at the same time increased animal survival, although in old mice MT did not interfere with the amyloidogenic effect. In addition, due to the existence of a link between cholesterol and amyloid pathology in asthma, MT is assigned an important place in the regulation of cholesterol metabolism.

As for the other group of facts, it is primarily about the ability of MT to prevent the manifestations of BAP toxicity. In studies on isolated neurons, it has been shown that the hormone provides them with successful protection from oxidative stress provoked by a pathogenic protein. It has a well-reasoned ability to serve as a "trap" for free radicals, expressed even better than that of such a well-known antioxidant as vitamin E. By inhibiting the processes of lipid peroxidation, MT prevents damage by aggressive forms of oxygen to mitochondrial membranes. Note that this action is carried out without the participation of specific MT receptors by some of its metabolites. The formation of one of these metabolites, N—acetyl-5-methoxykinurinamine, can be disrupted with age and in neurodegenerative brain diseases.

In addition to these methods of protection, the neuroprotective properties of MT are realized using other mechanisms. In particular, it reduces the sensitivity of N-methyl-D-aspartate (NMDA) receptors and thereby weakens the neuronal excitotoxicity of glutamic and quinolic acids by limiting the excessive accumulation of intracellular calcium ions. In this regard, it is interesting that the hormone also limits neurodegeneration caused by okadaic acid, which is considered as an experimental analogue of the corresponding changes in asthma. By interacting with the phosphorylation system, especially with the so-called stress kinases, MT weakens the process of tau hyperphosphorylation of proteins. It has distinct immunomodulatory properties provided through intervention in opioidergic transmission. Finally, the hormone can enhance reparative processes in the nervous tissue by increasing the production of individual neurotrophins and activating tyrosine kinase receptors.

These data suggest that age-related MT deficiency, especially in the case of asthma, may be a predisposing factor for the development of dementia. In this case, a violation of the mnemotropic activity of the hippocampus is of particular importance, which is under the undoubted epiphyseal control carried out by MT.

The place of the hippocampus in the realization of MT activity in relation to the prevention of dementia. In the 1980s, C. Maurizi was the first to suggest that senile dementia is not just associated with hippocampal dysfunction, but that defects in its plasticity in pathology are secondary and caused by chronic MT deficiency. Numerous data obtained later are in good agreement with this point of view.

The special importance of the hippocampus is indicated by the information already given above about early atrophic changes in the structure of asthma and its leading importance for the organization of memory processes. In addition to this, we can refer to a few more facts. Thus, in transgenic mice used to simulate AD, the highest density of senile plaques containing BAP is observed in the hippocampus. The granular cells of this structure and the frontal cortex of such animals show increased oxidative stress and increased accumulation of a number of inhibitory peptides. Intraventricular administration of amyloid peptide to rats impairs their memory and learning in a water maze while simultaneously disrupting the cholinergic innervation of the hippocampus and anterior neocortex with a decrease in choline acetylase activity. It is also assumed that in AD, it is in the hippocampus that the most active formation of a neurotoxic combination of BAP and apolipoprotein E4 occurs, which causes increased apoptosis of nerve cells.

MT is directly related to the control of normal and pathologically altered hippocampal activity. Both types (1 and 2) of MT receptors are shown in the dentate gyrus and pyramidal neurons of the CA1 and CA3 fields of the structure. Obviously, with their help, the hormone, when added to the culture of rat hippocampal tissue, changes the frequency of cell discharges, since this effect is eliminated by the specific receptor blocker lusindol. Chronic administration of MT to newborn baby rats enhances the proliferation of cellular elements in the dentate gyrus and increases the density of individual NMDA receptor subunits with indirect mobilization of secretory activity of the pineal gland due to prolonged exposure of rats in the dark. On the contrary, functional epiphysectomy (keeping animals in constant light) reduces the antioxidant protection of the hippocampal tissue of old, but not young, rats. On the other hand, according to our observations, local damage to their dorsal hippocampus weakens the psychotropic activity of MT.

The previously described neuroprotective properties of MT fully extend to pathological processes in this structure. As found on isolated sections of the rat hippocampus, the addition of MT to them weakened the depression of the synaptic response of pyramidal neurons to irritation of afferent Schaffner fibers and at the same time reduced the generation of free radicals, if both developed during modeling of ischemic hypoxia. In vivo experiments showed that repeated administration of high doses of MT (10-20 mg/kg) to rats prevented memory and learning disorders and delayed cell death in the CA1 and CA3 fields of the hippocampus, which were observed after concussion injury to the skull. The hormone also protected hippocampal neurons from glutamate excitotoxicity, while epiphysectomy potentiated cell death in stroke simulation by occlusion of the carotid artery. In addition, the use of the hormone and its derivatives prevented the death of neurons in the hippocampus, amygdala, and periform cortex, with a decrease in the corresponding behavioral and biochemical disorders in cases of intoxication caused by ochratoxin, homocysteine, kainic acid, or quinolic acid. At the same time, lipid peroxidation processes were weakened and apoptosis was inhibited as a result of inactivation of the pro-apoptotic protein Bax, as well as an increase in the level of the anti-apoptotic protein Bcl 2. In addition, a decrease in some NMDA receptor subunits was prevented.

Through similar mechanisms, hormonal protection is carried out in case of damage to the hippocampus in asthma. The addition of MT to the culture of rat hippocampal neurons prevents the development of apoptosis with chromatin condensation and DNA fragmentation caused by BAP Abeta. A decrease in its toxicity was also accompanied by a decrease in lactate dehydrogenase activity. In transgenic mice, prolonged (4 months) administration of MT, along with a decrease in mnestic disorders, reduced the accumulation of extracellular BAP and increased the activity of choline acetylase in the frontal cortex and hippocampal tissue. When fibrillar BAP was injected locally into the CA1 field of the rat hippocampus, a pattern of typical oxidative stress appeared, accompanied by an increase in the levels of nitrates, lipoperoxides, and proinflammatory cytokines in the structure. Oral administration of MT, as well as vitamin C and E preparations, limited these pathochemical shifts, and the hormone was clearly more active than traditional antioxidants. Epiphyseal hormone was able to weaken lipid peroxidation and increase glutathione levels in the rat hippocampus in parallel with improved

memory and learning when modeling asthma with chronic administration of ethyl alcohol. In such a situation, the old animals reacted much more strongly to MT than the young ones.

There are arguments in favor of a possible connection between the described neuroprotection and the pathogenesis of asthma in humans. As established by immunohistochemical technique, MT1 and MT2 receptors are actively expressed in the human hippocampus. Their density is noticeably reduced in old age, but expression is particularly sharply disrupted in AD in the pyramidal neurons of the main hippocampal fields and the granular layer of the structure.

Thus, using various cellular mechanisms, MT counteracts both hippocampal amyloidosis and its consequences, protecting the hippocampus from cytotoxic effects. Since this structure, which performs an important mnestic function, is one of the first to be affected in asthma, there is sufficient reason to link the pathogenesis of the disease, among other causes, with limited epiphyseal control over its activities. Therefore, it is logical to use MT to combat neurodegenerative pathology.

Therapeutic possibilities of MT in asthma

Despite the obvious feasibility of such a therapeutic approach, few clinical studies using the hormone have yet yielded reliable results.

In recent years, attempts to treat asthma with MT have been repeatedly made in a number of competent neurological clinics. The data obtained boils down to the fact that the use of a hormonal drug due to its chronotropic properties is not useless due to the undoubted optimization of nighttime sleep and the reduction of increased depression. However, a noticeable improvement in cognitive functions is not always noted. This depends on a number of reasons, primarily on the dose and duration of MT use. In the studies available to us, relatively low dosages of it were used (3 or 4 mg of the substance daily) for 3-4 weeks. In addition, the studies were conducted on fairly limited (7-10 people) groups of patients with dementia of varying severity. If they resorted to higher daily doses of MT (up to 10 mg), and the therapy lasted longer (2-3 years), then the effectiveness of the treatment was higher.

Although the clinical data do not match the therapeutic possibilities of MT that are expected based on experimental findings, this should not be an obstacle to further research in this direction. A clinical experiment conducted by D. Cardinali et al. allows us to refrain from excessive skepticism. Under their supervision were two men who were homozygous twins and suffered from genetically determined asthma of the same severity. Both patients received the same traditional pharmacotherapy, but one of them was additionally prescribed MT (6 mg/day) for a long time (36 months). As a result, after completing such a course of treatment, this patient was found to have a moderate improvement in memory and a milder variant of the disease than his sibling.

The reason for the restrained assessments of the therapeutic benefits of MT is probably also the significant variability in the individual sensitivity of patients to it, which is noted by many researchers. In our opinion, there are two possible explanations for this.

First, in severe cases of asthma, when the neurodegenerative process has gone too far, any pharmacotherapy should be considered unsuccessful, if not useless. Our analysis of the literature on the treatment of asthma with Ginkgo biloba preparations, which are currently recognized nootropic agents, is a confirmation. They are effective mainly in the treatment of

moderate dementia disorders. This makes it possible to have no doubt about the expediency of using MT mainly for preventive purposes in the early stages of the disease. Similar conclusions from experimental work based on the modeling of AD in transgenic mice are in good agreement with this.

Secondly, an individual approach to asthma therapy with MT drugs in order to increase its effectiveness probably requires the preliminary identification of patients with a more pronounced form of epiphyseal insufficiency. Such individuals must initially have particularly severe abnormalities in the secretory activity of the pineal gland or (presumably genetically determined) defects in the number and affinity of specific MT receptors.

However, it is obvious that, based not only on theoretical premises, MT exhibits anti-cement properties. However, they still need a reliable clinical justification using randomized and placebo-controlled trials.

Conclusions: Thus, by now, a sufficient amount of experimental and clinical evidence has been obtained for the pathogenetic association of asthma with age-related deterioration of epiphysis function. It has been established that the main hormone of the pineal gland, MT, is able to prevent the development of neurodegenerative processes in the brain by limiting amyloidogenesis and the toxic effect of beta—amyloid peptide on nerve cells, which gives reason to recommend it as a potential therapeutic agent in the complex therapy of asthma.

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