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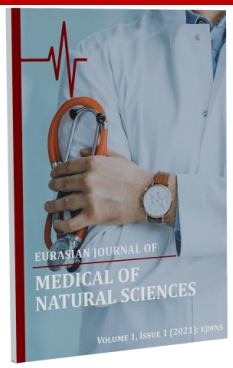

THE ROLE OF MELATONIN IN THE PATHOGENESIS AND THERAPY OF ALZHEIMER'S DISEASE

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ABSTRACT

The introduction comprehensively highlights the problem of the relationship between melatonin and Alzheimer's disease, including epidemiological data, current understanding of the pathogenesis and therapeutic perspectives. The text is structured logically, emphasizes the relevance of the problem and outlines the prospects for further research, while maintaining the scientific style of presentation and the accuracy of formulations.

Introduction. Alzheimer's disease (AD) is the most common cause of severe cognitive impairment in the elderly among organic brain lesions. Given the progressive rate of aging of the population of industrialized countries with an increasing number of people suffering from ASTHMA, the problem of its pathogenesis and therapy is acquiring not only medical but also social significance. This article attempts to summarize information according to which one of the factors predisposing to the development of asthma may be insufficient production of the main hormone melatonin (MT) by the epiphysis, and the hormone itself can be legitimately used as a means of pathogenetic therapy.

The biological role of the pineal gland and asthma

The epiphysis is an unpaired brain gland that has evolved into a kind of neuroendocrine organ that transforms photoreceptor information into a hormonal response. MT formed in pinealocytes, specific cellular elements of the gland, is synthesized only in the dark and destroyed in the light, which is why it participates in the organization of the basal circadian (circadian) biorhythm, determining, among other things, the dynamics of the sleep—wake cycle. MT has many extremely valuable pharmacological properties. In addition to participating in the organization of circadian periodicity and the duration of night sleep, it was able to regulate a number of physiological functions of the central nervous system and internal organs, demonstrating the possibility of its clinical use as a drug. The central and peripheral effects of MT are largely realized through specific MT receptors (type 1 and type 2).

An important biological feature of the pineal gland is its close connection with the aging processes of both humans and highly organized animals. Over the years, the gland, like the thymus, undergoes involution with increasing restriction of secretory activity. The maximum peak of plasma MT concentration at night in humans is observed in young and middle age (18-

50 years), followed by a progressive decrease in its production and a violation of the rhythm of production.

In patients with asthma, in contrast to people of the same age with signs of physiological old age, there are noticeable deviations in the normal activity of the epiphysis. Not only a more pronounced weakening of secretory processes is shown, but also a deformation of the pattern of nocturnal secretion of MT with variations in the position of the peak hormone production. The degree of decrease in its nocturnal level directly correlates with the severity of mental disorders in patients with dementia.

Since most of the MT is previously secreted into the CSF before being released into the blood plasma, the level of its content in it serves as a clearer criterion for adequate gland activity. At the same time, in patients with asthma, the hormone concentration in CSF is much lower than in healthy people. Moreover, according to the observations of some researchers, a drop in the level of MT in the CSF of patients with asthma is recorded already at the preclinical stage of the disease, due to which this indicator is even recommended to be used as an early diagnostic marker of the upcoming disease.

The described disorders in the work of the pineal gland in asthma can be determined by progressive dystrophic processes in the tissue of the gland itself in the form of increasing death of pinealocytes, and also have an extraepiphyseal origin. As we age, there is a gradual deterioration in the activity of the entire circadian rhythm management system, including control of epiphyseal secretion, and these disorders are more pronounced in the case of the disease.

The above facts indicate an obvious inferiority in the work of the epiphysis in asthma. The question arises — does the main hormone of the gland have the initial ability to improve cognitive processes? The results of experiments and studies on humans allow us to give a positive answer. According to our observations, MT has a noticeable optimizing effect on cognitive activity of the brain, improves memory and learning of animals in the Morris water maze, and epiphysectomy worsens these indicators. After repeated low-dose doses of the hormone, physically healthy young people tend to increase their visual and auditory memory. In people with a history of traumatic brain injury, this shift becomes quite distinct, statistically significant, and comparable to the effect of traditional nootropic drugs. At the same time, under the influence of MT, there is an improvement in visual perception, especially clear in the older age group (over 50 years old). In our opinion, such information gives the right to classify the hormone as a natural enhancer of cognitive activity.

The weakening of the secretory activity of the pineal gland is obviously not a simple paraphenomenon in asthma, but one of the links in its pathogenesis. Along with other factors, the occurrence of the disease may be favored by systemic disorders and cellular pathochemical shifts due to insufficient production of MT and, first of all, the weakness of its neuroprotective role.

From the point of view of the systemic organization, AD appears to be a typical chronopathology in the form of a breakdown of the normal structure of various kinds of biological rhythms, whereas MT should limit the clinical manifestations of the disease a priori due to its rhythm-stabilizing properties.

The importance of a chronobiological defect for the occurrence and maintenance of various disorders in the cognitive activity of the brain was considered by us earlier. The meaning of the arguments in favor of this was reduced to two main provisions. Firstly, in natural conditions, the processes of memory, perception, and attention have a rhythmic nature, which is disorganized by organic mental disability of various origins. Secondly, nootropic drugs with different types of cellular action are able to weaken dysrhythmic manifestations, and such an effect may be an integral element of their specific pharmacological activity.

Both of these points are obviously directly relevant to the issue under discussion. First of all, there is no doubt about the chronopathological nature of asthma. This is irrefutably evidenced by the fact that nighttime sleep disorders accompany the disease as an almost mandatory symptom. Compared with elderly people of the same age group, patients with asthma are more likely to show a change in sleep architecture with a significant decrease in the proportion of slow-wave and R phases, an increase in the time and frequency of awakenings. The severity of insomnia directly correlates with the progressive deterioration of memory and other cognitive indicators. In asthma, there is a breakdown not only of the leading circadian sleep—wake biorhythm, but also its misalignment with the circadian dynamics of body temperature, plasma levels of glucocorticoid hormones, etc.

The cause of dysrhythmia characteristic of asthma should be sought in the pathological shifts that occur in different parts of the biorhythm control system and, first of all, in the epiphysis itself. The degenerative processes in the gland tissue that increase with age and the progressive deficiency of MT lead to a weakening of its hypnogenic and rhythm-stabilizing activity. At the same time, the function of the driver of the circadian rhythm of the suprachiasmatic nuclei of the hypothalamus seems to suffer from the disease. In elderly people, a decrease in the number of cellular elements was detected in these nuclei, especially in dementia patients. The introduction of β-amyloid peptide (BAP) into the region of rat nuclei, which is given the main importance in neurodegeneration in asthma, disorganizes the rhythm of circadian locomotion in animals. It is important to note that such violations were eliminated by MT.

Meanwhile, these nuclei and the epiphysis are connected by close morphofunctional relationships. Receiving noradrenergic innervation with the participation of nuclei, the gland, in turn, controls their work through humoral MT. ASTHMA, apparently, is characterized by more severe isolated or complex disorders in the activity of a single retino-hypothalamic-epiphyseal system than with physiological aging. Among other things, due to the weakening of the noradrenergic control of the pacemaker over the condition of the gland in case of disease, the level of the MT precursor serotonin in its tissue may decrease and its enzymatic inactivation by the MAO enzyme (type A) may increase. This ultimately leads to a decrease in hormone production.

Consequently, concomitant disorders in the temporal organization of many physiological functions are systemic in nature. Having arisen primarily on the basis of cerebral pathology, they are likely to be further integrated into the structure of the disease, becoming its pathogenetic link.

Meanwhile, epiphyseal MT, being a natural chronobiotic and synchronizer of oscillatory processes in the body, clearly weakens insomnia, including concomitant asthma. In elderly people with somatic pathology suffering from insomnia, the administration of low doses (1-2 mg) of MT increases the quality of night sleep, facilitating falling asleep and normalizing its structure [10, 34, 37]. Similar results were obtained in patients with asthma. After regular intake (from several weeks to several months) of a hormonal drug (in doses of 3 or 6 mg daily), they registered an improvement in sleep indicators, coinciding with a noticeable optimization of cognitive functions. However, in one study, under the influence of a higher dosage of MT (10 mg per day, for 2 months) in asthma, there was only a tendency to improve graphically recorded sleep. However, the lack of a convincing result in this work can be fully explained by the fact that the authors used an inadequately high dose of the hormone in the absence of a linear dose—effect relationship in this case.

If we assume that the disorganization of biorhythms is pathogenetically related to asthma, then normalization of rhythm in any way, including by non-drug means, should facilitate the course of the disease. Indeed, the rhythmic effect of phototherapy or the physical rhythmogenic effect of patients staying in a low-frequency electromagnetic field can weaken cognitive disorders.

The systemic nature of neurodegenerative pathology of the AD type is also confirmed by the fact that cognitive decline depends on the involvement of many brain structures in the pathological process, including, in addition to the cortex of the frontal and temporal lobes, a number of subcortical limbic nuclei. Among the latter, the hippocampus plays an important role in the organization of memory processes. At the same time, this structure has pronounced rhythmogenic properties, acting as a secondary oscillator, subordinate to the signals of the leading pacemaker and responsible for organizing mental activity over time.

According to magnetic resonance imaging, AD is characterized by a decrease in the size of the hippocampus. It is significant that the first signs of atrophy can be detected several years before the full clinical picture of the disease is developed, therefore they are considered as its reliable predictor. Due to the fact that asthma is characterized by the disintegration of brain function, the lack of mnestic and chronotropic activity of the hippocampus can serve as a trigger for the painful process. Epiphyseal deficiency predisposes to this, since MT provides reliable protection of hippocampal neurons from damage.

Conclusions: Thus, at the level of the whole brain, asthma is characterized by both disorganization of biorhythms and breakdown of the well-coordinated, harmonious activity of brain structures. Both types of disorders, among other things, can be determined by insufficient production of MT by the epiphysis. This is confirmed by the fact that the administration of the hormone from the outside facilitates the restoration of rhythmic processes and improves the activity of brain structures that are key to memory formation.

References:

1. Baydas G., Reiter R.J., Akbulut M. Melatonin inhibits neural apoptosis induced by homocysteine in hippocampus of rats via inhibition of cytochrome c translocation and caspase-3 activation and by regulating pro- and anti- apoptotic protein levels. Neuroscience 2005; 135: 3: 879-886.

2. Baydas G., Yasar A., Tuzcu M. Comparison of the impact of melatonin on chronic ethanol-induced learning and memory impairment between young and aged rats. J Pineal Res 2005; 39: 4: 346-352.
3. Den Heijer T., Greelings I., Hoebeek F. et al. Use of hippocampal and amygdaloid volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. Arch Gen Psychiat 2006; 63: 1: 57-62.
4. Dickerson B.C., Salat D.H., Greve D.N. et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and Alzheimer`s disease. Neurology 2005; 65: 3: 404-411.
5. Harderland R. Antioxidative protection by melatonin — multiplicity of mechanism from radical detoxication to radical avoidance. Endocrine 2005; 27: 119-130.
6. Lee S.-H., Chun W., Kong P. et al. Sustained activation of Akt by melatonin contributes to the protection against kainic acid-induced neuronal death in hippocampus. J Pineal Res 2006; 40: 79-85.
7. Li X.C., Wang Z.F., Zhang J.X. et al. Effect of melatonin on calyculin-Ainduced tau hyperphosphorylation. Eur J Pharmacol 2005; 510: 25-30.
8. Maharaj D.S., Maharaj H., Antunes E.M. et al. 6-Hydroxymelatonin protects against quinolic-acid-induced oxidative neurotoxicity in the rat hip- pocampus. J Pharm Pharmacol 2005; 57: 7: 877-881.
9. Ozdemir D., Tugyan K., Uysal K. et al. Protective effect of melatonin against head trauma-induced hippocampal damage and spatial memory deficits in immature rats. Neurosci Lett 2005; 383: 3: 234-239.
10. Pandi-Perumal S.R., Zisapel N., Srinivasan V. et al. Melatonin and sleep aging population. Exp Gerontol 2005; 40: 911-925.
11. Quinn J., Kulhanek D., Nowin J. et al. Chronic melatonin therapy fails to alter amyloid burden or oxidative damage in old Tg 2576 mice: implications for clinical trials. Brain Res 2005; 1037: 209-213.
12. Rakhmonova H.N., Rakhmonov Z.M. Innervation Relationships of the Gallbladder Nerve Apparatus with Spinal and Rheumatic Nerve Ganglia (Literature Review). Eurasian Medical Research Periodical, 18, 105-108.
13. Rakhmonova Kh.N. Morphological bases of innervational connections of the nervous apparatus of the gallbladder Journal of Problems in Biology and Medicine, PBIM 2022 №6 (140), 387-392.
14. Savaskan E., Ayoub M.A., Ravid R. et al. Reduced hippocampal MT2 melatonin receptor expression in Alzheimer`s disease. J Pineal Res 2005; 38: 10-16.
15. Vega-Naredo I., Poggeler B., Sierra-Sanchez V. et al. Melatonin neutralizes neurotoxicity induced by quinolinic acid in brain tissue culture. J Pineal Res 2005; 39: 266-275.
16. Арушанян Э.Б. Гормон эпифиза мелатонин — новое ноотропное средство? Экспер и клин фармакол 2005; 68: 3: 74-79.
17. Арушанян Э.Б. Уникальный мелатонин. Ставрополь 2007; 399.
18. Арушанян Э.Б. Хронобиологическая природа нарушений познавательной деятельности мозга. Журн неврол и психиат 2005; 105: 11: 73-78.

19. Арушанян Э.Б., Бейер Э.В. Ноотропные свойства препаратов Гинкго билоба. Экспер и клин фармакол 2008; 71: 4: 57-63.
20. Левин Я.И. Мелатонин (мелаксен) в трапии инсомнии. Рус мед журн 2005; 13: 7: 1-3.
21. Яхно Н.Н., Преображенская И.С. Болезнь Альцгеймера: клиника, патогенез, лечение. Рус мед журн 2006; 14: 9: 641-646.