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ORGANOPROTECTIVE AND IMMUNOMODULATING EFFECTS OF MELATONIN

Actuality. *Melatonin is the main hormone of the pineal gland, which affects the regulation of vital organs and systems, has an organoprotective and immunomodulating effect. The mechanism of action of melatonin under pharmacodynamic influence is associated with changes in the pro-oxidant-antioxidant, energy exchange indicators of the immune system and genetic code.*

The aim of the study is *to establish the organoprotective and immunomodulating properties of melatonin.*

Research methods: *data analysis of domestic and foreign literature, online publications, SCOPUS data, "Web of Science", Google Scholar.*

Research results. *Various aspects of the effect of melatonin on the central nervous system, its hypnotic, calming, and anti-depressant effects are shown. The effects of melatonin related to its effect on the cardiovascular system are described in detail. The effect of melatonin on kidney function is also mentioned. The effects of melatonin on the digestive system are described, its effect on the function of the liver, pancreas, and intestines is mentioned. Separately, the immunotropic and anti-inflammatory effects of melatonin are distinguished. The effect of melatonin on pregnant women is described, and the hormone-like effect, as well as the effect on the immune system, are discussed separately.*

Conclusions. *New data indicate that melatonin has an organoprotective effect on the central nervous system, cardiovascular system, organs of the digestive system, immunomodulatory and anti-inflammatory effects, which allows to expand the range of its use, including in treatment regimens for serious diseases. Thus, melatonin is the main hormone of the pineal gland, which affects almost all organs and functions of the body, and its drugs increase the activity and reduce the toxicity of drugs of other groups.*

Key words: *melatonin, organoprotective, neurotropic, cardiotropic, hepatotropic, pulmoprotective, immunomodulating effect.*

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ОРГАНОПРОТЕКТОРНА ТА ІМУНОМОДУЛЮЮЧА ДІЯ МЕЛАТОНІНУ

Актуальність. *Мелатонін – головний гормон епіфізу, що впливає на регуляцію життєво важливих органів та систем, проявляє органопротекторну та імуномодулюючу дію. Механізм дії мелатоніну у разі фармакодинамічного впливу пов'язаний зі змінами прооксидантно-антиоксидантного, енергетичного обміну показників імунної системи та генетичного коду.*

Мета дослідження *– встановити органопротекторні та імуномодулюючі властивості мелатоніну.*

Методи дослідження: *аналіз даних вітчизняної та зарубіжної літератури, інтернет-видань, даних SCOPUS, "Web of Science", Google Scholar.*

Результати дослідження. *Показані різні аспекти впливу мелатоніну на ЦНС, його снодійна, заспокійлива, антидепресивна дія. Детально описані ефекти мелатоніну, які пов'язані з його впливом на серцево-судинну систему. Також згадується вплив мелатоніну на функцію нирок. Описані ефекти мелатоніну стосовно травної системи, згадується його дія на функцію печінки, підшлункової залози, кишечника. Окремо виділяють імунотропну і протизапальну дію мелатоніну. Описана дія мелатоніну на вагітних, окремо зупиняються на гормоноподібній дії, а також впливі на імунну систему.*

Висновки. *Нові дані свідчать, що мелатонін володіє органопротекторною дією на ЦНС, серцево-судинну систему, органи травної системи, має імуномодулюючий та протизапальний ефекти, що дозволяє розширити спектр його застосування, включаючи у схеми лікування важких захворювань. Таким чином, мелатонін – основний гормон епіфізу, який впливає практично на всі органи і функції організму, а його препарати підвищують активність і знижують токсичність препаратів інших груп.*

Ключові слова: *мелатонін, органопротекторна, нейротропна, кардіотропна, гепатотропна, пульмопротекторна, імуномодулююча дія.*

Introduction. Actuality. Considering that melatonin is the main hormone of the pineal gland, Yale University professor Aaron Lerner (Baburina ta in., 2021) was able to isolate an extract from cow pineal glands, determined the structure of the main N-acetyl-5-mitoxytriptaline complex and called it melatonin. Lerner considered its main effect to be the ability to lighten the skin due to the destruction of pigments. Further studies showed that melatonin itself can regulate circadian rhythms and promotes falling asleep, the transition of sleep to the fast stage, and has a positive effect on night rest. Gradually, the possible influence of melatonin on other functions of the central nervous system, the feasibility of taking it in depressive states, epilepsy and other pathological conditions were established. Melatonin has also shown effectiveness in cardiovascular diseases. Its cardioprotective effect was mainly due to its antioxidant properties. Melatonin also plays a role in stabilizing blood pressure, protecting against atherosclerosis, metabolic disorders (obesity, diabetes).

Gradually, melatonin was determined to have pulmoprotective, nephroprotective, gastro- and hepatoprotective properties, which confirms its organoprotective properties.

But for medical practice, melatonin has become a valuable tool because it can be used to treat cancer and COVID-19 due to its immunomodulatory and anti-inflammatory effects. Melatonin is available in tablets and capsules. The Kyiv Vitamin Plant named the drug Vita-melatonin. A sublimated form of tablets (Melafresh) appeared.

The aim of the study – to establish the organoprotective and immunomodulating properties of melatonin.

Research methods: analysis of data from domestic and foreign literature, online publications, SCOPUS data, "Web of Science", Google Scholar.

Research results. Melatonin is the main hormone of the pineal gland, but it can be synthesized by enterochromaffin cells of the gastrointestinal tract, neuroendocrine cells, and also by cells of many organs. Most of the experimental and clinical studies on determining the pharmacodynamics of natural and synthetic melatonin are devoted to its effect on the central nervous system. Melatonin, which is produced in the body, is released into the blood and cerebrospinal fluid, while melatonin, synthesized in the periphery, manifests its effects there and only a small amount enters the blood.

Now melatonin is obtained from algae, microorganisms, phytomelatonin was obtained from plants. However, many synthetic substitutes are now available (Ahmad et al., 2023; Arnao et al., 2023). Regardless of the source of melatonin, their mechanism was linked to effects on the arylalkylamine transferase enzyme and RNA levels (Yasmin et al., 2020; Kopustinskiene & Bernatoniene, 2021).

Melatonin penetrates inside cells, organelles, nuclei and interacts with biologically active substances. Melatonin affects such enzymes as cAMP-phosphodiesterase, calmodulin, and also the synthesis of nitric oxide. At the same time, melatonin accelerates electron transfer and ATP production. Penetrating into the mitochondria with the help of transporters, melatonin provides antioxidant protection due to the activation of SOD, glutathione peroxidase, glutathione reductase and catalase enzymes (Pishak ta in., 2022; Reiter ta in., 2018).

There are several types of melatonin receptors. Membrane receptors associated with G-proteins, divided into M1 and M2, which are encoded by the proteins MINRIα and MINRIβ, which are localized in regions 4q35 and IIq21-22. MT3 receptors are now also isolated at low-affinity cytosolic sites, identified as QR2 (quinoreductase-2 – a detoxifying enzyme by means of which melatonin exerts an antioxidant effect and induces apoptosis in tumors).

There are also nuclear melatonin receptors RORα/RZRβ that are active to both melatonin and calmodulin.

While RORα1 and RORα2 receptors are associated with the effects of melatonin on the immune system and antioxidant action, RZRβ receptors identified in the pineal gland are associated with hormonal effects (Jockers ta in., 2016; Yasmin ta in., 2020).

Melatonin, which is also found in mitochondrial membranes, enters the mitochondria with the help of PEPT1 and PEPT2 transporters, which are located on the mitochondrial membrane. It is these receptors that provide the antioxidant effect of melatonin. In mitochondria, melatonin acts as an absorber of oxygen radicals, stimulates antioxidant enzymes – superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, suppressing pro-oxidant enzymes, reducing the level of malondialdehyde, diene conjugates (Reiter et al., 2018).

Melatonin stimulates the synthesis of nitric oxide, reducing the formation of peroxynitrite radicals, lipoxidase. At the same time, melatonin protects cells from hyperperoxidation of polyunsaturated fatty acids, which is associated with its anti-stress effect (Chen ta in., 2020). There are low-affinity cytosolic binding sites for melatonin – MT3 QR2 (quinoreductase-2-detoxifying enzyme), which helps melatonin's antioxidant and kinotherapy effects.

The above-mentioned mechanisms of action allow us to note a wide spectrum of action of melatonin. Among the indications for the use of melatonin is the possibility of taking it as a sleeping aid to facilitate falling asleep with a lack of complete rest and its associated consequences (chronic fatigue, weakness, irritability). Melatonin is recommended as a sleep aid for the purpose of correcting the circadian rhythm in the event of a sudden change in time zones, including for children (Samantha, 2020).

The synthetic analogue of melatonin does not cause addiction with long-term use and rebound syndrome – increased symptoms of insomnia, has a positive effect on cognitive functions.

Melatonin is recommended for patients with depressive conditions who have mental illnesses. In these patients, melatonin was shown to be highly effective, and it was also effective as part of the COVID-19 therapy. Melatonin is now included in the treatment regimens of degenerative diseases such as Alzheimer's disease, parkinsonism, and is also recommended in the treatment of epilepsy (Gunata ta in., 2020).

Further, the expediency of prescribing melatonin to patients with parkinsonism in case of late phase sleep disturbance, in the presence of pain syndrome, was established (Shkodina, 2021). Also, in these patients, melatonin positively normalized the circadian rhythm, influenced various other neurological processes, in particular, reduced pain syndrome. This may be due to the improvement of the functioning of the descending system of pain modulation and the restoration of the rhythmic expression of the genes of the internal clock, which affect the expression of antinociceptive receptors and metabolites (Bumgarner et al., 2021; Brzezinski et al., 2021).

By affecting the central nervous system, melatonin regulates homeostasis, the release of neurotransmitters, lowers the level of glutamate and increases GABA.

Of the emergency conditions in which the inclusion of melatonin in the treatment regimen is appropriate and important in the manifestation of the therapeutic effect, post-traumatic brain syndrome should be noted, since melatonin reduces the apoptosis of neurons in the hippocampus (Kamfar et al., 2024; Cardinali, 2023; Markowska et al., 2023).

The neurotropic effect of melatonin is evidenced by its effect on the organs of vision. Melatonin has receptor-mediated and non-receptor-mediated effects on the retina. The decrease and absence of melatonin synthesis leads to keratopathy, degeneration of the corpus luteum, spots and pathologies caused by ultraviolet radiation.

Further, the influence of course administration of melatonin on morphofunctional changes in the optic nerve of experimental animals with hypopinealism was determined. Hypopinealism in descending atrophy of the optic nerve is accompanied by atherosclerotic and dystrophic changes in the retina.

The mechanism of action of melatonin explains a wide spectrum, it is prescribed from violations of circadian rhythms and sleep to nocturnal incontinence, treatment of epilepsy and mental disorders during COVID-19 (Boutin et al., 2023; Mannino et al., 2021; Cardinali, 2021; Ahmadi et al., 2024; Burke et al., 2024; Liu et al., 2024; Acuña-Castroviejo et al., 2020).

Important studies have been conducted on the effects of melatonin on the organs of vision. Melatonin has receptor and non-receptor effects on the retina. These receptors are located in many tissues of the eye (retinal neurons, pigment epithelium, cornea, sclera, lens). Melatonin protects photoreceptors from photooxidative stress (Pishak et al., 2022).

Atrophy of the optic nerve is observed in degenerative disorders, inflammation or damage to the optic nerve, edema. At the same time, loss of small blood vessels, thinning, disintegration of nerve fibers, reactive gliosis, fibrosis, atherosclerotic and dysmorphic changes in the retina are possible.

In addition to the pineal gland, melatonin can be produced by other cells, including retinal photoreceptors and the epithelium of the ciliary body. In the eye, melatonin takes part in the renewal of photoreceptors in the retina, production of intraocular fluid, modulation of intraocular pressure, healing of wounds on the surface of the eye, antioxidant action in the lens. When simulating atrophy of the optic nerve in rabbits under 24-hour illumination, course administration of melatonin had an anti-edematous effect, greater with long-term administration (26–28 months) (Nedzvetska et al., 2023).

We also conducted a study of the combined effect of melatonin and quercetin on the indicators of the systemic inflammatory response, carbohydrate and lipid metabolism in the blood serum of rats that were in conditions of round-the-clock lighting and took a carbohydrate-lipid diet.

It was established that under the given conditions of the experiment, only the combined administration of melatonin with quercetin improved the indicators of the biochemical system, reducing the inflammatory reaction. At the same time, under round-the-clock illumination, serum tumor necrosis factor α, C-reactive protein, insulin, very low-density lipoproteins, triglycerides, and high-density lipoprotein concentration increased (Frankel et al., 2024).

The use of melatonin is advisable for cardiovascular diseases (Zaychenko et al., 2019). Melatonin in the cardiovascular system, as well as in the nervous system, affects membrane, mitochondrial, nuclear receptors, can be a scavenger of free radicals and has antioxidant activity.

Due to its antioxidant properties, melatonin can have a cardioprotective and antiarrhythmic effect, lower blood pressure, and prevent manifestations of cardiotoxicity of other drugs. Melatonin causes vasodilation of blood vessels, controlling Ca^{2+}-channels in the membranes, suppresses the release of tissue factor from the vessel walls.

Melatonin can regulate the circadian rhythms of blood pressure (high in the active phase and low in the resting phase). It acts directly in the paraventricular nucleus and the hypothalamic-pituitary axis, regulating the baroreflex, reducing the sympathetic tone, and increasing the parasympathetic tone in the anterolateral area of the medulla oblongata. An additional mechanism is the interaction of melatonin with the renin-angiotensin system (Cipolla-Neto & Amaral, 2018). Melatonin reduces pulmonary artery pressure and resistance in pulmonary hypertension (Chitimus et al., 2020).

It is believed that the anti-atherosclerotic effect of melatonin is similar to that of atorvastatin (Sezgin et al., 2020). Melatonin is able to penetrate cells and subcellular compartments, overcome morphofunctional barriers, and therefore has a cardioprotective effect both in heart failure and cardiomyopathy.

In heart failure in rats caused by the administration of doxorubicin, melatonin not only prevented changes in the ECG and echocardiogram, but also prevented disturbances in the content of glucosalization of ketone bodies, a decrease in the activity of succinate oxidase and adenosine triphosphate (Thonusin et al., 2023). Melatonin restored the contractility of biochemical indicators in the myocardium and blood in septic cardiomyopathy (Taha et al., 2023).

Due to the direct effect on the metabolism of mitochondria, melatonin is able to normalize the glucose content in patients with diabetes, it is effective in heart failure as part of polymorbid pathology (Reiter et al., 2024).

It is especially important to prescribe melatonin to patients with heart failure when immune system disorders are detected. Melatonin also had an anti-ischemic and anti-arrhythmic effect due to the metabolic effect and the restoration of the function of the endothelium (endothelial dysfunction is observed in atherosclerosis) and neutralizing oxidative stress (Zhang et al., 2023; Mendes et al., 2024).

The effect on the endothelium is associated with the effect on MT2 receptors, which leads to an increase in the synthesis of nitric oxide, which contributes to the formation of soluble guanylate cyclase in smooth muscle cells. This leads to an increase in cyclic guanosine monophosphate and to vasodilation. Melatonin reduces the release of reactive oxygen species in mitochondria and prevents myocardial damage observed in ischemia. In case of arrhythmia, melatonin affects repolarization and improves the function of the ventricles, prevents expansion of the action potential (Durkina et al., 2023; Mendes et al., 2024).

Violations of circadian rhythms are reflected in the cardiovascular system – vascular tone is disturbed, metabolic diseases occur. In cardiovascular diseases, ligand exchange, the content of triglycerides and low-density lipids are disturbed (Reiter et al., 2024). It is believed that in coronary heart disease, melatonin can relieve endoplasmic stress, increase metabolic processes in cells to original values (Chakraborty et al., 2023).

The positive effect of melatonin in cardiovascular diseases is due to its antioxidant and anti-inflammatory activity, which is especially effective in combined therapy (Taha et al., 2023). Melatonin combines well with ascorbic acid in the treatment of cardiomyopathy (Üstündağ et al., 2023). Melatonin is prescribed for heart failure in poisoning (Ali et al., 2022). Due to its antioxidant effect, melatonin can be prescribed for diseases of the heart and blood vessels accompanied by oxidative stress, including for COVID-19 (Zhang et al., 2023). Melatonin should be prescribed for cardiovascular diseases, including atherosclerosis, accompanied by endothelial dysfunction (Sezgin et al., 2020).

People with diseases of the cardiovascular system often have impaired kidney function, where the inclusion of melatonin is important in acute and chronic kidney diseases. Therefore, it is very important for patients with chronic kidney diseases to include melatonin in their treatment regimens, which affects homeostasis, has a cytoprotective effect as an anti-inflammatory agent and an antioxidant (Markowska et al., 2023).

In recent years, it has been established that melatonin improves the level of glomerular filtration and significantly lowers the level of kidney tissue damage (Tang et al., 2023; Yang et al., 2023).

In clinical studies, a correlation was found in patients with varying degrees of renal dysfunction between melatonin concentration and glomerular filtration rate, which indicated a negative effect. It has been established that melatonin synthesis is disrupted in patients with chronic kidney disease during hemodialysis, especially at night. Melatonin-forming dysfunction is age-dependent (Kondratiuk et al., 2019).

Currently, many facts are accumulating about the involvement of melatonin in the activity of the cardiovascular and urinary systems. The relationship between sleep disorders, the melatonin-producing function of the pineal gland and arterial hypertension in patients with chronic kidney disease continues to be studied (Petrova et al., 2020; Nedohoda et al., 2017).

Clinical studies have established that in patients with stage 5 chronic kidney disease, who are being treated with hemodialysis, there is a fairly widespread violation of the melatonin-producing function of the pineal gland and arterial hypertension. A low level of melatonin was accompanied by a high value of blood pressure. Addition of melatonin to complex pharmacotherapy reduced cardiovascular complications (Petrova & Karpenko, 2020).

They emphasize the significant effect of melatonin in kidney diseases on glomerular filtration and reduction of kidney tissue damage (Yue et al., 2023). The inclusion of melatonin in the scheme of treatment of acute septic renal failure enhances the therapeutic effect of other drugs (Deng et al., 2023).

There are data highlighting the role of melatonin as a pulmonary protector. Chronic pulmonary pathology is often accompanied by an increase in connective tissue elements (pneumofibrosis), which leads to impaired gas exchange, ventilation, and respiratory failure. When searching for drugs to improve gas exchange, attention was paid to melatonin, which has unique adaptogenic properties at different functional levels in relation to various organs and systems, and is also a regulator of reproductive and immune processes. The effect of melatonin at a dose of 5 mg/kg when administered orally to young rats for 28 days was determined. On the 28th day, the area of the alveolar surface increased, the number of connective tissue elements in the lungs decreased, which promotes gas exchange (Berezovskyi et al, 2015).

In addition, a decrease in the thickness of the interalveolar membranes, a decrease in the content of total and an increase in the content of free oxyproline in the lungs were established. It is recommended to include melatonin in a complex of pharmacotherapeutic agents for lung inflammation and obstructive diseases due to its anti-inflammatory activity, antioxidant effect, ability to normalize sleep (Wang & Gao, 2021).

The protective properties of melatonin in lung diseases are explained by its role as a scavenger of free radicals and general antioxidant action (Li et al., 2022). Melatonin is an effective treatment for radiation-induced pneumonia and pulmonary fibrosis. The effect of melatonin is associated with an increase in the activity of catalase, superoxide dismutase, glutathione, and nicotinamide coenzymes (Sheikholeslami et al., 2021).

A certain part of the works is devoted to the influence of melatonin on the organs of the abdominal cavity. Most of them consider the possibility of hepatoprotective effects of melatonin. Violations of the activity of liver enzymes can occur in the event of a violation of the activity of the gallbladder, alcohol and other poisonings, damage to cell barriers, enterochromaffin cells (LeFort et al., 2023).

Hepatoprotective properties of melatonin are expressed due to antioxidant, cytoprotective action, normalization of cytochemical and biochemical indicators (Erdogan et al., 2023). When exposed to radiation, prior administration of melatonin prevents changes in superoxide dismutase, catalase, tumor necrosis factor and other immunobiological indicators, as well as nucleic acid content (Yalcin et al., 2023).

Later, it was shown that in case of damage to liver tissues, melatonin increases the synthesis of bile acids, inhibits the phenomena of fibrosis, inhibits the growth factor of fibroblasts, and promotes the removal of toxic bile acids (Liu et al., 2023). Melatonin increases the stability of liver tissues, reducing the absorption of triglycerides and the manifestations of metabolic syndrome (Terziev & Terzieva, 2023). Melatonin protects the liver from toxic poisons, even in nanoscale, improving histochemical, biochemical, and immunological indicators (Faride et al., 2023).

The expediency of prescribing melatonin for comorbid pathology has been established, when patients with obesity and hypertension are diagnosed with irritable bowel syndrome with constipation. Under the influence of melatonin, constipation and pain in the intestines are reduced, which is associated with the improvement of biochemical indicators (Mishchuk & Grygoruk, 2022).

The positive effect of melatonin in the complex treatment of pancreatitis and atherosclerosis was established. The positive effect was characterized by an improvement in patients' lipid profile, a decrease in fat and an increase in muscle mass, which is explained by the antioxidant, anti-inflammatory effect of melatonin, the ability to synthesize NO (Sirchak & Opalenyk, 2019).

Melatonin is recommended to be prescribed in conditions with disorders of carbohydrate, lipid and protein metabolism. In case of oxidative stress, melatonin reduces the content of 4-hydroxynonanal, one of the more toxic aldehydes of lipid peroxidation, and prevents the increase in the levels of homocysteine and amyloid beta-42. The levels of serotonin, dopamine, and glutamate decrease. Melatonin has a proven antiapoptotic effect, the ability to influence through signaling pathways. In case of oxidative stress, melatonin acts as a powerful antioxidant capable of overcoming the blood-brain barrier and suppressing low-intensity chronic inflammation.

Melatonin has significant cytoprotective properties, prevents the consequences of oxidative stress in metabolic syndrome due to its effect on adipose tissue, lipolysis and mitochondrial processes, antioxidant and anti-inflammatory properties. Melatonin combines the effect on the daily rhythm with cytoprotective action (Masengaet al., 2023; Serhiienko et al., 2024).

Intracellular crosstalk between melatonin and insulin signaling pathways may be involved in cellular mechanisms controlling body weight and circadian rhythms of blood glucose. With metabolic syndrome, melatonin is an additional medicine for insulin resistance (Serhiienko et al., 2024).

It was also determined that melatonin is an important mediator in the formation of bone tissue. It can prevent premature destruction of bone tissue and promotes its restoration by affecting melatonin-mediated receptors and receptors of independent action (Litovka et al., 2014).

Antioxidants, their anti-inflammatory properties and effect on bone tissue are the basis of osteoarthritis treatment (Zhang et al., 2022). Melatonin affects the immune system and has anti-inflammatory effects. It is believed that it acts mainly on cellular immunity (T and B-lymphocytes) (Calvo & Maldonado, 2024).

As an immunoregulator, melatonin has the ability to regulate the expression of cytokine genes, reducing the production of pro-inflammatory cytokines. Melatonin can increase the production of interleukin-4-inducible synthase, nitric oxide, and lipoxygenase. In addition, melatonin restores the activity of T-helpers and the production of interleukin-2, playing an important role in the regulation of immune balance. By influencing the neuroendocrine system and stimulating natural immune reactivity together with the phagocytic system, melatonin affects the initial link of immune defense (Akyuz, 2021).

There is evidence of the expediency of including melatonin in complex anticancer therapy (Smorodin et al., 2024). Melatonin affects the initiation, progression, and metastasis phase of cancer. The inclusion of melatonin in the composition of complex therapy increases the sensitivity of the tumor to drugs. It inhibits molecular processes associated with metastasis. In addition, the drug reduces the acute and long-term toxicity of specific therapy drugs.

The anticancer effect of melatonin was established in experiments in vivo and in vitro, affecting cells of various types of cancer. The greatest effect of melatonin was observed when combined with chemotherapy and radiotherapy (Talib et al., 2021). The presence of melatonin's calming and anti-aggressive effect is of certain importance in anticancer therapy (Wang et al., 2022).

Currently, melatonin is approved for clinical use in the treatment of COVID-19 due to its antioxidant, hepatoprotective, anti-stress, immunomodulatory, and anti-inflammatory activity (Solovyov et al., 2022). The authors modeled the antioxidant activity by comparing the results of quantum chemical tests obtained at the nanolevel with changes in the macroscopic parameters of the electrorepulsion of reactive oxygen species in the presence of melatonin.

Correlation of results has been proven, effectiveness of melatonin has been confirmed. Due to its anti-inflammatory and immunomodulatory effects, melatonin activates phospholipase A2, lipoxidase and cytokines (interleukin-1 and tumor necrosis factor α) at an early stage. The anti-inflammatory effect is associated with suppression of Th-1 function and activation of Th-2 lymphocytes, slowing down of NF-κB binding to DNA, reducing the expression of inducible synthase, cyclooxygenase, and decreasing the activity of protein lipase A2, lipoxygenase, and cytokines. It protects nuclear DNA, proteins, lipids of cells, neutralizes reactive forms of oxygen.

Exogenous melatonin restores anti-inflammatory interleukins and antiviral interferon through membranes and nuclear receptors. Melatonin reduces the production of antibodies, pro-inflammatory cytokines, which is useful for COVID-19 (Mamchur, 2021).

Melatonin has a certain importance for the female reproductive system. The fact that melatonin affects the reproductive system is evidenced by the spread of its receptors in the reproductive organs. Melatonin can model the production and function of gonadotropins, steroid hormones, affects puberty, follicular genesis and ovulation.

It has been proven that melatonin simulates the synthesis of progesterone after ovulation, stabilizes the level of estradiol and prolactin, and testosterone. Melatonin has a positive effect on ovulation and improves the quality of oocytes, which contributes to the onset of pregnancy and the birth of healthy children in natural cycles. It can be used together with other reproductive technologies (Malachynska & Veresnyuk, 2019; Cipolla-Neto & Amaral, 2018).

Receptors to melatonin are expressed under the influence of the embryo and fetus, that is, it can affect their normal development. Melatonin levels may increase in the third trimester and decrease to normal after delivery. The fetus has melatonin receptors, including in the brain (Carlomagno et al., 2018). The circadian rhythms of the fetus and newborn are linked to the maternal rhythms. Violation of the normal cycle at certain periods of pregnancy can have negative consequences (Chitimus et al., 2020). There are data that melatonin has the properties of a modulator of HSP70. We found that melatonin normalizes the energy metabolism of the ischemic brain due to the positive modulation of HSP70/HIF-1α-dependent mechanisms of activation and regulation of the malate-aspartate shuttle mechanism. It was established that melatonin limits the destructive effect of oxidative stress in the ischemic brain due to HSP70/GSH-dependent mechanisms of activation of the antioxidant system. It was established for the first time that course administration of melatonin increases the density of neurons of the sensorimotor zone of the cortex, inhibits neuroapoptosis, increases the content of RNA in neurons of the sensorimotor zone of the cortex and, as a result, reduces the manifestations of neurological and cognitive disorders in experimental animals (Belenichev et al., 2023; 2024).

The results of experimental and clinical studies, as well as the cited literature data, testify to the importance of melatonin as a regulator of the main systems of the human body, because melatonin is a universal molecule that is present in every living organism.

Due to the fact that melatonin is synthesized in almost all systems and organs, melatonin preparations can be prescribed for the treatment of socially significant diseases, and also contribute to the development of new approaches for their prevention and treatment.

Conclusions

Thus, melatonin is the main hormone of the pineal gland, which affects almost all organs and functions of the body, and its drugs increase the activity and reduce the toxicity of drugs of other groups.

Among the main properties of melatonin its neurotropic, cardiotropic, antihypertensive, antiarrhythmic, pulmonary and nephroprotective, immunomodulatory, and anti-inflammatory effects should be highlighted.

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