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Melatonin and Alzheimer's Disease

Abdullayeva N.N
Kasimov A.A.
Eshpo'latov Sh. S.
Norbekov B. Sh.
Department of Neurological Diseases
Samarkand State Medical University

Abstract:
Alzheimer's disease (AD) is the most common cause of severe cognitive impairment in old age among organic brain lesions. Given the progressive aging of the population in industrialized countries and the increasing number of people suffering from AD, the problem of its pathogenesis and treatment becomes not only of medical, but also of social importance.

Keywords: Alzheimer's disease, epiphysis, melatonin.

Introduction

This paper attempts to summarize the evidence that one of the factors predisposing to the development of AD may be the insufficient production of the key hormone melatonin (MT) by the epiphysis, and that the hormone itself is legitimately used as a pathogenetic therapy. The epiphysis is an unpaired medullary gland, which has evolved into a kind of neuroendocrine organ transforming photoreceptive information into hormonal response. Formed in specific glandular cellular elements, pinacocytes, MT is synthesized only in darkness and degraded in light, thus participating in the organization of the basal circadian (circadian) biorhythm, determining, among others, the dynamics of the sleep-wake cycle. MT has many valuable pharmacological properties. In addition to its involvement in the organization of circadian periodicity and the duration of nocturnal sleep, it has been shown to regulate several physiological functions of the CNS and internal organs, demonstrating its potential for clinical use as a drug. The central and peripheral effects of MTs are largely mediated by specific MT-receptors (type 1 and type 2).

An important biological feature of the epiphysis is its close relationship with the aging process in both humans and highly organized animals. The gland, like the thymus, undergoes involution with an increasing limitation of secretory activity over the years. The maximum peak of plasma concentration of MT at night in people is observed at young and middle age (18-50 years), subsequently there is a progressive fall of its production and violation of the rhythm of production.

In AD patients, unlike individuals of the same age with signs of physiological aging, there are marked deviations in the normal activity of the epiphysis. Not only a more pronounced weakening of secretory processes, but also a deformation of the nocturnal MT pattern with variations in the position of the peak of hormone production.The degree of decrease in its nocturnal level directly correlates with the severity of mental disorders in patients with dementia.

As most of MT is secreted into the CSF before it enters the blood plasma, its level in the CSF serves as a clearer criterion of the gland's adequate activity. Moreover, in patients with AD the concentration of the hormone in the CSF is significantly lower compared to healthy controls.Moreover, according to some researchers, the decrease of MT level in SMF of AD patients is registered in the preclinical stage of the disease, so this index is even recommended to be used as an early diagnostic marker of the forthcoming disease.

The described dysfunction of the epiphysis in AD may be determined by progressive dystrophic processes in the gland tissue itself in the form of increasing pinacocyte hygiene as well as having an extra-epiphyseal origin. As the gland ages, there is a gradual deterioration of the entire glandular control system, including the control of epiphyseal secretion, and these disorders are more pronounced in the case of the disease.

These facts point to an obvious inadequacy in the functioning of the epiphysis in AD. The question arises - Does the major gland hormone have an innate ability to improve cognition? The results of experiments and studies on humans allow us to give a positive answer. According to our observations , MT has a markedly optimizing effect on brain cognitive activity and improves memory and learning of animals in the Morris water maze, whereas hemispherectomy worsens these parameters. After repeated low-dose doses of the hormone, physically healthy young people tend to show an increase in visual and auditory memory. In subjects with a history of brain trauma, this shift is statistically significant and comparable to the effect of traditional nootropic agents. At the same time, the effect of MT is associated with an improvement in visual perception, especially clear in the older age group (over 50 years). In our opinion, such data allow us to classify the hormone as a natural cognitive enhancer.

The weakened secretory activity of the epiphysis is obviously not a simple paraphenomenon in AD, but a part of its pathogenesis. Systemic abnormalities and cellular pathochemical shifts due to insufficient MT production and weakness primarily of its neuroprotective role may also contribute to the onset of the disease along with other factors. In terms of systemic organization, AD appears as a typical chronopathology in the form of a breakdown in the normal structure of various

biological rhythms, whereas MT should a priori limit the clinical manifestations of the disease due to its rhythm-stabilizing properties.

The significance of the chronobiological defect for the emergence and persistence of a variety of disorders in cognitive brain activity has been previously discussed. The rationale for this was summarized in two main points. First, under natural conditions, the processes of memory, perception, and attention have a rhythmic nature, which is disorganized in organic mental insufficiency of various genesis. Second, nootropic drugs with different types of cellular action can attenuate dysrhythmic manifestations, and this effect may be a component of their specific pharmacological activity .

Both of these points are obviously of direct relevance to the issue at hand. Above all, there is no doubt about the chronopathological nature of AD. This is undeniably evidenced by the fact that nighttime sleep disturbances are almost always associated with the disease. Compared to elderly people of the same age group, AD patients are more often affected by altered sleep architecture, with a significant decrease in the proportion of slow-wave and REM phases, and an increase in the time and frequency of awakening. The severity of the insomnia directly correlates with progressive deterioration of memory and other cognitive measures. In AD, not only the leading daily biorhythm of sleep and wakefulness is disrupted, but also its misalignment with the circadian dynamics of body temperature, plasma content of glucocorticoid hormones, etc.

The dysrhythmia characteristic of AD is caused by pathological shifts occurring in different parts of the biorhythm control system, primarily in the epiphysis itself. Increasing with age, degenerative processes in the gland tissue and progressive MT deficiency leads to a weakening of its hypnogenic and rhythm stabilizing activity. The disease has been shown to affect the circadian rhythm of the suprachiasmatic nuclei of the hypothalamus, which are the most important rhythmic nuclei of the hypothalamus. At the same time, the disease appears to impair the circadian rhythmic driver function of the suprachiasmatic nuclei of the hypothalamus. A decrease in the number of cellular elements was detected in these nuclei in elderly people, especially in dementia patients. Introduction of β-amyloid peptide (BAP), which is considered to be of major importance in neurodegeneration in AD, into the rat nuclei disorganizes the rhythm of diurnal locomotion in the animals. It is important to note that such disturbances were eliminated by MTs.

Meanwhile, these nuclei and the epiphysis are linked by a close morpho functional relationship. The gland receives noradrenergic innervation with the participation of the nuclei and, in its turn, controls their work through humoral MTs. In AD, isolated or complex alterations in the activity of the unified retinohypothalamic-epiphyseal system appear to be more severe than in physiological aging. Among other things, the

weakening of noradrenergic rhythm control in the disease may lead to a decrease in the MT precursor serotonin in the tissue and increased enzymatic inactivation by the MAO enzyme (type A). This ultimately results in impaired hormone production.

Consequently, AD-related abnormalities in the temporal organization of many physiological functions are systemic in nature. The primary origin of cerebral pathology is likely to be incorporated into the structure of the disease, becoming its pathogenetic link.

Meanwhile, epiphyseal MT, as a natural chronobiotic and synchronizer of oscillatory processes in the body, clearly alleviates insomnia, including that associated with AD. In elderly people with somatic pathology suffering from insomnia, prescribing already low doses (1-2 mg) of MT improves nighttime sleep quality, facilitating falling asleep and normalizing its structure. Similar results have been obtained in patients with AD. After regular use (from several weeks to several months) of a hormone (at doses of 3 or 6 mg daily), both showed improvement in sleep quality and coincided with marked optimization of cognitive function. However, in one study, a higher dosage of MT (10 mg daily, for 2 months) in AD was associated with only a tendency to improve graphically recorded sleep. However, the absence of a convincing result in this study may be 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.

Assuming that biorhythm disorganisation is pathogenetically related to AD, rhythm normalisation by itself by any means, including non-medication, should alleviate the disease. Indeed, the rhythm-organising effect of phototherapy or the physical rhythmogenic effect of exposing patients to a low-frequency electromagnetic field can attenuate cognitive disorders.

Consistency of neurodegenerative pathology of the type AD is also confirmed by the fact that the decline in cognitive functions 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 organizing memory processes. At one time, this structure possesses pronounced rhythmogenic properties, performing the function of a secondary oscillator subordinated to the signals of the leading rhythm driver and responsible for the organization of mental activity in time.

According to magnetic resonance imaging, AD is highly characterized by a reduction in the size of the hippocampus. Significantly, the first signs of atrophy can be detected several years before the full clinical picture of the disease develops, so they are considered to be a reliable predictor of AD. Because AD is characterized by disintegration of brain function, a lack of mnemonic and chronotropic activity of the hippocampus may be a factor in the initiation of the disease process. Epiphyseal

deficits predispose to this, as MTs provide robust protection of hippocampal neurons from damage.

Thus, at the whole-brain level, AD is characterized by both biorhythm disorganization and a breakdown in the coordinated, harmonious activity of the brain structures. Both types of disorders may be caused by a lack of epiphysis production of MTs, among others. This is borne out by the fact that introducing the hormone from outside facilitates the reestablishment of rhythmic processes and improves the activity of key brain structures involved in memory formation.

The cellular mechanisms of action of MT

According to modern concepts, deposition of the cytotoxic protein beta-amyloid peptide (BAP), which serves as an insoluble product of its highly soluble precursor, in the cerebral tissue and cerebral vessel walls is of crucial pathogenetic significance in AD pathogenesis. This process of transformation and deposition of BAP in the form of extracellular senile plaques is favored by several factors, including formation of pathological forms of apolipoprotein and hyperlipidemia. A characteristic morphological feature of AD appears to be the formation of fibrillar nodules in neurons, which are altered microtubules of the cytoskeleton and consist of hyperphosphorylated tau- protein. These morphological shifts lead to cytotoxic effects, causing nerve cell degranulation in various ways. The development of oxidative stress also plays a significant role.

Although the origin of organic and functional abnormalities in AD at the cellular level is not conclusively established, there is reason to believe that deficient epiphysis activity contributes to their genesis. This is supported by indications that epiphyseal hormone may modify BAP formation processes and the consequences of its toxic effects on cerebral neuronal function. These findings can be grouped into two main groups.

The first of these includes the results of *in vitro* experiments on human neuroblastoma cells and a culture of rat hippocampal neurons, 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 formation of its neurotoxic complex with BAP [64, 66]. The intake of MTs with water for several months in transgenic mice, which were modeled BA type amyloidogenesis, inhibited brain amyloid peptide formation, decreased protein nitrification and simultaneously increased animal survival, although MTs did not prevent amyloidogenic effect in old mice. Moreover, due to the link between cholesterolemia and amyloid pathology in AD, MT is considered to be important in the regulation of cholesterol metabolism .

Another group of facts is primarily the ability of MTs to inhibit the toxicity manifestations of BAP. In studies on isolated neurons, the hormone was shown to

provide successful protection against oxidative stress induced by pathogenic protein. It has a well-founded ability to serve as a "trap" for free radicals, which is even better expressed than that of the well-known antioxidant, vitamin E. By inhibiting the processes of lipid peroxidation, MTs prevent damage of mitochondria membranes by aggressive oxygen species. Note that this action is performed without the participation of MT-specific receptors by some of its metabolites. The formation of one of these metabolites, N-acetyl-5-methoxykinurinamine, may be impaired with age and in neurodegenerative brain diseases .

In addition to these defense mechanisms, the neuroprotective properties of MT are realized through other mechanisms. In particular, it decreases the sensitivity of N-methyl-D-aspartate (NMDA) receptors and thereby attenuates neuronal excitotoxicity of glutamic and quinolinic acids by limiting the excessive accumulation of intracellular calcium ions. In this regard, it is interesting that exactly the same hormone limits neurodegeneration caused by okadaic acid, which is considered as experimental analogue of the corresponding changes in AD. Interacting with the phosphorylation system, especially with the so-called stress kinases, MT attenuates the process of protein tau- hyperphosphorylation. It has been shown to have distinct immunomodulatory properties, ensured through interference with opioidergic transmission. Finally, the hormone can enhance repair processes in nervous tissue by increasing the production of individual neurotrophins and activation of tyrosine kinase receptors .

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

The place of the hippocampus in implementing MT activity in relation to preventing the development of dementia. In the 80s C. Maurizi [52] 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 are caused by chronic deficiency MT. Numerous later data are in good agreement with this view.

The particular importance of the hippocampus is indicated by the aforementioned evidence of early atrophic changes in the structure in AD and its leading importance in organizing memory processes. In addition, we can refer to several other facts. For example, transgenic mice used to model AD have the highest density of BAP-containing nil plaques in the hippocampus. Increased oxidative stress and increased accumulation of several inhibitory peptides were shown in the granular cells of this structure and the frontal cortex of these animals . Intraventricular administration of amyloid peptide to rats impairs memory and learning in the water maze with

simultaneous disruption of cholinergic innervation of the hippocampus and anterior neocortex with decreased choline acetylase activity. It is also assumed that in AD, it is in the hippocampus that the most active neurotoxic combination of BAP and apolipoprotein E4 occurs, which causes increased apoptosis of nerve cells .

MTs are directly related to the control of normal and abnormal hippocampal activity. Both types (1 and 2) of MT receptors are shown in the dentate gyrus and pyramidal neurons CA1 and CA3 of the structure fields. Apparently, the hormone, when added to rat hippocampal tissue culture, changes the frequency of cell discharges because this effect is eliminated by the specific receptor blocker lusindol. Chronic MT administration to newborn rats increases cell proliferation in the dentate gyrus and increases the density of individual NMDA receptor subunits during indirect mobilization of epiphysis secretory activity by exposing rats to darkness for prolonged periods of time. On the contrary, functional epiphysectomy (keeping animals under constant light) reduces antioxidant protection of hippocampal tissue in old, but not young rats. On the other hand, according to our observations, local damage of their dorsal hippocampal tissue weakens the psychotropic activity of MTs.

The previously described neuroprotective properties of MTs are also fully applicable to the pathological processes in this structure. As established on isolated rat hippocampal slices, the addition of MTs attenuated the depression of the synaptic response of pyramidal neurons to the stimulation of afferent Schaffner fibers and simultaneously reduced the generation of free radicals if both were developed during the simulation of ischemic hypoxia . *In vivo* experiments, it was found that repeated administration of high doses of MTs (10-20 mg/kg) to rats prevented memory and learning disorders and delayed cell death in CA1 and CA3 fields of the hippocampus, observed after cranial contusion injury. The hormone also protected hippocampal neurons from glutamate excitotoxicity, while epiphysectomy potentiated cell death in simulated stroke by carotid artery occlusion . 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 or quinoline acids. At the same time, lipid peroxidation processes were impaired and apoptosis was inhibited due to inactivation of the pro- apoptotic protein Bax, as well as increased levels of the anti- apoptotic protein Bcl 2. In addition, the decline of some NMDA receptor subunits was prevented.

By similar mechanisms, hormonal protection is achieved in hippocampal lesions in AD. The addition of MTs to a culture of rat hippocampal neurons prevents apoptosis with chromatin condensation and DNA fragmentation caused by the BAP Abeta prepar- ture. Its toxicity reduction was also accompanied by a decrease in lactate

dehydrogenase activity. In transgenic mice, prolonged (4 months) administration of MTs along with alleviation of mnemonic disorders decreased extracellular BAP accumulation and increased choline acetylase activity in the frontal cortex and hippocampal tissue . Local injection of fibrillary BAP into the CA1 field of rat hippocampus produced a pattern of typical oxidative stress, which was accompanied by increased levels of nitrates, lipoperoxides and pro-inflammatory cytokines in the structure. Oral administration of MT, as well as vitamin C and E preparations, limited these pathochemical shifts, and the hormone activity was clearly superior to conventional antioxidants. Epiphyseal hormone proved to be able to attenuate lipid peroxidation and increase glutathione levels in rat hippocampus in parallel with the improvement of memory and learning in AD simulated by chronic administration of ethanol. In this situation, older animals responded much more strongly to MTs than younger animals .

There are arguments for a possible link between the described neuroprotection and the pathogenesis of AD in humans. The MT1 and MT2 receptors are actively expressed in the human hippocampus by immunohistochemical techniques. Their density is markedly reduced in old age, but the expression is particularly disrupted during AD in the pyramidal neurons of the main hippocampal fields and the granular layer of the structure .

Thus, through various cellular mechanisms, MT counteracts both hippocampal amyloidosis and its consequences, protecting the hippocampus from cytotoxic effects. Since this structure, which has an important mnemonic function, is one of the first to be affected in AD, there is enough evidence to link the pathogenesis of the disease among other causes to a limitation of epiphyseal control of its activity. It is therefore logical to use MTs to combat neurodegenerative pathology.

Therapeutic options for MT in AD

Despite the obvious usefulness of this treatment approach, few clinical trials using the hormone have yet yielded reliable results.

Although the clinical data do not agree with the expected therapeutic potential of MT based on the experimental findings, this should not preclude further research in this area. A clinical trial conducted by Cardinali et al. Cardinali et al. They followed two men who were homozygous twins with genetically determined AD of equal severity. Both patients received identical conventional pharmacotherapy; however, one of them was treated with an additional MT (6 mg/day) for an extended period (36 months). Eventually, at the end of this treatment, this patient showed a moderate improvement in memory and a milder version of the disease than his sibling .

It is also probably due to the wide variation in the individual sensitivity of patients, which has been noted by many researchers, that the therapeutic benefits of CBT have been underestimated. There are, in our opinion, two possible explanations for this.

First, in severe cases of AD, when the neurodegenerative process has gone too far, any pharmacotherapy should be recognized as of little success, if not useless. A review of the literature on the treatment of AD with Ginkgo biloba, now recognized as a novel treatment, confirms this. They are predominantly effective in the treatment of moderately severe dementia. This suggests that MTs should be used mainly for prophylactic purposes in the early stages of the disease. Similar findings from experimental work based on the simulation of AD in transgenic mice are in good agreement.

Secondly, an individualized approach to MT therapy to improve its efficacy appears to require prior identification of patients with a more severe form of epiphyseal deficiency. Such individuals must have particularly severe abnormalities in the secretory activity of the epiphysis or (presumably genetically determined) defects in the number and affinity of specific MT receptors.

However, it is clear that, not only on theoretical grounds, MT shows antidemetic properties. However, these still need robust clinical validation through randomised and placebo- controlled trials.

Conclusions:

Thus, there is sufficient experimental and clinical evidence for a pathogenetic link between AD and age-related deterioration of epiphysis function. It was found that MT, the main hormone of epiphysis, is able to prevent the development of neurodegenerative processes in the brain by limiting amyloidogenesis and the toxic effect of β-amyloid peptide on nerve cells, which provides the basis for its recommendation as a potential therapeutic agent in the complex treatment of AD.

LITERATURE

1. Akramova D. et al. Stroke incidence and association with risk factors in women in Uzbekistan //Cerebrovascular Diseases. – Allschwilerstrasse 10, Ch-4009 Basel, Switzerland : Karger, 2017. – T. 43.

2. Bobomuratov T.A., Sharipova O.A., Akramova N.T. Assessing the impact of secondary prevention among boys with bronchiectasis and delayed pubertal development // Science and Innovations in the Globalized world. San Diego, 2016. Vol. 1. P. 114-119.

3. Khamdamov B.Z. Indicators of immunocitocine status in purulent-necrotic lesions of the lover extremities in patients with diabetes mellitus.//American Journal of Medicine and Medical Sciences, 2020 10(7) 473-478.
5. M. I. Kamalova, N.K.Khaidarov, Sh.E.Islamov,Pathomorphological Features of hemorrhagic brain strokes, Journal of Biomedicine and Practice 2020, Special issue, pp. 101-105
6. Kamalova Malika Ilkhomovna, Islamov Shavkat Eriyigitovich, Khaidarov Nodir Kadyrovich. Morphological Features Of Microvascular Tissue Of The Brain At Hemorrhagic Stroke. The American Journal of Medical Sciences and Pharmaceutical Research, 2020. 2(10), 53-59
7. Khodjieva D. T., Khaydarova D. K., Khaydarov N. K. Complex evaluation of clinical and instrumental data for justification of optive treatment activites in patients with resistant forms of epilepsy. American Journal of Research. USA. № 11-12, 2018. C.186-193.
8. Khodjieva D. T., Khaydarova D. K. Clinical and neuroph clinical and neurophysiological ch ogical characteristics of teristics of post-insular cognitive disorders and issues of therapy optimization. Central Asian Journal of Pediatrics. Dec.2019. P 82-86
9. Kasimov, Arslanbek; Abdullaeva, Nargiza; Djurabekova, Aziza; Shomurodova, Dilnoza//Features of diagnosis and clinic of post-traumatic epilepsy against the background of concomitant somatic diseases. International Journal of Pharmaceutical Research (09752366) . Jul-Sep2020, Vol. 12 Issue 3, p1788-1792. 5p.
10. Kasimov Arslanbek Atabaevich, Bozorova Sabohat Normo'min qizi, & Gulkhayo Eshmatovna Zhumanova. (2022). Results of a study of clinical and neurophysiological changes in patients with post-traumatic epilepsy with concomitant somatic diseases on the basis of complex drug therapy. World bulletin of public health 10, 186-190
11. Kasimov Arslanbek Atabaevich. (2022). Dynamics of clinical and neurophysiological changes against the background of complex medical therapy in patients with posttraumatic epilepsy with concomitant somatic diseases. Frontline Medical Sciences and Pharmaceutical Journal, 2(03), 78–87.
12. Khudaynazarova Muattar Tokhirjonovna, Ruziyev Jononbek Elmurodovich, & Kasimov Arslanbek Atabayevich. (2022). Peculiarities of diagnosis and clinical picture of posttraumatic epilepsy against the background of concomitant somatic diseases. *World bulletin of public health*, *10*, 121-126.
13. Uralov, F. S. ., Khurramov, M. B. ., Kasimov, A. A. ., & Mamurova, M. M. . (2022). Modern Methods of Epilepsy Treatment and Prevention of Tactical and Therapeutic Errors in Epilepsy Treatment. *International Journal Of Health Systems And Medical Sciences*, *1*(4), 374–377.

14. Шомуродова Д. С., Джурабекова А. Т., Мамурова М. М. Особенности и прогноз поражения нервной системы у беременных женщин с преэклампсией характеризуемые методами функциональной диагностики //журнал неврологии и нейрохирургических исследований. – 2020. – Т. 1. – №. 2.

15. Мамурова, М., Рузиева, Ш., Олланова, Ш., Хакимова, С., & Джурабекова, А. (2015). Клинико-неврологические особенности Хронических цереброваскулярных заболеваний, обусловленных Артериальной гипертензией, у пациентов молодого возраста. Журнал вестник врача, 1(4), 39–42.

16. Мамурова М. М., Джурабекова А. Т., Игамова С. С. Оценка когнитивных вызванных потенциалов головного мозга (р-300) у лиц молодого возраста с артериальной гипотензией //журнал неврологии и нейрохирургических исследований. – 2021. – Т. 2. – №. 1.

17. 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.

18 Рузиева, Ш., Мамурова, М., Хакимова, С., & Джурабекова, А. (2016). Клиническая характеристика больных с транзиторными ишемическими атаками. Журнал проблемы биологии и медицины, (2 (87), 79–82.