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Circadian rhythms and neuroprotective effects of melatonin in the central nervous system

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Abstract. This article summarizes current data on the role of melatonin in regulating circadian rhythms and maintaining the functional activity of the central nervous system. It examines the main mechanisms of neuroendocrine control of melatonin secretion, as well as the role of the suprachiasmatic nucleus of the hypothalamus and the pineal gland in maintaining the body's circadian rhythm. Current concepts regarding the receptor mechanisms of melatonin action and the functional characteristics of MT1 and MT2 receptors in brain structures are discussed. In addition to its chronobiological effects, melatonin participates in cellular defense mechanisms. The role of melatonin as an endogenous antioxidant and modulator of cellular signaling processes has been analyzed. Particular attention is paid to its role in regulating mitochondrial function, supporting oxidative phosphorylation, controlling oxidative stress, and maintaining cellular homeostasis. Data are presented on the participation of melatonin in the functioning of the brain's glymphatic system, the elimination of neurotoxic metabolites, and the maintenance of metabolic balance in nervous tissue. An analysis of the results of studies was carried out, which confirm the neuroprotective and anti-inflammatory effects of melatonin in lesions of the central nervous system. Accumulated experimental and clinical data confirm the promise of further study of melatonin as a biologically active molecule with a wide spectrum of effects on the body.

Keywords: circadian rhythms; central nervous system; melatonin; neuroprotection; mitochondria; antioxidant activity.

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INTRODUCTION

Circadian rhythms are a fundamental mechanism of temporal organization of physiological processes, which ensures the adaptation of the organism to cyclic changes in the environment and maintenance of internal homeostasis. The regulation of daily biorhythms is carried out by a complex neuroendocrine system, the central link of which is the suprachiasmatic nucleus (SCN) of the hypothalamus, which functions as the main circadian pacemaker of the organism [1].

The pineal gland plays a central role in ensuring the daily organization of physiological processes, the functional activity of which is associated with the "light-dark" cycle and neurohumoral regulation of biological rhythms.

One of the primary functions of the pineal gland is the transformation of information about changes in the light regime of the environment into neuroendocrine signals that shape the body's adaptation to daily fluctuations. Through the synthesis and secretion of melatonin (MT), the pineal gland participates in maintaining circadian rhythmicity and functional balance.

Since MT regulates biological rhythms, it influences sleep and wakefulness, thermoregulation, hormone secretion, metabolic processes, and the body's adaptive responses. Thus, the pineal gland serves as an important chronobiological center that coordinates the synchronization of internal physiological processes with external environmental conditions [1, 2].

MT not only functions as a circadian rhythm regulator and antioxidant, but also acts as an important modulator of gene expression. It regulates the activity of a large number of genes in the central nervous system (CNS), particularly in the SCN [3].

In addition, it modulates genetic activity in various peripheral tissues, which indicates its systemic effect on the functioning of the body and the coordination of biorhythms at the molecular level. Such properties of this hormone emphasize its importance in maintaining physiological balance and adaptation to changes in the external environment. The interaction of epigenetic mechanisms with "clock" genes (Per1, Per2, Cry1, Cry2, Bmal1) provides photoperiodic regulation of circadian and seasonal changes in the physiological functions of the body. Jenwitheesuk et al. [4] in their article indicate that the diversity of melatonin receptor isoforms determines the selectivity of its interaction with natural ligands, and also determines differences in the regulation of the expression of these receptors both in different tissues and at different stages of ontogenesis.

The wide range of biological effects of the neurohormone is largely due to its physicochemical properties and ability to penetrate biological membranes, in particular through the selective blood-brain barrier, reaching the structures of the CNS. In the scientific literature, melatonin is considered one of the most effective endogenous antioxidants in the CNS. Its antioxidant action is realized both by direct neutralization of free radicals (in particular, reactive forms of oxygen and nitrogen), and indirectly by activation of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and suppression of pro-oxidant processes. In addition, this molecule helps to stabilize cell membranes, protect mitochondria and reduce the level of oxidative stress, which is important for the optimal functioning of neurons and neuroprotection [5].

According to modern scientific data, considerable attention is paid to the participation of MT in the functioning of the glymphatic system of the brain, which ensures the elimination of neurotoxic compounds and maintenance of neurometabolic balance [6, 7].

The results of experimental and clinical studies identify MT as a highly effective endogenous scavenger of free radicals, which exhibits pronounced cytoprotective properties. In particular, its potential role in the prevention and modulation of the course of neurodegenerative diseases, epilepsy, as well as certain forms of malignant neoplasms has been demonstrated. Such an effect is due to both direct antioxidant activity and the ability to influence key cellular signaling pathways. Scientific works in vitro and in vivo deepen and expand the ideas formed during the last decades, confirming the central role of melatonin in the system of antioxidant protection and anti-inflammatory processes [5, 8, 9].

Scientists [10, 11] are particularly interested in the neurohormone's ability to influence the functional state of mitochondria, stabilize oxidative phosphorylation processes, and reduce the manifestations of oxidative stress.

Due to its anti-inflammatory properties, MT is able to reduce the levels of pro-inflammatory cytokines and suppress the reactive activation of astrocytes and microglia [12, 13].

Separate studies indicate the involvement of the SIRT1 signaling pathway in the implementation of the neuroprotective effects of melatonin [14, 15].

The aim of the study: to summarize the current literature data on the role of melatonin in the regulation of circadian rhythms, the functioning of mitochondria and the provision of neuroprotective mechanisms in the central nervous system.

MATERIALS AND METHODS

This study was conducted as a descriptive literature review incorporating elements of a systematic analysis of current scientific sources. The search for scientific articles was conducted in the international scientometric databases PubMed and Web of Science. The analysis included publications from the past 10 years. The inclusion criteria were full-text articles, systematic reviews, meta-analyses, and experimental and clinical studies focused on the investigation the

role of melatonin in the regulation of circadian rhythms, central nervous system function, mitochondrial activity, and neuroprotective mechanisms. No statistical data analysis was performed within the scope of this study, as the work is of a review nature.

RESULTS AND DISCUSSION

The circadian system and neuroendocrine regulation of melatonin secretion

The suprachiasmatic nucleus of the hypothalamus plays a key role in the regulation of circadian rhythms and the neuroendocrine control of melatonin secretion. It has been established that photoperiodic information reaches the pineal gland after being processed by the SCN of the hypothalamus. Through a feedback mechanism, melatonin modulates rhythmic activity and metabolic processes in this region [16, 17].

The light information detected by the photoreceptors of the retina is transmitted along the fibers of the optic nerve to the SCN of the hypothalamus. Ganglion cells, which express melanopsin and directly perceive light stimuli, play an important role in this process. From the CNS, nerve impulses are transmitted by descending pathways through the hypothalamus and brainstem to the cervical spinal cord.

Then the signals pass through sympathetic fibers through the upper cervical sympathetic ganglion and again go to the skull cavity, reaching the pineal gland. Thus, in scientific research [18, 19] show that such a neuronal network ensures synchronization of the functional activity of the pineal gland with changes in the "light-dark" cycle.

In the central nervous system, SCN neurons directly or indirectly project to various brain regions, such as the hypothalamus, limbic system, choroid plexus, pituitary, median eminence, pineal gland, area postrema, vascular organ of lamina terminalis, periaqueductal gray, ventral tegmental area, and hippocampus (Fig.) [3].

It has been established that in the dark, the activity of most neurons in the SCN decreases, accompanied by the release of norepinephrine, which mediates the activation of pinealocytes and enhances the synthesis of enzymes necessary for the production of the pineal

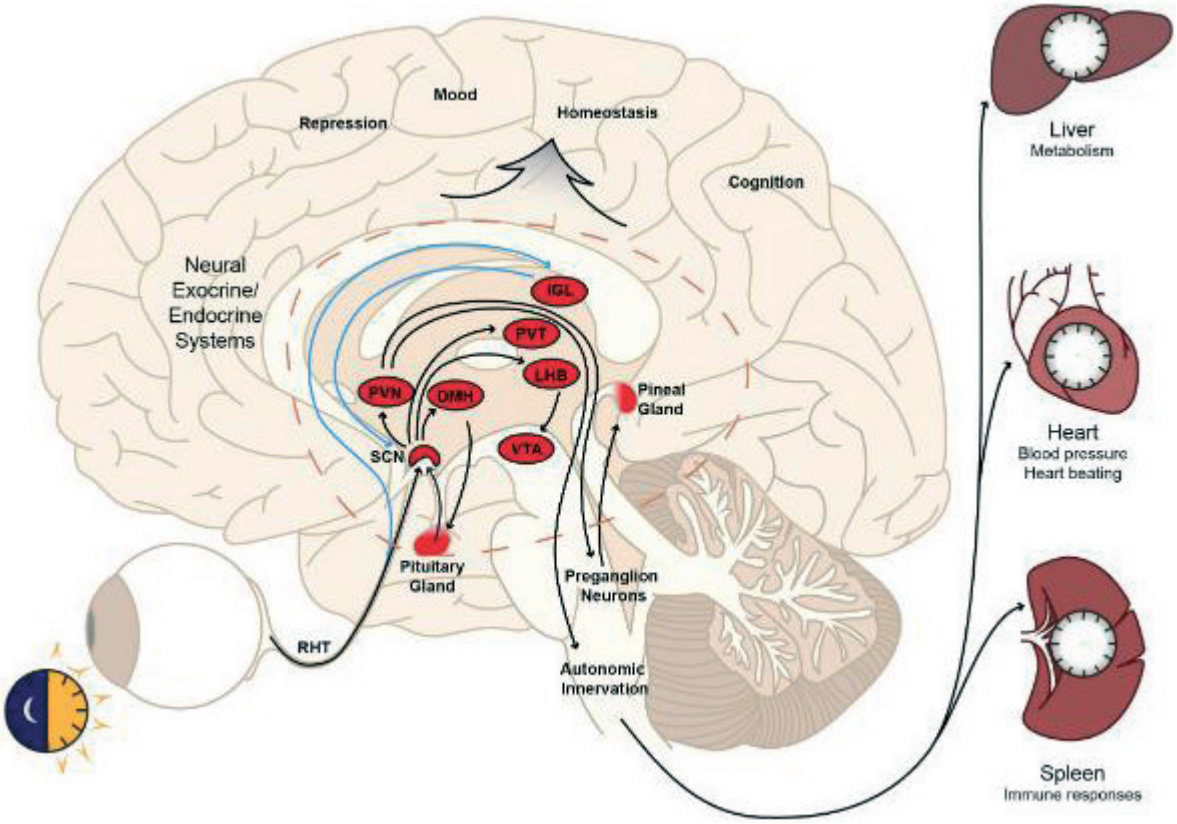

Fig. Circadian clock networks in the brain. *The SCN receives photic information via the RHT and conveys it to other parts of the brain and body (solid black lines). The IGL also receives photic information via the RHT and combines this with nonphotic information. Then, the IGL transmits combined information to the SCN via the GHT (solid blue lines). The majority of photic information is transferred to the SCN via the RHT. The IGL-GHT pathway contributes only a minor part to the photic entrainment process. RHT, the retinohypothalamictract; GHT, the geniculohypothalamic tract; IGL, the intergeniculate leaflet; PVN, the paraventricular nucleus; DMH, the dorsomedial hypothalamus; PVT, the paraventricular thalamic nuclei; LHB; the lateral habenula; VTA, the ventral tegmental area.* ***Source:*** *[3].*

hormone. Bright light rapidly suppresses its secretion, whereas in the absence of light, the circadian rhythm of production is maintained due to the endogenous rhythmic activity of the SCN. The data obtained confirm the existence of an internal circadian mechanism capable of maintaining the temporal coordination of physiological processes even in the absence of external light signals [1, 19].

According to the literature, the daily production of MT by the pineal gland is on average 0.1–0.9 mg [20].

Melatonin secretion is clearly synchronized with the day-night cycle: the highest concentrations are observed during the night period, with maximum levels mainly between midnight and 4 a.m., while during the day its amount is significantly reduced to baseline levels. Such a circadian profile of secretion ensures synchronization of biological rhythms of the body and adaptation of physiological processes to changes in environmental lighting [21, 22].

Rhythmic fluctuations in the neurohormone level are directly related to the peculiarities of its biosynthesis.

The precursor of melatonin is the amino acid tryptophan, which comes from blood plasma. The biosynthesis of indolamine begins with the conversion of tryptophan to 5-hydroxytryptophan, and then to serotonin. The next step is acetylation of serotonin with the participation of the enzyme arylalkylamine-N-acetyltransferase (AA-NAT) with the formation of N-acetylserotonin. This reaction is the key regulatory stage of indoleamine biosynthesis, which determines the speed and intensity of its formation. The final stage includes methylation of N-acetylserotonin by hydroxyindole-O-methyltransferase with the formation of melatonin [23].

The metabolism of the pineal hormone is primarily mediated by cytochrome P450 enzymes in the liver. During biotransformation, it undergoes 6-hydroxylation to form 6-hydroxymelatonin, which is subsequently sulfated and excreted in the urine as 6-sulfatoxymelatonin [24].

It has been established that indoleamine synthesis occurs not only in the pineal gland but also in other tissues and cells of the body, including the retina, bone marrow, immune system cells, organs of the gastrointestinal tract, skin, and placenta [25].

Melatonin receptors and signaling mechanisms

The selective action of MT is mediated by various types of receptors located in many tissues – both on cell membranes and in the cell nucleus. This causes a wide range of physiological effects of the hormone [5, 16, 17].

A significant portion of melatonin's physiological effects is mediated by the MT1 and MT2 membrane receptors, which are encoded by the MTNR1A and MTNR1B genes, located in the 4q35 and 11q21-22 regions, respectively, and belong to the superfamily of G protein-coupled receptors (G protein-coupled receptors, GPCR) [26].

In the central nervous system, MT1 receptors are primarily localized in structures involved in the regulation of circadian rhythms, emotional and neuroendocrine processes, particularly in the hypothalamus, hippocampus, cerebellum, substantia nigra, and ventral tegmental area. Their expression in these structures is associated with melatonin's role in regulating the sleep-wake cycle, cognitive functions, neuroplasticity, and neuroprotection.

MT1 receptors are widely distributed throughout the peripheral nervous system, including the cardiovascular system – such as the heart, aorta, and peripheral blood vessels – where they play a role in regulating vascular tone and blood pressure. In addition, MT1 receptors are found in organs of the immune system – the spleen and lymph nodes – as well as in the reproductive organs. They are also identified in the liver, kidneys, adrenal cortex, pancreas, placenta, mammary gland, and skin, indicating the multifunctional role of melatonin in coordinating metabolic, endocrine, immune, and reproductive processes. Recent studies also indicate that MT1 receptors are involved in antioxidant defense mechanisms, the regulation of mitochondrial function, inflammatory responses, and the maintenance of cellular homeostasis [27, 28].

Unlike MT1 receptors, the distribution of MT2 receptors is less pronounced; however, they are expressed in many tissues and organs. MT2 receptors are found in structures of the central nervous system, including the hypothalamic SHS, the cerebral cortex, the retina, and the pituitary gland. In addition, they are expressed in cells of the immune and reproductive systems, blood vessels, kidneys, the gastrointestinal tract, adipose tissue, and the skin. In addition to their chronobiological function, their activation is associated with the modulation of cellular metabolism, inflammatory processes, and neuroprotective mechanisms [27, 28].

In addition to the highly related membrane receptors MT1 and MT2, low-affinity cytosolic melatonin binding sites (MT3) have been described, which have been identified as the enzyme quinone reductase 2 (QR2). It participates in cellular detoxification processes and the maintenance of redox homeostasis. The interaction of melatonin with MT3/QR2 is associated with the exercise of its antioxidant activity, the regulation of apoptosis, and increased sensitivity of tumor cells to chemotherapeutic agents, which allows this system to be considered a promising therapeutic target in oncology [29, 30].

Lépinay et al. [31] experimentally demonstrated that, following the binding of MT to specific membrane receptors, intracellular signaling cascades are activated, particularly the phospholipase C system. Activation of this pathway is accompanied by the hydrolysis of

phosphatidylinositol-4,5-bisphosphate (PIP2) to form secondary messengers – inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). A subsequent increase in intracellular calcium concentration and activation of protein kinase C regulate gene expression, cellular secretory activity, and neuroendocrine signaling.

Mitochondrial function and melatonin

Scientific evidence suggests a key role for mitochondria in regulating various aspects of melatonin function, including its biosynthesis, metabolism, and receptor-mediated effects. Unlike the classical concept, according to which hormone production is controlled by circadian rhythms (light/dark cycle) and the pineal gland, modern concepts point to the ability of these organelles to autonomously control its synthesis according to intracellular needs.

MT is localized in mitochondrial membranes and is able to penetrate into their inner space with the help of oligopeptide transporters PEPT1 and PEPT2 located on the membrane. Mitochondria are the central organelles of cellular metabolism, since it is in them that the main synthesis of ATP and the formation of reactive oxygen species (ROS) takes place. At the same time, they are able to accumulate MT, which comes from the bloodstream endogenously or exogenously, and synthesize it independently [32].

Melatonin circulating in the blood can be actively taken up by mitochondria with subsequent accumulation against the concentration gradient [33].

Scientific research [34, 35] have shown that these intracellular energy structures can induce local melatonin synthesis in response to elevated levels of oxidative stress, enabling the cell to adapt rapidly to metabolic changes. It has been established that the concentration of melatonin in mitochondria significantly exceeds its level in the systemic circulation, which is likely due to the need to effectively neutralize ROS, which are intensively generated during the functioning of the electron transport chain. Thus, it has been hypothesized that the primary role of melatonin in mitochondria is to protect the organelle from oxidative stress. In addition, mitochondria-associated melatonin not only acts as an antioxidant but also helps stabilize the membrane potential, optimize oxidative phosphorylation processes, and prevent the opening of the mitochondrial pores. This, in turn, limits the activation of apoptotic cascades and helps maintain cellular viability. Thus, mitochondria are considered not only as a target for melatonin's action but also as an important local center for its synthesis, which is of fundamental importance for maintaining cellular homeostasis.

The study by Gloria Somali-Barranco et al. [36] developed the first photoactivated melatonin ligand with mitochondrial targeting. The authors took into account the high lipophilicity and permeability of the hormone, which ensure its ability to interact with both plasma membrane receptors and receptors located in mitochondria. The obtained results confirmed the functional activity of mitochondrial MT1 receptors and their participation in the regulation of oxidative phosphorylation processes.

In studies conducted by D.X. Tan et al. [35], melatonin was found to stimulate mitophagy – a mechanism for the selective elimination of damaged and dysfunctional mitochondria [37].

As noted by the authors A. De Gaetano et al. [38], this is considered one of the key functions of MT, since an imbalance between mitophagy and the formation of reactive oxygen species is associated with accelerated aging and the progression of neurodegenerative changes.

Neuroprotective effects of melatonin in the central nervous system

Scientific experiments have shown that MT is synthesized and functions in neurons and glial cells as well, confirming its role in the local regulation of CNS functions. The presence of the hormone in brain structures enables the implementation of intracrine, paracrine, and autocrine mechanisms, through which it participates in maintaining CNS homeostasis, controlling neurogenesis, and modulating neurotransmitter release [31, 39].

Melatonin is also characterized by pronounced neuroprotective and antitoxic properties. They are associated with a decrease in the activity of glutamate, suppression of excessive excitability of neurons and increased activity of the GABA-ergic system. Thanks to this, the hormone helps to stabilize the neurotransmitter balance, protect neurons from oxidative stress, and ensure the functional integrity of nervous tissue [40].

Due to its anti-inflammatory properties, MT is capable of reducing levels of the pro-inflammatory cytokines IL-6, TNF-α, and IL-1ß in experimental models of ischemic-reperfusion brain injury, subarachnoid hemorrhage, traumatic brain injury, and hypoxia. It has been established that one of the mechanisms of its neuroprotective action is the inhibition of reactive activation of astrocytes and microglia, accompanied by a reduction in neuroinflammatory reactions in the CNS [13, 41, 42].

It has been demonstrated that the administration of this hormone in cases of traumatic brain injury reduces astrocyte reactivity and inhibits neuronal apoptosis in the hippocampus and dentate gyrus [43, 44].

C. Zhang et al. [45] summarized the results of recent studies indicating that melatonin reduces the extent of ischemic brain damage and the severity of cerebral edema following pathological changes, as well as improves neurological status. These effects are achieved by modulating oxidative stress, neuroinflammatory reactions, apoptosis and autophagy processes,

inhibiting glutamate-mediated excitotoxicity, and correcting mitochondrial dysfunction.

In addition, in neurodegenerative diseases and traumatic brain injuries, melatonin exhibits significant neuroprotective properties by reducing microglial activation and the intensity of the neuroinflammatory response. It has been established that this molecule is capable of inhibiting the transmission of pro-inflammatory signaling pathways, reducing the production of inflammatory mediators, and limiting the development of secondary damage to nervous tissue. These effects preserve the functional state of neurons, reduce oxidative stress, and stabilize cellular homeostasis in the CNS [46, 47].

The brain is one of the organs with the highest metabolic rate, which is accompanied by the intensive production of metabolic byproducts. Consequently, maintaining neuronal homeostasis is an extremely complex yet critically important process, in which the glymphatic system plays a key role [7].

An important component of melatonin's cytoprotective effect is its role in the functioning of this system, whose activity is linked to the circadian regulation of physiological processes.

The delivery of the hormone directly to the cerebrospinal fluid ensures its high concentrations in the ventricular system and subsequent penetration into the nervous tissue through the subarachnoid space and Virchow-Robin spaces [6]. In brain tissue, it realizes pronounced antioxidant, anti-inflammatory and neuroprotective effects due to the elimination of metabolic products and neurotoxic compounds, in particular beta-amyloid and tau protein [48].

Studies conducted using experimental models [14, 15] have shown that indoleamine protects nerve cells not only through its antioxidant activity but also by regulating intracellular signaling mechanisms. It has been established that SIRT1 (silent information regulator 1), which belongs to the family of NAD□-dependent deacetylases, may act as one of the downstream molecular targets of melatonin. Activation of SIRT1 is associated with a reduction in neuroinflammation, suppression of oxidative stress, maintenance of mitochondrial function, and protection of neurons from damage. It has been shown that activation of this signaling pathway contributes to the hormone's cytoprotective effects in neurodegenerative processes and ischemic brain injury. At the same time, the mechanisms of melatonin's interaction with SIRT1 during inflammatory activation of astrocytes remain poorly understood and require further investigation.

Therefore, melatonin is an important regulator of circadian organization, metabolic homeostasis and neuroprotective mechanisms in the central nervous system. Modern studies demonstrate its ability to influence the functioning of mitochondria, the glymphatic system, the processes of neuroinflammation and cellular signaling, which substantiates the prospects of using this therapeutic potential.

CONCLUSIONS

It has been established that melatonin's wide range of biological effects is mediated through interactions with membrane-bound and intracellular receptors, the activation of signaling cascades, and the regulation of the expression of "clock" genes. This accounts for its role in regulating neuroendocrine, metabolic, immune, and adaptive processes, as well as in maintaining the circadian stability of the central nervous system.

Modern studies confirm the important role of melatonin in the functioning of mitochondria. The hormone contributes to the stabilization of oxidative phosphorylation processes, the preservation of the membrane potential of mitochondria, the limitation of the formation of reactive oxygen species and the inhibition of apoptotic mechanisms.

It has been been proven that melatonin reduces the intensity of neuroinflammation, suppresses the activation of astrocytes and microglia, reduces the production of pro-inflammatory cytokines, and supports the functional state of neurons in traumatic and neurodegenerative brain lesions. An important mechanism of cytoprotective action is its participation in the regulation of the glymphatic system and the elimination of neurotoxic metabolites from nervous tissue

Prospects for further research include a detailed study of the molecular mechanisms of melatonin's action in the CNS, in particular its impact on mitochondrial function, neuroinflammatory processes, SIRT1-dependent signaling pathways, and the regulation of "clock" genes. Further experimental and clinical studies are necessary for an in-depth study of the role of melatonin in the functioning of the glymphatic system, as well as substantiating the feasibility of its use in medicine as a potential therapeutic and neuroprotective agent in disorders associated with circadian disorganization, oxidative stress, and inflammatory processes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Циркадні ритми та нейропротекторні ефекти мелатоніну в центральній нервовій системі

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Анотація. У статті узагальнено сучасні дані щодо ролі мелатоніну в регуляції циркадних ритмів та забезпеченні функціональної активності центральної нервової системи. Розглянуто основні механізми нейроендокринного контролю секреції мелатоніну, роль супрахіазматичного ядра гіпоталамуса й епіфіза у підтриманні добової ритмічності організму. Висвітлено сучасні уявлення про рецепторні механізми дії мелатоніну та особливості функціонування MT1- і MT2-рецепторів у структурах головного мозку. Поряд із хронобіологічними ефектами мелатонін бере участь у механізмах захисту клітин. Проаналізовано значення мелатоніну як ендогенного антиоксиданта та модулятора клітинних сигнальних процесів. Особливу увагу приділено його участі у регуляції функціонального стану мітохондрій, підтриманні процесів окисного фосфорилювання, контролі оксидативного стресу та забезпеченні клітинного гомеостазу. Наведено дані щодо участі мелатоніну у функціонуванні глімфатичної системи мозку, елімінації нейротоксичних метаболітів та підтриманні метаболічної рівноваги в нервовій тканині. Проведено аналіз результатів досліджень, які підтверджують нейрозахисні та протизапальні ефекти мелатоніну при ураженнях центральної нервової системи. Накопичені експериментальні та клінічні відомості підтверджують перспективність подальшого вивчення мелатоніну як біологічно активної молекули з широким спектром впливу на організм.

Ключові слова: циркадні ритми; центральна нервова система; мелатонін; нейропротекція; мітохондрії; антиоксидантна активність.