Melatonin and Epilepsy

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Abstract

Epilepsy is a chronic neurological disease with recurrent seizures. Its incidence, the social and psychological aspects of epilepsy-associated stigmatization in society, the medical risk of severe seizures, and the challenges in treatment confirm its medical and social significance. The pathogenesis of the disease is associated with abnormal activity of a population of neurons due to various mechanisms, the most frequent being oxidative stress, glutamate excitotoxicity, and mitochondrial dysfunction. In the last 3–4 decades, the possible connection between epilepsy and melatonin – a neurohormone secreted by the pineal gland – has been sought and studied. Various physiological functions of melatonin in humans have been proven – regulation of circadian rhythms (diurnal, seasonal), sleep and wakefulness, participation in the processes of thermoregulation, tumor growth and aging, sexual activity and reproductive functions. It also has immunomodulatory, cytoprotective and antioxidant activity. The results from the studies with experimental models with animals conducted so far in search of a correlation between melatonin and epileptogenesis are mainly in support of the hypothesis of its anticonvulsant effect. The studies with humans are diverse in design, with a smaller number of participants, and the results are not always in explicit support of this hypothesis. The correlation between melatonin concentration and the course of the disease in patients with epilepsy has been discussed. The possibility of adding melatonin to anti-epileptic therapy has also been studied recently.

Keywords

anticonvulsant, antioxidant, melatonin serum concentration, neuroprotective, seizures

INTRODUCTION

Melatonin is a neurohormone synthesized and secreted by the pineal gland. It has an important role in the regulation of circadian rhythms, as well as proven neuroprotective, antioxidant, and anticytotoxic effects on the central nervous system (CNS). In recent years, the relationship between melatonin concentration and the frequency and severity of seizures in patients with epilepsy has been sought. The possibility of adding melatonin to the antiepileptic therapy and proving its antiepileptic effect has been discussed. Studies have shown conflicting results regarding the effect of melatonin on seizure frequency. The researchers have presented various hypotheses about the correlation between the hormone concentration and the course of the disease.

Epilepsy – definition, epidemiology, pathogenesis

Epilepsy is a chronic neurological disease with social significance. According to WHO data as of 2018 worldwide, approximately 50 million people have been diagnosed with epilepsy, and in 50%–60% of the cases the onset is in childhood and adolescence. No less important are the stigmatization in society and the quality of life of epileptic patients, as well as the negative consequences for the psyche and the development of depression. Mortality is up to 4 times higher than that in the healthy population, with the most common causes being seizure trauma (5%), convulsive epileptic statuses (10%) and “sudden death syndrome” (8–17%). Epidemiological data show a similarity in the incidence of epilepsy in countries with different economic development, ranging from 2.3 to 22.8/1000. However,
morbiditity statistics show a significant difference as the average for high-income countries is 45 per 100 000 population, and for the rest – 81.7/100 000. In Bulgaria, epileptic patients are about 50 000. According to the 2006 definition of the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), epilepsy is a brain disease characterized by a persistent predisposition to generate epileptic seizures and the neurobiologic, cognitive, psychological, and social consequences of seizure recurrences. Epileptic seizures are defined as episodes of a sudden occurrence of quantitative and/or qualitative disorder of consciousness, sensory, motor, autonomic and mental functions. In 2014, the ILAE recommended an expanded definition, according to which epilepsy is a brain disease that occurs under any of the following conditions: 1) at least 2 unprovoked (or provoked) seizures observed over a period of more than 24 hours; 2) one unprovoked (or provoked) seizure and the presence of factors that determine a higher (over 60%) probability of subsequent seizures, similar to that after 2 unprovoked seizures (seizures 30 days after stroke, with established brain structural abnormalities and epileptiform EEG); 3) diagnosis of an epileptic syndrome (Roland’s epilepsy with low risk of recurrent seizures, Landau-Kleffner syndrome, epileptic encephalopathy with prolonged spike-slow wave complexes during sleep).

Regarding the pathogenesis of epilepsy, it is assumed that it is violation of the balance between excitatory and suppressive processes in a neuronal population with impaired cognitive functions. In 2014, the ILAE recommended an expanded definition, according to which epilepsy is a brain disease that occurs under any of the following conditions: 1) at least 2 unprovoked (or provoked) seizures observed over a period of more than 24 hours; 2) one unprovoked (or provoked) seizure and the presence of factors that determine a higher (over 60%) probability of subsequent seizures, similar to that after 2 unprovoked seizures (seizures 30 days after stroke, with established brain structural abnormalities and epileptiform EEG); 3) diagnosis of an epileptic syndrome (Roland’s epilepsy with low risk of recurrent seizures, Landau-Kleffner syndrome, epileptic encephalopathy with prolonged spike-slow wave complexes during sleep).

In regard to pharmacological reactivity, epilepsy is divided into 3 types: pharmacosensitive, drug-requiring and pharmaco-resistant epilepsy. The one that does not recur is considered pharmaco-sensitive. It occurs with well-controlled seizures and treatment is effective. Pharmaco-requiring is epilepsy, in which the seizures are well controlled, but with a high risk of recurrence when stopping drug treatment. Pharmaco-resistant epilepsy affects 25-33% of patients. In these cases the disease remains resistant to the drugs used. Patients are severely disabled and at increased risk of sudden death. According to the definition proposed by the ILAE (2009), drug-resistant patients are those who fail to receive adequately applied, appropriately selected and well tolerated 2 antiepileptic drugs (AEDs) in monotherapy or in combination, to achieve prolonged seizure freedom (for a period of 1 year or 3 times longer than the longest inter-seizure period during the last year). It is important for clinical practice to distinguish between the concepts of resistance and pseudo-resistance. In pseudo-resistant epilepsy, seizures are caused by factors unrelated to epilepsy or that may be affected after diagnostic reassessment and therapeutic adaptation. It is observed in about 20% of patients diagnosed with resistant epilepsy. Pseudo-resistance is associated with the so-called ‘errors’ in diagnosing and analyzing the course of the disease, as well as its treatment, or with poor compliance.

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**Melatonin**

Melatonin is an indolamine with the chemical formula N-acetyl-5-methoxytryptamine – a heterocyclic organic compound derived from the essential amino acid tryptophan. It is synthesized mainly in the pineal gland during the dark phase of the day-night cycle, with a peak between 2 and 4 a.m. The hypothalamic suprachiasmatic nucleus, which receives information from the retinal photoreceptors, is of major importance in the regulation of melatonin synthesis. It is known that the production and secretion of melatonin increase when the activity of the nucleus is low. The neurotransmitter noradrenaline also influences this process by inducing the biosynthesis and release of melatonin. The results of the research are unanimous that light is the most important exogenous factor that affects the concentration of melatonin in the blood. Terzieva et al. studied and published for the first time reference values of melatonin for the Bulgarian population depending on the photoperiod (Table 1). On the one hand, melatonin is an endogenous neurohormone the secretion of which from the pineal gland is controlled by the circadian rhythm. On the other hand, melatonin affects the regulation of the circadian system. Its various physiological functions in humans have been proven – as a regulator of sleep and circadian rhythms (diurnal, seasonal), sleep and wakefulness,

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sexual activity and reproductive functions, involved in the processes of tumor growth and ageing. It also has immunomodulatory and cytoprotective effects, as well as antioxidant activity. The action of melatonin is mediated by two main types of membrane-coupled receptors – MT1 and MT2. They are highly specific G protein-coupled receptors that regulate the retinal function, circadian rhythms and reproduction. In addition, they are related to learning processes, mood disorders and tumour growth. Less studied is MT3 – the receptor, which is currently known to have low affinity and is found in the kidneys, brain and other organs. It reduces intracellular pressure by regulating the activity of the calcium-calmodulin system.\textsuperscript{12,17-20,27} The function of melatonin as a multifactorial antioxidant plays a particularly important role in the realization of its cytoprotective (including neuroprotective) effect. In addition to hepatic monoxygenases, melatonin can be metabolized intracellularly and extracellularly by a nonenzymatic mechanism by direct uptake of free radicals or by other oxidative molecules to N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK). These products are thought to be responsible for the direct antioxidant effect of the hormone. AFMK and AMK themselves capture and inactivate not only the reactive oxygen but also the nitrogen radicals as well as peroxynitrite. In the brain, melatonin is metabolized to kynurenic acid, which is an antioxidant substance. Besides, the indirect antioxidant effect is manifested in the performance of a signalling function responsible for the regulation of redox-sensitive enzymes. Melatonin stimulates the expression of antioxidant enzyme genes. Another interesting mechanism of effect is the inhibition of lipid peroxidation of membrane structures in mitochondria by concentrations close to the physiological concentration. It also has a potentiating effect on classical antioxidants, as it is believed that its antioxidant capacity is 5-15 times higher than that of reduced glutathione. On the other hand, it is important that it has no proven pro-oxidant effect.\textsuperscript{21-26} In modern medical practice, melatonin is used to treat jet lag syndrome and it has no proven pro-oxidant effect.\textsuperscript{21-26} In modern medical practice, melatonin is used to treat jet lag syndrome and it has no proven pro-oxidant effect. In 1998, Mevissen and Ebert demonstrated the same effect of the hormone. The same study also described the suppression of generalized seizures with the use of melatonin in a model with amygdala stimulation.\textsuperscript{31} A study by Costa-Lotufo et al.\textsuperscript{32} used rats with suppressed melatonin synthesis after removal of the pineal gland. In the group with induced epilepsy by kainic acid, an increase in the degree of brain damage was observed. These findings support the neuroprotective function of melatonin in the CNS. It was also found that the use of melatonin significantly increased the electroconvulsive threshold.\textsuperscript{30} In 1998, Mevissen and Ebert demonstrated the same effect of the hormone. The same study also described the suppression of generalized seizures with the use of melatonin in a model with amygdala stimulation.\textsuperscript{31} In a study by Costa-Lotufo et al. melatonin showed a weak anticonvulsant effect on pilocarpine-induced seizures.\textsuperscript{32} In experimental conditions, penicillin-induced epilepsy resembles myoclonic epilepsy in humans. This model was used in a study by Yildirim et al. in rats in which intraventricular melatonin was administered at various doses (20, 40, 80 μg) 10 minutes before penicillin administration. There was a significant dose-related reduction in the frequency of seizures compared to the penicillin group, as well as a prolonged latency at the beginning of the paroxysmal activity.\textsuperscript{33} Moezi et al. confirmed the additive anticonvulsant effect of melatonin and agmatine, probably mediated by MT1 and 2 receptors, in rats with pentylentetrazole
(PTZ) – induced epileptic seizures. In a study by Aguiar et al., in 2012, using an experimental model with PTZ and pilocarpine-induced epileptic seizures, demonstrated the anticonvulsant activity of agomelatine. However, no similar effect was observed in seizures caused by strychnine and electroshock. Only high doses of agomelatine are thought to significantly delay seizures and death from pilocarpine induction. These anticonvulsant effects are probably related to a GABA-ergic mechanism. Turgut et al. used an experimental model with pregnant rats after removal of the pineal gland and pilocarpine stimulation of epileptic activity. They found damage in the hippocampal neurogenesis in the generation. It was shown that the damage process can be suppressed by the administration of melatonin. Petkova et al. studied an experimental model of rats with temporal lobe epilepsy (TLE) with kainate-induced status epilepticus, in which long-term administration of melatonin was performed. The results proved the anticonvulsant effect of the hormone and its ability to reduce epileptogenic activity and neuronal damage in the hippocampus and piriform cortex. Forcelli et al. published interesting results – the effect of melatonin on the action of phenobarbital in a model of newborn rats with PTZ-induced epileptic seizures. It was found that melatonin alone did not have a significant effect on seizures. However, in combination with phenobarbital, the barbiturate effect is significantly potentiated by increasing the latency of paroxysms and reducing the severity of epileptic seizures. Based on these results and previous studies in this direction, it was hypothesized that the GABA-ergic and NO-systems could play a role in the potentiating effect of melatonin on phenobarbital.

In 2018, Tchekalarova et al. performed a study on an experimental model with pregnant rats after removal of the pineal gland and pilocarpine stimulation of epileptic activity. They found damage in the hippocampal neurogenesis in the generation. It was shown that the damage process can be suppressed by the administration of melatonin. Petkova et al. studied an experimental model of rats with temporal lobe epilepsy (TLE) with kainate-induced status epilepticus, in which long-term administration of melatonin was performed. The results proved the anticonvulsant effect of the hormone and its ability to reduce epileptogenic activity and neuronal damage in the hippocampus and piriform cortex. Forcelli et al. published interesting results – the effect of melatonin on the action of phenobarbital in a model of newborn rats with PTZ-induced epileptic seizures. It was found that melatonin alone did not have a significant effect on seizures. However, in combination with phenobarbital, the barbiturate effect is significantly potentiated by increasing the latency of paroxysms and reducing the severity of epileptic seizures. Based on these results and previous studies in this direction, it was hypothesized that the GABA-ergic and NO-systems could play a role in the potentiating effect of melatonin on phenobarbital.

Studies with humans

In 1974, Antón-Tay et al. conducted a study with volunteers who received a single intravenous dose of melatonin 1.25 micrograms. After 5 hours of electroencephalographic recording, a decrease in the amplitudes of both background and epileptiform activity was registered. In another study by the same team, patients were given fast-acting melatonin orally (total daily dose of 2 grams) for 30 days. In addition to a reduction in seizure frequency, a reduction in paroxysmal activity was observed in all patients. One of the first modern studies by Muñoz-Hoyos et al., showing the relation between melatonin and epilepsy, was performed in children with drug-resistant epilepsy who did not respond to conventional anticonvulsant therapy. They received melatonin as the only treatment – in doses of 5 and 10 mg in the evening, and as a result, a decrease in seizure frequency was demonstrated. In most human studies, melatonin was added to antiepileptic drugs. Peled et al. administered melatonin at a dose of 3 mg/day to a child with severe seizures together with anticonvulsant therapy for a period of 3 months. There was a significant decrease in epileptic activity, especially at night. Other studies focused on monitoring serum melatonin concentrations in children with various types of epilepsy and they were compared to healthy controls. Such models were published by Guo et al. and Paprocka et al. The results showed lower levels of melatonin in patients with epilepsy. In 2013, Jain and Besag tried to answer the question whether melatonin affected epileptic seizures and analyzed 26 previously published studies in this area. In most cases, a possible relationship between the addition of melatonin to therapy and the reduction of seizures was objectified. A small number of studies found a statistically significant anticonvulsant effect of the hormone. There were few studies examining the effect of seizures on serum melatonin concentrations. From the described results, it is clear that in patients with poorly controlled epilepsy, the levels of neurohormone are lower compared to those of healthy individuals. Having in mind the proven protective effect of melatonin on oxidative stress and neuronal damage associated with epilepsy, some studies have focused on patients with epileptic status, in whom changes in the antioxidant enzyme system were assessed. For this purpose M. Gupta et al. used melatonin in combination with anticonvulsants. The same team also studied a monotherapy group in which melatonin was administered at doses of 6-9 mg/day. A reduction in oxidative stress as a result of the effect of the hormone on glutathione reductase and glutathione peroxidase has been observed, and its neuroprotective role has also been demonstrated. Similar studies indicated the possibility of melatonin antiepileptic effect to be associated with affecting GABA and glutamate receptors. Molina-Carballo et al. conducted a study among 54 children with convulsive seizures – epileptic and febrile. Serum concentrations of melatonin during seizure, as well as at 1 and 24 hours after seizure were analyzed. The results showed a significant increase in hormone levels during seizure, normal values after 1 hour and after 24 hours, when normalization of circadian rhythms was registered. The data obtained lead to an interesting conclusion – convulsive states are associated with stimulation of melatonin production, which could be related to the body’s response to epileptic seizure and abnormal brain activity. Motta et al. presented an interesting hypothesis in a study of the circadian profile of melatonin secretion in saliva and its concentration after seizure in patients with pharmaco-resistant epilepsy. The study included 30 young patients with resistant epilepsy. Samples were taken immediately after the seizure and 2 hours after the seizure. The data from this study showed that the circadian profile of melatonin secretion in patients with epilepsy did not differ significantly from that in healthy individuals. Significantly higher concentrations of morning melatonin in patients with predom-
In recent years, several studies have focused on the effect of melatonin on epilepsy-related sleep disorders. Elkhayat et al. published the results of a study of two groups of children – 23 with resistant epilepsy and 14 with good disease control, who received melatonin in the evening before going to bed. The results showed an improvement in sleep related disorders in children with refractory epilepsy, as well as an effect on the severity of seizures in the same group. Goldberg-Stern et al. published a placebo-controlled study of 10 patients with a resistant disease (aged between 9 and 32 years) who received melatonin at a dose of 10 mg in the evening within 3 weeks. There was a reduction in the frequency of daily seizures while taking melatonin compared with placebo. There was no change in the maximum number and duration of seizures, sleep efficiency and latency, and behaviour.

**CONCLUSIONS**

Data from the scientific literature indicate that melatonin has potential anticonvulsant properties not only in experimental animal models but also in patients with epilepsy. It influences the bioelectrical activity of neurons and regulatory processes in the central nervous system through its proven neuroprotective, antioxidant, and anticytotoxic effects. A more detailed study of the mechanisms of its effect has been of interest in recent years. Having in mind the social significance of epilepsy, the need to expand knowledge in the field of epileptology and therapeutic possibilities is indisputable. Research-based evidence about the anticonvulsant effect of melatonin with virtually no significant side effects would be useful in expanding therapeutic options.

**REFERENCES**


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Резюме
Эпилепсия – хроническое неврологическое заболевание с повторяющимися приступами. Его частота, социальные и психологоческие аспекты стигматизации, связанной с эпилепсией в обществе, медицинский риск тяжёлых припадков и трудности лечения подтверждают его медицинское и социальное значение. Патогенез заболевания связан с аномальной активностью популяции нейронов из-за различных механизмов, наиболее распространенными из которых являются окислительный стресс, эсайготоксиничность глутамата и дисфункция митохондрий. В последние 3-4 десятилетия искали и изучали возможную связь между эпилепсией и мелатонином – нейрогормоном, секретируемым шишковидной железой. Доказаны различные психологические функции мелатонина у человека – регуляция сердечного ритма (суточного, сезонного), сна и бодрствования, участие в процессах терморегуляции, рост опухоли и старение, сексуальная активность и репродуктивные функции. Он также обладает иммуномодулирующей, цитопротекторной и антиоксидантной активностью. Результаты исследований с экспериментальными моделями на животных, проведённых до сих пор в поисках корреляции между мелатонином и эпилептогенезом, в основном подтверждают гипотезу о его противосудорожном действии. Исследования на людях разнообразны по дизайну, с небольшим количеством участников, и результаты не всегда убедительно подтверждают гипотезу. Обсуждается взаимосвязь между концентрацией мелатонина и течением заболевания у больных эпилепсией. Возможность добавления мелатонина к антиэпилептической терапии также обсуждается в последние годы.

Ключевые слова
противосудорожное средство, антиоксидант, концентрация мелатонина в сыворотке крови, нейропротекторный, судороги