UDC 615.35+616.12-008.331.1-085+577.125+616-008.3/.5+612.018+615.214.32
DOI: 10.56871/RBR.2023.32.88.007

A NEW LOOK AT THE PROTECTIVE ROLE OF MELATONIN IN CASE OF POLYMORBID CARDIOVASCULAR PATHOLOGY

© Vasiliy N. Tsygan, Maksim A. Antyukhin, Aleksandr S. Parcernyak

Military Medical Academy named after S.M. Kirov. Akademician Lebedev st., 6, Saint Petersburg, Russian Federation, 194044

Contact information: Aleksandr S. Parcernyak — Candidate of Medical Sciences, Lecturer at the Department of Military Field Therapy.
E-mail: partsernyak@mail.ru ORCID ID: 0000-0002-9721-1319

For citation: Tsygan VN, Antyukhin MA, Parcernyak AS. A new look at the protective role of melatonin in case of polymorbid cardiovascular pathology // Russian biomedical research (St. Petersburg). 2023; 8(3): 50-60. DOI: https://doi.org/10.56871/RBR.2023.32.88.007

Received: 22.05.2023 **Revised: 17.07.2023** **Accepted: 21.09.2023**

Abstract. Over the past years, close attention of the world scientific community has been directed to the main hormone of the pineal gland — melatonin. In the course of many studies, the protective properties of this hormone were found in various pathological conditions. Thus, in a chronic inflammatory process, melatonin stimulates the production of anti-inflammatory and suppresses the activity of pro-inflammatory cytokines and neuronal NO-synthases and cyclooxygenase-2, participates in the removal of reactive oxygen species from the cell, and also optimizes mitochondrial function through mitofusin-2. Melatonin performs its antihypertensive function by regulating the renin-angiotensin system, suppressing endothelin expression, enhancing the production of nitrosyl radical and endothelial nitric oxide synthase, and also by interacting with the central nervous system by modulating melatonin activity due to GABAergic signaling in neurons from the suprachiasmatic nucleus to various parts of the central nervous system, including the ventrolateral part of the medulla oblongata. In addition, it modulates the SIRT1/mitofusin 2 pathway by reducing the production of reactive oxygen species, deactivates LDL-induced pyroptosis in endothelial cells via the MEG3/miR-223/NLRP3 axis, and inhibits serum cholesterol absorption and biosynthesis, thereby achieving a lipid-lowering effect. Another significant function of melatonin is participation in the regulation of glycemia and control of insulinemia. It reduces insulin secretion through the melatonin 1 receptor by inhibiting the adenylate cyclase — cyclic adenosine monophosphate pathway, and through the melatonin 2 receptor it inhibits the guanylate cyclase — cyclic guanosine monophosphate pathway. On the other hand, melatonin can also stimulate insulin secretion by releasing inositol triphosphate through interaction with the melatonin 2 receptor. It should be noted that the antidepressant effect of melatonin is achieved by modulating neuroplastic reactions in the hippocampus and stimulating neurogenesis, axogenesis, and dendritogenesis. Thus, melatonin is an important protective factor in polymorbid cardiovascular pathology due to its positive effect on lipid metabolism, obesity and insulin resistance, correction of arterial hypertension level of glucose, as well as antidepressant action.

Key words: melatonin; polymorbid cardiovascular pathology; lipid metabolism; obesity; insulin resistance; correction of arterial hypertension, level of glucose; antidepressant effect.

НОВЫЙ ВЗГЛЯД НА ПРОТЕКТИВНУЮ РОЛЬ МЕЛАТОНИНА ПРИ ПОЛИМОРБИДНОЙ СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ

© Василий Николаевич Цыган, Максим Александрович Антюхин, Александр Сергеевич Парцерняк

Военно-медицинская академия им. С.М. Кирова. 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6

Контактная информация: Александр Сергеевич Парцерняк — к.м.н., преподаватель кафедры военно-полевой терапии.
E-mail: partsernyak@mail.ru ORCID ID: 0000-0002-9721-1319

Для цитирования: Цыган В.Н., Антюхин М.А., Парцерняк А.С. Новый взгляд на протективную роль мелатонина при полиморбидной сердечно-сосудистой патологии // Российские биомедицинские исследования. 2023. Т. 8. № 3. С. 50–60. DOI: https://doi.org/10.56871/RBR.2023.32.88.007

Поступила: 22.05.2023 **Одобрена: 17.07.2023** **Принята к печати: 21.09.2023**

Резюме. В прошедшие годы пристальное внимание мирового научного сообщества было направлено на основной гормон шишковидной железы — мелатонин. В ходе множества проведенных исследований были обнаружены протективные свойства данного гормона при различных патологических состояниях. Так, при хроническом воспалительном процессе мелатонин стимулирует продукцию противовоспалительных и подавляет активность провоспалительных цитокинов, нейрональных NO-синтаз и циклооксигеназы-2, участвует в удалении активных форм кислорода из клетки, а также оптимизирует митохондриальную функцию посредством митофузина-2. Антигипертензивную функцию мелатонин осуществляет за счет регуляции ренин-ангиотензиновой системы, подавления экспрессии эндотелина, усиления продукции нитрозил-радикала и эндотелиальной синтазы оксида азота и, кроме этого, благодаря взаимодействию с центральной нервной системой посредством модулирования активности мелатонина за счет ГАМК-эргической передачи сигналов в нейронах от супрахиазматического ядра к различным частям центральной нервной системы, в том числе и к вентролатеральной части продолговатого мозга. Кроме того, он моделирует путь SIRT1/митофузина-2 путем снижения продукции активных форм кислорода, деактивирует индуцированный липопротеинами низкой плотности (ЛПНП) пироптоз в эндотелиальных клетках через ось MEG3/miR-223/NLRP3 и ингибирует абсорбцию и биосинтез холестерина в сыворотке, благодаря чему достигается гиполипидемический эффект. Еще одной значимой функцией мелатонина является участие в регуляции уровня гликемии и контроль инсулинемии. Он снижает секрецию инсулина через рецептор мелатонина-1, ингибируя путь аденилатциклазы — циклического аденозинмонофосфата, а через рецептор мелатонина-2 подавляет путь гуанилатциклазы — циклического гуанозинмонофосфата. В то же время мелатонин может также стимулировать секрецию инсулина за счет высвобождения инозитолтрифосфата — через взаимодействие с рецептором мелатонина-2. Нельзя не отметить антидепрессивное действие мелатонина, которое достигается путем модулирования нейропластических реакций в гиппокампе и стимуляции нейрогенеза, аксогенеза и дендритогенеза. Таким образом, мелатонин является важным защитным фактором при полиморбидной сердечно-сосудистой патологии за счет положительного влияния на липидный обмен, ожирение и инсулинорезистентность, коррекции артериальной гипертензии, гликемии, а также антидепрессивного действия.

Ключевые слова: мелатонин; полиморбидная сердечно-сосудистая патология; липидный обмен; ожирение; инсулинорезистентность; коррекция артериальной гипертензии, гликемии; антидепрессивное действие.

Over the last decade, the scientific community has paid special attention to a wide range of biological activity of melatonin (MT) and its role in intra- and intercellular regulation, intersystem interactions, maintenance of homeostasis and protection of the organism in interaction with constantly changing environmental factors [23]. An important feature of MT is regulating circadian rhythms . It is a high-level function of the brain that includes physiological, endocrine and behavioural changes arising in connection with the change of a daily cycle.

MT, or N-acetyl-5-methoxytryptamine, is a highly conserved indolamine molecule (Fig. 1) that is found in all plants, animals [45] and microorganisms [44]. MT is mainly synthesised in the epiphysis [12, 17], but it can also be produced in the retina, thymus, spleen, heart, muscle, liver, stomach, pancreas, intestine, placenta, bone marrow, skin, hair follicles, cerebral cortex and many other parts of the body [4, 42, 49].

The substrate for MT synthesis is tryptophan amino acid, which is converted into serotonin by hydroxylation and decarboxylation, from which MT is formed with the help of N-acetyltransferase and hydroxyindole-O-methyltransferase enzymes (Fig. 2) [23]. Information on light from retinal ganglion cells passes through the retinohypothalamic tract to the suprachiasmatic nucleus (SCN), then to the upper cervical ganglia, and then through the sympathetic noradrenergic nerves reaches the pineal gland and activates pinealocytes, suppressing the production and secretion of MT. In this regard, the maximum level of MT in human

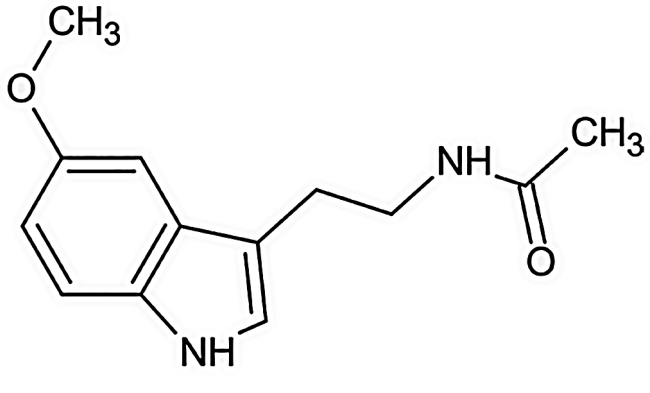

Fig. 1. Structural formula of melatonin molecule

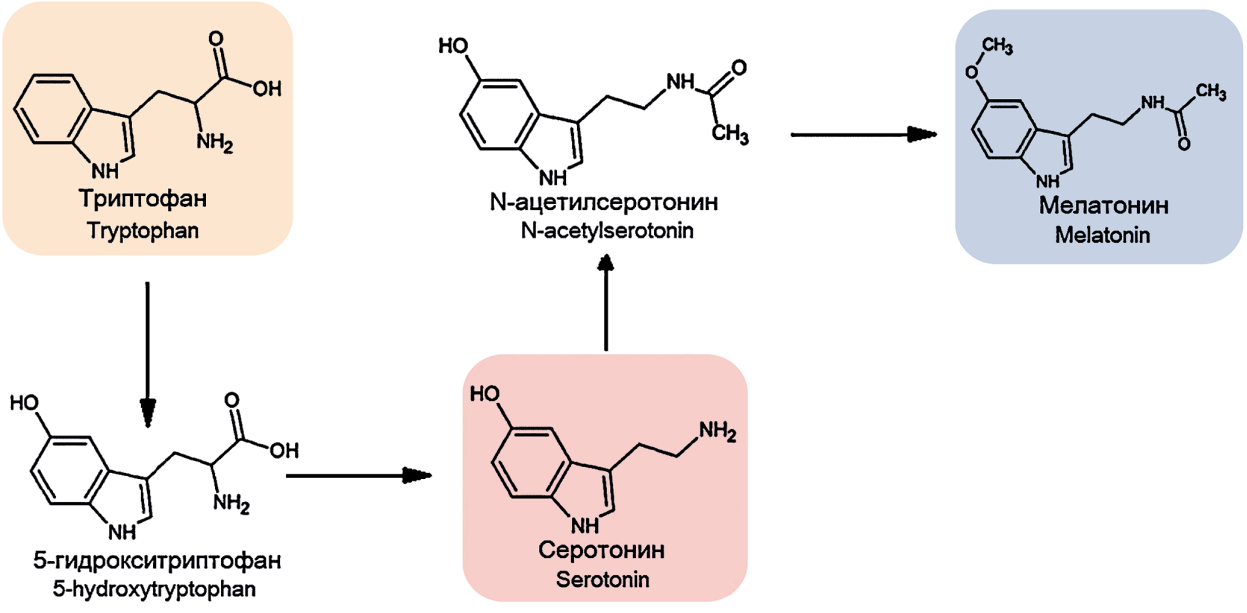

Fig. 2. Classical pathway of melatonin synthesis in humans

epiphysis and blood is observed at midnight, and the minimum — in the daytime [30]. In turn, the daytime plasma MT fraction is of peripheral origin [11]. MT plays a key role in regulating seasonal, circadian rhythms, as well as metabolism, immune response, reproductive function and other vital physiological processes [9].

The development of technology does not always lead to positive consequences. Thus, the widespread use of mobile gadgets, personal computers and other computing equipment in the dark time of day has a negative impact on the body, causing cartilage destruction due to a decrease in MT synthesis. This can further lead to negative consequences, such as the formation of various types of oncopathology (breast, prostate, endometrial, ovarian, colon, skin, etc.); as well as cardiovascular diseases; digestive disorders; diabetes mellitus; obesity; depression; sleep deprivation; cognitive impairment and premature aging [8, 10, 36].

Besides regulating biological rhythms, MT has many different functions [33]. It is known to affect gastrointestinal (GI) motility through membrane receptors that include MT receptors (melatonin receptor type 1 (MT 1) and type 2 (MT 2)) and serotonin (5-HT). At physiological levels, MT acts as a serotonin antagonist in the regulation of intestinal motility [46]. The immunomodulatory effect of MT is based on the endocrine response of circulating immunological cells and progenitor cells in the bone marrow that express its receptors. Rhythmic synthesis of MT has been found to be essential for modulating both circadian and seasonal fluctuations in immune functions, as well as for the efficient functioning of the immune-pineal axis [25]. MT influences growth processes and thyroid hormone synthesis [38]. Its antioxidant function is also important to note [23]. It has the ability to scavenge free radicals and also induces the expression of antioxidant enzymes (superoxide dismutase and glutathione peroxidase) with the formation of indirect antioxidant effects [3]. Next, we are going to discuss the role of MT in various somatic pathologies.

MELATONIN AND INFLAMMATION

The main anti-inflammatory action of MT is enhancing the activity of anti-inflammatory cytokines and suppressing the production of leptin and pro-inflammatory cytokines such as interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor-α (TNF-α) [16]. In addition, MT suppression of pro-inflammatory cytokines can lead to multiple antioxidant effects, removal of reactive oxygen species (ROS), inhibition of neuronal NO synthases and cyclooxygenase-2 (COX-2), and inhibition of Nod-like receptor containing pyrin domain 3 (NLRP3) inflammasome formation [24]. Nuclear factor kappa-B (NF-κB) and NLRP3 are inhibited through activation of the MT-dependent gene for the NAD-dependent sirtuin deacetylase-1 (SIRT1) protein (Fig. 3) [18].

Importantly, the anti-inflammatory effect of MT is also related to its ability to optimize mitochondrial function. It exerts a beneficial effect on mitochondria via mitofusin-2 (Fig. 4), which modulates the neuronal activity of orexigenic agouti-related protein (AgRP) and diet-induced obesity, as well as the intrinsic regulation of the apoptotic cascade [41].

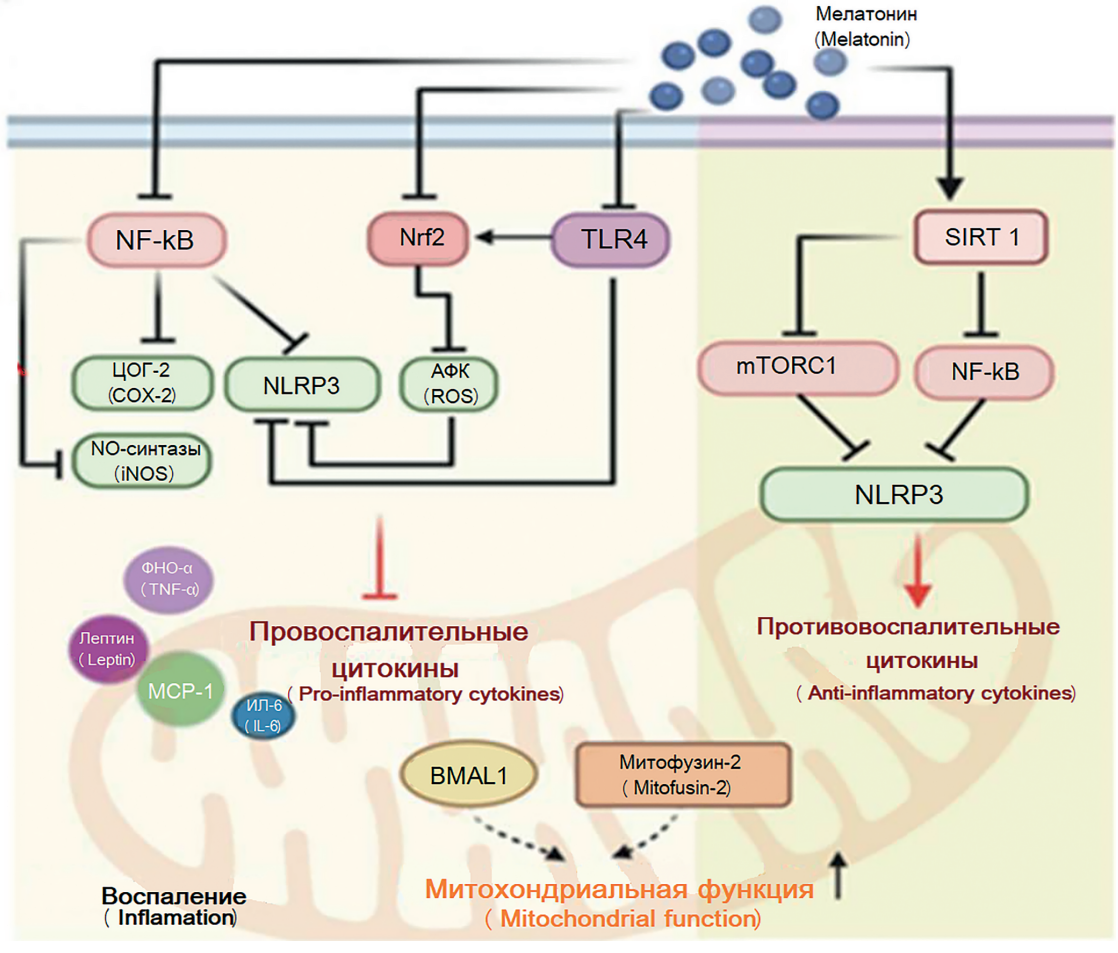

Fig. 3. **Reduction of inflammation activity by melatonin through inhibition of NF-κB, NRF2, TLR4, and SIRT1 signaling pathways, resulting in suppression of proinflammatory and enhancement of anti-inflammatory cytokines. AFC, reactive oxygen species; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; COX-2, cyclooxygenase-2; BMAL1, aromatic hydrocarbon nuclear translocator-like protein-1; MCP-1, monocyte chemotactic protein-1; mTORC1, mammalian target of rapamycin signaling complex; NF-κB, nuclear factor kappa-bi; NLRP3, Nod-like receptor containing pyrin domain 3; Nrf2, erythroid 2-dependent nuclear factor; SIRT1, sirtuin NAD-dependent deacetylase-1 protein; TLR4, toll-like receptor 4**

A number of experiments have confirmed anti-inflammatory properties of MT. Thus, the results of a clinical study conducted at the Second Hospital of Jilin University of the People's Republic of China (PRC) demonstrated that MT prevents inflammation-induced hepatocyte damage in laboratory mice. It reduces mitochondrial oxidative stress through activation of the Akt-SIRT3 pathway involved in antioxidant synthesis, and at the same time regulates reactive oxygen species (ROS) formation [34].

MELATONIN AND HYPERTENSION

Hypertension (HT) is one of the most common causes of mortality in the adult population [2]. Persistent hypertension leads to chronic tension of arterial walls, which in turn is associated with their stiffness, inflammatory process in the intima and atherogenesis.

The positive effect of MT in terms of HT has been known for a long time. Thus, in the study of 1976, conducted by the Department of Medicines of the county of Herdfordshire (UK), it was found that pinealectomy in rats led to a pronounced HT. The findings suggest a positive effect of endogenous MT on blood pressure regulation [19].

It was also found that patients with cardiovascular diseases associated with HT have decreased serum MT levels [51]. MT may reduce hypertension through regulation of vasoconstriction and vasodilation and interaction with the renin-angiotensin system [7]. A study conducted at Suzhou University Medical College (PRC) demonstrated that endothelial cells cultured under high blood pressure conditions expressed significantly more vasoactive substances including endothelin and angiotensin II [37]. Co-incubation of MT with these cells resulted in suppression of endothelin and angiotensin II and increased nitrosyl radical production and endothelial nitric oxide synthase expression [51].

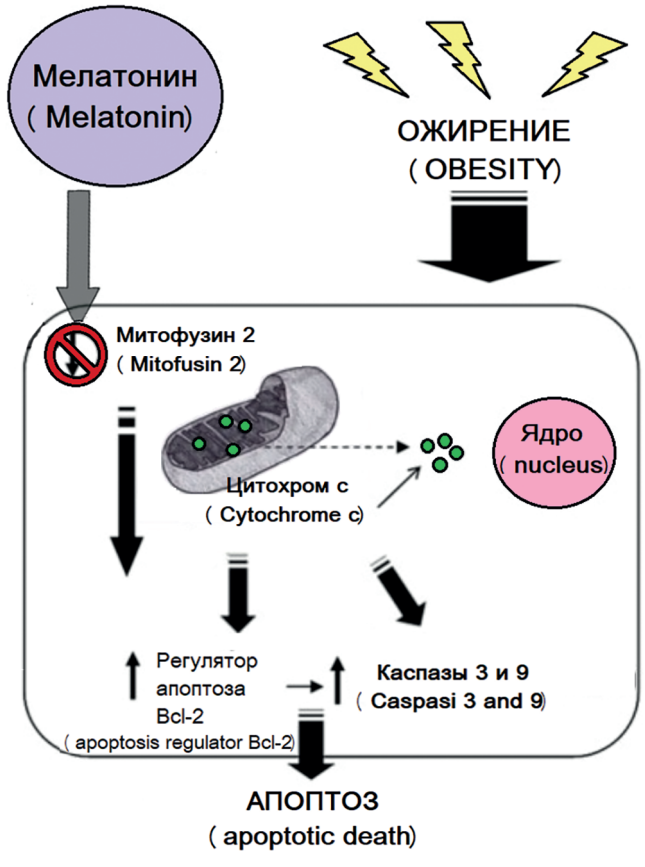

Fig. 4. Schematic representation of the inhibitory effect of melatonin on the intrinsic, mitochondria-driven apoptotic cascade and apoptosis pathways induced by mitofusin-2-mediated changes in the kidney on the background of obesity

The anti-remodeling effect of MT should be emphasized as well. A study conducted at Comenius University in Bratislava (Slovakia) demonstrated that MT reduced fibrosis activity in rats with spontaneous hypertension [40], hypertension induced by N-ω-nitro-L-arginine methyl ester (L-NAME), and hypertension induced by constant exposure to light (Fig. 5) [39].

In addition to its effects on the vascular system, MT may also exert antihypertensive effects through interaction with the central nervous system (CNS). On the one hand, MT release is controlled by sympathetic afferentation to the pineal gland, involving the interaction of light with the retina, suprachiasmatic nucleus, paraventricular nucleus and stimulation of β1- and α1-adrenoreceptors of the pineal gland [39]. On the other hand, transmission of signals by GABA from the suprachiasmatic nucleus to various parts of the CNS, including the ventrolateral part of the medulla oblongata, may be modulated by MT activity, providing a protective mechanism against excessive sympathetic excitation [31].

MELATONIN AND HYPERLIPIDAEMIA

Hyperlipidemia is a consequence of an aberrant process of increasing levels of low-density lipoprotein (LDL), total cholesterol (TC), triglycerides and decreasing levels of high-density lipoprotein (HDL). According to the University Hospital of the Canary Islands (Spain), an inverse correlation between serum levels of endogenous MT and LDL was found in patients with atherosclerosis [13]. In vitro studies have also demonstrated the beneficial effects of MT in the metabolic function of hepatocytes through modelling the SIRT1/mitofusin-2 pathway, by reducing ROS production. Pretreatment of HepG2 cell line with MT showed improved lipid consumption and activation of PPARα and carnitine palmitoyl-CoA transferase 1, which are lipolytic genes essential for metabolism [51].

According to Harbin Medical University (PRC), MT appeared to deactivate LDL-induced pyroptosis in endothelial cells via the MEG3/miR-223/NLRP3 axis [52]. It should be added that LDLs trigger inflammation activation and pro-inflammatory factor secretion, whereas MT significantly reduces NLRP3-inflammatory production by NLRP3-inflammasomes and IL-1 secretion in macrophages [51]. In another study conducted by the State University of São Paulo (Brazil), healthy laboratory rats were compared with rats which undergone pineal gland resection. Thus, the animals had a significant decrease in serum HDL level after surgery, but normalization of the level of this lipoprotein was observed when MT was administered [14].

Researchers from the University of Granada (Spain) reported MT positively influenced on overweight and lipid profile in obese and diabetic rats [5]. Prolonged stimulation of MT synthesis is able to reduce weight gain [47], inhibit the absorption and biosynthesis and serum levels of OX [21], and enhance its catabolism [32]. MT reduces cholesterol by enhancing the mechanisms of endogenous cholesterol clearance through bilirubin acid synthesis and inhibition of LDL receptor activity. The hypolipidemic effect of MT is also determined by an increase in the level of circulating irisin, which enhances the excretion of total cholesterol by its clearance into bile [16].

MELATONIN AND DIABETES MELLITUS

The results of a number of foreign studies prove that circadian rhythm disturbance may contribute to the development of both diabetes and cardiovascular diseases [29]. A correlation between MT secretion and insulin at night has been described in young patients with metabolic syndrome [1]. The large-scale Nurses' Health Study found an association between MT secretion, assessed by urinary 6-sulfatoxymelatonin levels, and the subsequent development of

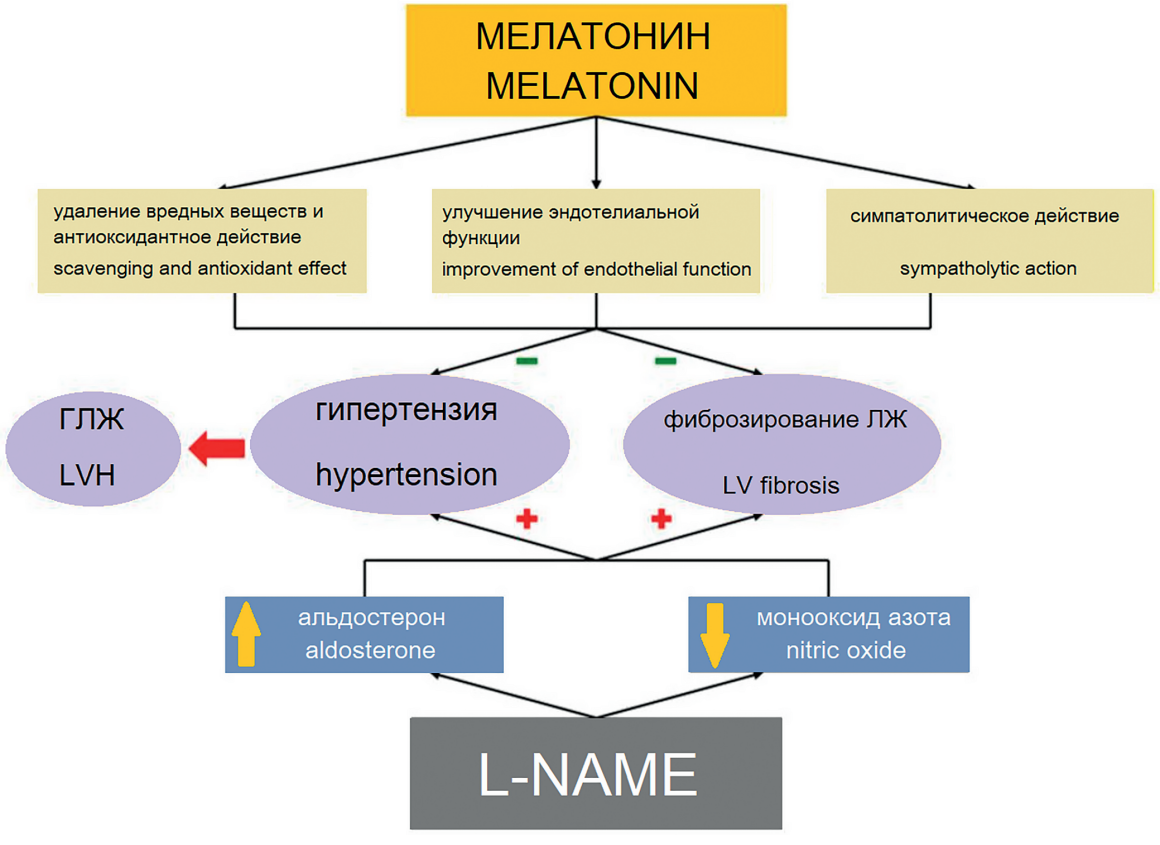

Fig. 5. Mechanisms of the protective effect of melatonin in hypertension induced by N-ω-nitro-L-arginine methyl ester. Chronic administration of L-NAME provokes the development of arterial hypertension, left ventricular (LV) fibrosis, and as a consequence of increased hemodynamic load, left ventricular hypertrophy develops. Melatonin reduces free radicals through its antioxidant action, improves endothelial function and has a central sympatholytic effect. These actions of melatonin lead to normalization of blood pressure, prevention of further myocardial remodeling in the left ventricle

type 2 diabetes mellitus (DM 2). Individuals with the lowest levels of MT secretion had a twofold risk of developing DM 2 compared to subjects with normal or high levels of its secretion [26].

In addition, MT regulates blood glucose levels. Several hypotheses are proposed to explain this process. Thus, the “Equilibrium Hypothesis” suggests that both increased and decreased MT signaling can cause carbohydrate disorders [27]. Another hypothesis suggests a functional antagonism between MT secretion and food intake. Low MT levels during the day potentiate normal glycemic tolerance after a food load, while high MT levels during overnight fasting ensure pancreatic beta-cell recovery. Elevated MT concentrations during meal periods result in pathological changes in glucose metabolism in both nighttime eaters and those awake during dark periods [15]. Despite conflicting data and hypotheses, it is clear that the pineal hormone performs fine-tuning of carbohydrate metabolism through its receptors in the pancreas, liver and adipose tissue [28].

Experimental studies have revealed that MT receptors in pancreas are associated with several parallel signaling pathways affecting insulin secretion. Thus, MT decreases insulin secretion via the MT 1 receptor by inhibiting the adenylate cyclase-cyclic adenosine monophosphate pathway, and inhibits the guanylate cyclase-cyclic guanosine monophosphate pathway via the MT 2 receptor. In addition, MT can also stimulate insulin secretion by releasing inositol triphosphate — through interaction with the MT 2 receptor [28].

It has also been found that patients with DM have a decreased number of MT1 and MT2 receptors in beta cells. According to a study by King’s College London, MT stimulates glucagon secretion by alpha cells followed by a paracrine-mediated indirect increase in insulin levels by β cells. MT also modulates somatostatin secretion by delta cells in both healthy individuals and DM 2 patients [35].

MTNR1B is an important diabetic gene encoding the MT2 receptor protein. A decade ago It was associated with pancreatic beta-cell dysfunction which gave a huge impetus to research the correlation between pineal hormone

signaling, receptor polymorphism and impaired carbohydrate metabolism. *MTNR1B* rs10830963 C > G was associated with elevated fasting glucose levels in a large cohort of individuals of European origin. Moreover, the presence of a minor G allele of the same polymorphism was associated with an increased risk of DM 2 in a meta-analysis of 18,236 cases from a cohort of 64,453 patients. The rs10830963G allele determines both elevated fasting glucose levels and a low early insulin response to glucose loading [28].

In addition, several meta-analyses have shown an association between the *MTNR1B* rs10830963 and the development of gestational diabetes mellitus (GDM). Carriers of GG genotype have a 78% higher risk of developing GDM compared to SS carriers, regardless of ethnicity [6, 20, 22].

A number of other common polymorphisms of the *MTNR1B* gene also modulate fasting glucose levels and early insulin secretion by beta cells, thereby influencing the risk of developing DM2 and GDM in different ethnic groups. Moreover, the same polymorphisms may determine different effects of lifestyle modification and/or drug treatment in metabolic disorders [28].

Taking into account the expression of MT receptors in many tissues, studies have revealed the influence of MT signaling on glucose metabolic processes in peripheral tissues such as liver, skeletal muscle and pancreas. MT is required for insulin-stimulated activity of phosphatidylinositol-3-kinase and protein kinase B. MT mediated glycogen synthesis in hepatocyte cells through insulin receptor substrate 1 via Gi protein. Notably, MT promotes SIRT 1 expression and phosphorylation of signal transducer and activator of transcription 3 in rat liver to regulate gluconeogenesis. MT also activates the IRS1-PI3K-PKCζ pathway to promote glucose uptake in skeletal muscle [16].

MELATONIN AND DEPRESSIVE SPECTRUM DISORDERS

An observational study conducted at Uppsala University (Sweden) found a negative correlation between evening MT levels and quantitative measures of depressive symptoms in young patients seeking psychiatric care. Similarly, patients with low MT levels demonstrated worsening of symptoms on the MADRS-S scale in a prospective study [43].

A possible mechanism for the antidepressant action of MT is its ability to modulate neuroplastic responses in the hippocampus. A wide range of meta-analyses points to structural and functional abnormalities of the hippocampus in depression. In addition, inflammatory processes significantly contribute to structural changes in the hippocampus in depressive disorders [50]. Preclinical data have shown that the hippocampus is one of the main targets for MT action in the brain, with MT promoting branching of distal dendrites in layers II/III of cortical pyramidal cells [48]. It was also found that MT stimulates neurogenesis, axogenesis and dendritogenesis of neurons in the limbic region of the brain. Disruption of MT expression, which further promotes meta-inflammation and decreases the cytoprotective and neuroprotective effects of hippocampal cells, may be one of the major mechanisms underlying the pathophysiology of depression [50].

CONCLUSION

Melatonin has a wide range of protective properties in various pathological processes, it has a positive effect on lipid metabolism, promotes weight loss in obesity and, as a consequence, the degree of severity of insulin resistance. Melatonin normalizes blood pressure and elevated glycemic levels and has antidepressant functions, which are attributed to their role in regulating circadian rhythms, the renin-angiotensin system, insulin levels, as well as lipid metabolism and deactivation of chronic inflammation. Although melatonin is a neurohormone, it plays a pivotal role in modulating oxidative stress through both direct antioxidant action and induction by inflammation. Thus, regulation of circulating melatonin levels may serve as a potential target for reducing the intensity of oxidative stress leading, among other things, to meta-inflammation.

So far, there is still no consensus on the possible role of melatonin as an adjuvant drug for the treatment of metabolic diseases, although it shows great potential in many aspects. The wide range of positive properties of melatonin leads us to the conclusion that it is necessary to study the use of MT exogenous form as an adjunct to the main therapy in various diseases, primarily metabolic and anxiety-depressive spectrum disorders. Exogenous melatonin, as well as endogenous one, reduces the level of pro- inflammatory cytokines and suppresses the activity of oxidative stress, which can be used for prevention and adjuvant treatment of polymorbid pathology. Melatonin is relatively safe and has few mild side effects such as dizziness, headache, nausea, morning drowsiness, which makes it an excellent agent for preventing many pathological conditions.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Antyukhin M.A., Partsernyak A.S. Izucheniye roli melatonina i khronicheskogo vospaleniya v razvitii i progressirovanii metabolicheskogo sindroma u lits molodogo vozrasta. [Study of the role of melatonin and chronic inflammation in the development and progression of the metabolic syndrome in young adults]. Izvestiya Rossiyskoy Voyenno-Meditsinskoy Akademii. 2020; 39(1-1): 9–12. (in Russian).
2. Kryukov Ye.V., Potekhin N.P., Fursov A.N. i dr. Gipertonicheskiy kriz: sovremennyy vzglyad na problemu i optimizatsiya lechebno-diagnosticheskikh podkhodov. [Hypertensive crisis: a modern view on the problem and optimization of treatment and diagnostic approaches]. Klinicheskaya Meditsina. 2016; 94(1): 52–6. (in Russian).
3. Partsernyak A.S., Kryukov Ye.V., Tsygan V.N. i dr. Metabolicheskiy sindrom i ateroskleroz u molodykh muzhchin. Metabolic syndrome and atherosclerosis in young men. Lecheniye i profilaktika. 2021; 4: 5–11. (in Russian).
4. Acuna-Castroviejo D., Noguiera-Navarro M.T., Reiter R.J. Melatonin actions in the heart: more than a hormone. Melatonin Res. 2018; 1(1): 21–6.
5. Agil A., Navarro-Alarcon M., Ruiz R. et al. Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. J Pineal Res. 2011; 50(2): 207–12.
6. Bai Y., Tang L., Li L. et al. The roles of ADIPOQ rs266729 and MTNR1B rs10830963 polymorphisms in patients with gestational diabetes mellitus: A meta-analysis. Gene. 2020.
7. Baltatu O.C., Amaral F.G., Campos L.A. et al. Melatonin, mitochondria and hypertension. Cell Mol Life Sci. 2017; 74(21): 395–64.
8. Bass J., Lazar M.A. Circadian time signatures of fitness and disease. Science. 2016; 354(6315): 994–9.
9. Boden M.J., Varcoe T.J., Kennaway D.J. Circadian regulation of reproduction: From gamete to offspring. Progress in Biophysics and Molecular Biology. 2013; 113(3): 387–97.
10. Bonmati-Carrion M.A., Arguelles-Prieto R., Martinez-Madrid M.J. et al. Protecting the melatonin rhythm through circadian healthy light exposure. International Journal of Molecular Sciences. 2014; 15(12): 23448–500.
11. Chen C., Fichna J., Bashashati M. et al. Distribution, function and physiological role of melatonin in the lower gut. World Journal of Gastroenterology. 2011; 17(34): 3888–98.
12. Claustrat B., Leston J. Melatonin: Physiological effects in humans. Neurochirurgie. 2015; 61(2–3): 77–84.
13. Dominguez-Rodriguez A., Abreu-Gonzalez P., Garcia-Gonzalez M. et al. Elevated levels of oxidized low-density lipoprotein and impaired nocturnal synthesis of melatonin in patients with myocardial infarction. Atherosclerosis. 2005; 180 (1): 101–5.
14. Dos Santos R.M., Marani F., Chiba F.Y. et al. Melatonin promotes reduction in TNF levels and improves the lipid profile and insulin sensitivity in pinealectomized rats with periodontal disease. Life Sciences. 2018; 213: 32–9.
15. Garaulet M., Qian J., Florez J.C. et al. Melatonin Effects on Glucose Metabolism: Time To Unlock the Controversy. Trends Endocrinol Metab. 2020; 31 (3): 192–204.
16. Guan Q., Wang Z., Cao J. et al. Mechanisms of Melatonin in Obesity: A Review. nternational Journal of Molecular Sciences. 2022; 23 (1): 218.
17. Hardeland R., Pandi-Perumal S.R., Cardinali Melatonin D.P. The International Journal of Biochemistry & Cell Biology. 2006; 38(3): 313–6.
18. Hardeland R. Melatonin and inflammation-story of a double-edged blade. J Pineal Res. 2018; 65 (4).
19. Holmes S.W., Sugden D. Proceedings: The effect of melatonin on pinealectomy-induced hypertension in the rat. British Journal of Pharmacology. 1976; 56 (3): 360–1.
20. Huang B., Wang Y., Qin L. et al. A functional polymorphism rs10830963 in melatonin receptor 1B associated with the risk of gestational diabetes mellitus. Bioscience Reports. 2019; 39(12).
21. Hussain S. Effect of melatonin on cholesterol absorption in rats. J Pineal Res. 2007; 42 (3): 267–71.
22. Jia G., Gao Y., Li C. et al. Effects of MTNR1B Genetic Variants on Individual Susceptibility to Gestational Diabetes Mellitus: A Meta-Analysis. American Journal of Perinatology. 2020; 37(6): 607–12.
23. Kvetnoy I., Ivanov D., Mironova E. et al. Melatonin as the Cornerstone of Neuroimmunoendocrinology. International Journal of Molecular Sciences. 2022; 23(3): 1835.
24. Liu Z., Gan L., Xu Y. et al. Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue. J. Pineal Res. 2017; 63 (1).
25. Markus R.P., Fernandes P.A., Kinker G.S. et al. Immune-pineal axis — acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes. British Journal of Pharmacology. 2018; 175 (16): 3239–50.
26. McMullan C.J., Schernhammer E.S., Rimm E.B. et al. Melatonin secretion and the incidence of type 2 diabetes. Journal of the American Medical Association. 2013; 309(13): 1388–96.
27. Mulder H. Melatonin signalling and type 2 diabetes risk: too little, too much or just right? Diabetologia. 2017; 60 (5): 826–9.

28. Nikolaev G., Robeva R., Konakchieva R. Membrane Melatonin Receptors Activated Cell Signaling in Physiology and Disease. International Journal of Molecular Sciences. 2022; 23 (1): 471.
29. Otamas A., Grant P.J., Ajjan R.A. Diabetes and atherothrombosis: The circadian rhythm and role of melatonin in vascular protection. Diab Vasc Dis Res. 2020; 13(3).
30. Pandi-Peruumal S.R., Cardinali D.P. Melatonin: Biological Basis of its Function in Health and Disease. CRC Press. 2005.
31. Pechanova O., Paulis L., Simko F. Peripheral and central effects of melatonin on blood pressure regulation. Int J Mol Sci. 2014; 15(10): 17920–37.
32. Pita M.L., Hoyos M., Martin-Lacave I. et al. Long-term melatonin administration increases polyunsaturated fatty acid percentage in plasma lipids of hypercholesterolemic rats. J Pineal Res. 2002; 32 (3): 179–86.
33. Posadzki P.P., Bajpai R., Kyaw B.M. et al. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. BMC Medicine. 2018; 16 (1).
34. Qiu J., Liu D., Li P. et al. NADPH Oxidase Mediates Oxidative Stress and Ventricular Remodeling through SIRT3/FOXO3a Pathway in Diabetic Mice. Antioxidants. 2022; 11 (9): 1745.
35. Ramracheya R.D., Muller D.S., Squires P.E. et al. Function and expression of melatonin receptors on human pancreatic islets. J Pineal Res. 2008; 44 (3): 273–9.
36. Schlafer O., Wenzel V., Hogl B. Sleep disorders among physicians on shift work. Anaesthetist. 2014; 63 (11): 844–51.
37. Shao G., Zhang S., Nie J. et al. Effects of melatonin on mechanisms involved in hypertension using human umbilical vein endothelial cells. Journal of Toxicology and Environmental Health. 2017; 80 (23–24): 1342–8.
38. Shavali S.S., Haldar C. Effects of continuous light, continuous darkness and pinealectomy on pineal-thyroid-gonadal axis of the female Indian palm squirrel, Funambulus pennant. Journal of Neural Transmission. 1998; 105 (4–5): 407–13.
39. Simko F., Baka T., Krajcirovicova K. et al. Effect of Melatonin on the Renin-Angiotensin-Aldosterone System in l-NAME-Induced Hypertension. Molecules. 2018; 23 (2): 265.
40. Simko F., Pechanova O., Pelouch V. et al. Effect of melatonin, captopril, spironolactone and simvastatin on blood pressure and left ventricular remodelling in spontaneously hypertensive rats. J Hypertens Suppl. 2009; 27(6): 5–10.
41. Stacchiotti A., Favero G., Giugno L. et al. Mitochondrial and metabolic dysfunction in renal convoluted tubules of obese mice: protective role of melatonin. PLOS One. 2014; 9 (10).
42. Stefulj J., Hortner M., Ghosh M. et al. Gene expression of the key enzymes of melatonin synthesis in extrapineal tissues of the rat. Journal of Pineal Research. 2001; 30(4): 243–7.
43. Sundberg I., Ramklint M., Stridsberg M. et al. Salivary Melatonin in Relation to Depressive Symptom Severity in Young Adults. PLOS One. 2016; 11(4).
44. Tan D., Zheng X., Kong J. et al. Fundamental issues related to the origin of melatonin and melatonin isomers during evolution: relation to their biological functions. International Journal of Molecular Sciences. 2014; 15(9): 15858–90.
45. Tan D.X., Hardeland R., Manchester L.C. et al. Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science. Journal of Experimental Botany. 2012; 63(2): 577–97.
46. Thor P.J., Krolczyk G., Gil K. et al. Melatonin and serotonin effects on gastrointestinal motility. Journal of Physiology and Pharmacology. 2007; 58: 97–103.
47. Tung Y., Chiang P., Chen Y. et al. Effects of Melatonin on Lipid Metabolism and Circulating Irisin in Sprague-Dawley Rats with Diet-Induced Obesity. Molecules. 2020; 25(15): 3329.
48. Valdes-Tovar M., Estrada-Reyes R., Solis-Chagoyan H. et al. Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. British Journal of Pharmacology. 2018; 175 (16): 3200–8.
49. Venegas C., Garcia J.A., Escames G. et al. Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. Journal of Pineal Research. 2012; 52(2): 217–27.
50. Won E., Na K., Kim Y. Associations between Melatonin, Neuroinflammation, and Brain Alterations in Depression. International Journal of Molecular Sciences. 2022; 23 (1): 305.
51. Zhang R., Ni L., Di X. et al. Potential Role of Melatonin as an Adjuvant for Atherosclerotic Carotid Arterial Stenosis. Molecules. 2021; 26 (4).
52. Zhang Y., Liu X., Bai X. et al. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. J Pineal Res. 2018; 64 (2).

ЛИТЕРАТУРА

1. Антюхин М.А., Парцерняк А.С. Изучение роли мелатонина и хронического воспаления в развитии и прогрессировании метаболического синдрома у лиц молодого возраста. Известия Российской Военно-медицинской академии. 2020; 39(1-1): 9–12.
2. Крюков Е.В., Потехин Н.П., Фурсов А.Н. и др. Гипертонический криз: современный взгляд на проблему и оптимизация лечебно-диагностических подходов. Клиническая медицина. 2016; 94(1): 52–6.
3. Парцерняк А.С., Крюков Е.В., Цыган В.Н. и др. Метаболический синдром и атеросклероз у молодых мужчин. Лечение и профилактика. 2021; 4: 5–11.
4. Acuna-Castroviejo D., Noguiera-Navarro M.T., Reiter R.J. Melatonin actions in the heart: more than a hormone. Melatonin Res. 2018; 1(1): 21–6.
5. Agil A., Navarro-Alarcon M., Ruiz R. et al. Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. J Pineal Res. 2011; 50(2): 207–12.
6. Bai Y., Tang L., Li L. et al. The roles of ADIPOQ rs266729 and MTNR1B rs10830963 polymorphisms in patients with gestational diabetes mellitus: A meta-analysis. Gene. 2020.
7. Baltatu O.C., Amaral F.G., Campos L.A. et al. Melatonin, mitochondria and hypertension. Cell Mol Life Sci. 2017; 74(21): 395–64.

8. Bass J., Lazar M.A. Circadian time signatures of fitness and disease. Science. 2016; 354(6315): 994–9.
9. Boden M.J., Varcoe T.J., Kennaway D.J. Circadian regulation of reproduction: From gamete to offspring. Progress in Biophysics and Molecular Biology. 2013; 113(3): 387–97.
10. Bonmati-Carrion M.A., Arguelles-Prieto R., Martinez-Madrid M.J. et al. Protecting the melatonin rhythm through circadian healthy light exposure. International Journal of Molecular Sciences. 2014; 15(12): 23448–500.
11. Chen C., Fichna J., Bashashati M. et al. Distribution, function and physiological role of melatonin in the lower gut. World Journal of Gastroenterology. 2011; 17(34): 3888–98.
12. Claustrat B., Leston J. Melatonin: Physiological effects in humans. Neurochirurgie. 2015; 61(2-3): 77–84.
13. Dominguez-Rodriguez A., Abreu-Gonzalez P., Garcia-Gonzalez M. et al. Elevated levels of oxidized low-density lipoprotein and impaired nocturnal synthesis of melatonin in patients with myocardial infarction. Atherosclerosis. 2005; 180 (1): 101–5.
14. Dos Santos R.M., Marani F., Chiba F.Y. et al. Melatonin promotes reduction in TNF levels and improves the lipid profile and insulin sensitivity in pinealectomized rats with periodontal disease. Life Sciences. 2018; 213: 32–9.
15. Garaulet M., Qian J., Florez J.C. et al. Melatonin Effects on Glucose Metabolism: Time To Unlock the Controversy. Trends Endocrinol Metab. 2020; 31 (3): 192–204.
16. Guan Q., Wang Z., Cao J. et al. Mechanisms of Melatonin in Obesity: A Review. nternational Journal of Molecular Sciences. 2022; 23 (1): 218.
17. Hardeland R., Pandi-Perumal S.R., Cardinali Melatonin D.P. The International Journal of Biochemistry & Cell Biology. 2006; 38(3): 313–6.
18. Hardeland R. Melatonin and inflammation-story of a double-edged blade. J Pineal Res. 2018; 65 (4).
19. Holmes S.W., Sugden D. Proceedings: The effect of melatonin on pinealectomy-induced hypertension in the rat. British Journal of Pharmacology. 1976; 56 (3): 360–1.
20. Huang B., Wang Y., Qin L. et al. A functional polymorphism rs10830963 in melatonin receptor 1B associated with the risk of gestational diabetes mellitus. Bioscience Reports. 2019; 39(12).
21. Hussain S. Effect of melatonin on cholesterol absorption in rats. J Pineal Res. 2007; 42 (3): 267–71.
22. Jia G., Gao Y., Li C. et al. Effects of MTNR1B Genetic Variants on Individual Susceptibility to Gestational Diabetes Mellitus: A Meta-Analysis. American Journal of Perinatology. 2020; 37(6): 607–12.
23. Kvetnoy I., Ivanov D., Mironova E. et al. Melatonin as the Cornerstone of Neuroimmunoendocrinology. International Journal of Molecular Sciences. 2022; 23(3): 1835.
24. Liu Z., Gan L., Xu Y. et al. Melatonin alleviates inflammasome-induced pyroptosis through inhibiting NF-κB/GSDMD signal in mice adipose tissue. J. Pineal Res. 2017; 63 (1).
25. Markus R.P., Fernandes P.A., Kinker G.S. et al. Immune-pineal axis — acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes. British Journal of Pharmacology. 2018; 175 (16): 3239–50.
26. McMullan C.J., Schernhammer E.S., Rimm E.B. et al. Melatonin secretion and the incidence of type 2 diabetes. Journal of the American Medical Association. 2013; 309(13): 1388–96.
27. Mulder H. Melatonin signalling and type 2 diabetes risk: too little, too much or just right? Diabetologia. 2017; 60 (5): 826–9.
28. Nikolaev G., Robeva R., Konakchieva R. Membrane Melatonin Receptors Activated Cell Signaling in Physiology and Disease. International Journal of Molecular Sciences. 2022; 23 (1): 471.
29. Otamas A., Grant P.J., Ajjan R.A. Diabetes and atherothrombosis: The circadian rhythm and role of melatonin in vascular protection. Diab Vasc Dis Res. 2020; 13(3).
30. Pandi-Peruumal S.R., Cardinali D.P. Melatonin: Biological Basis of its Function in Health and Disease. CRC Press. 2005.
31. Pechanova O., Paulis L., Simko F. Peripheral and central effects of melatonin on blood pressure regulation. Int J Mol Sci. 2014; 15(10): 17920–37.
32. Pita M.L., Hoyos M., Martin-Lacave I. et al. Long-term melatonin administration increases polyunsaturated fatty acid percentage in plasma lipids of hypercholesterolemic rats. J Pineal Res. 2002; 32 (3): 179–86.
33. Posadzki P.P., Bajpai R., Kyaw B.M. et al. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. BMC Medicine. 2018; 16 (1).
34. Qiu J., Liu D., Li P. et al. NADPH Oxidase Mediates Oxidative Stress and Ventricular Remodeling through SIRT3/FOXO3a Pathway in Diabetic Mice. Antioxidants. 2022; 11 (9): 1745.
35. Ramracheya R.D., Muller D.S., Squires P.E. et al. Function and expression of melatonin receptors on human pancreatic islets. J Pineal Res. 2008; 44 (3): 273–9.
36. Schlafer O., Wenzel V., Hogl B. Sleep disorders among physicians on shift work. Anaesthetist. 2014; 63 (11): 844–51.
37. Shao G., Zhang S., Nie J. et al. Effects of melatonin on mechanisms involved in hypertension using human umbilical vein endothelial cells. Journal of Toxicology and Environmental Health. 2017; 80 (23–24): 1342–8.
38. Shavali S.S., Haldar C. Effects of continuous light, continuous darkness and pinealectomy on pineal-thyroid-gonadal axis of the female Indian palm squirrel, Funambulus pennant. Journal of Neural Transmission. 1998; 105 (4–5): 407–13.
39. Simko F., Baka T., Krajcirovicova K. et al. Effect of Melatonin on the Renin-Angiotensin-Aldosterone System in l-NAME-Induced Hypertension. Molecules. 2018; 23 (2): 265.
40. Simko F., Pechanova O., Pelouch V. et al. Effect of melatonin, captopril, spironolactone and simvastatin on blood pressure and left ventricular remodelling in spontaneously hypertensive rats. J Hypertens Suppl. 2009; 27(6): 5–10.
41. Stacchiotti A., Favero G., Giugno L. et al. Mitochondrial and metabolic dysfunction in renal convoluted tubules of obese mice: protective role of melatonin. PLOS One. 2014; 9 (10).
42. Stefulj J., Hortner M., Ghosh M. et al. Gene expression of the key enzymes of melatonin synthesis in extrapineal tissues of the rat. Journal of Pineal Research. 2001; 30(4): 243–7.

43. Sundberg I., Ramklint M., Stridsberg M. et al. Salivary Melatonin in Relation to Depressive Symptom Severity in Young Adults. PLOS One. 2016; 11(4).
44. Tan D., Zheng X., Kong J. et al. Fundamental issues related to the origin of melatonin and melatonin isomers during evolution: relation to their biological functions. International Journal of Molecular Sciences. 2014; 15(9): 15858–90.
45. Tan D.X., Hardeland R., Manchester L.C. et al. Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science. Journal of Experimental Botany. 2012; 63(2): 577–97.
46. Thor P.J., Krolczyk G., Gil K. et al. Melatonin and serotonin effects on gastrointestinal motility. Journal of Physiology and Pharmacology. 2007; 58: 97–103.
47. Tung Y., Chiang P., Chen Y. et al. Effects of Melatonin on Lipid Metabolism and Circulating Irisin in Sprague-Dawley Rats with Diet-Induced Obesity. Molecules. 2020; 25(15): 3329.
48. Valdes-Tovar M., Estrada-Reyes R., Solis-Chagoyan H. et al. Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. British Journal of Pharmacology. 2018; 175 (16): 3200–8.
49. Venegas C., Garcia J.A., Escames G. et al. Extrapineal melatonin: analysis of its subcellular distribution and daily fluctuations. Journal of Pineal Research. 2012; 52(2): 217–27.
50. Won E., Na K., Kim Y. Associations between Melatonin, Neuroinflammation, and Brain Alterations in Depression. International Journal of Molecular Sciences. 2022; 23 (1): 305.
51. Zhang R., Ni L., Di X. et al. Potential Role of Melatonin as an Adjuvant for Atherosclerotic Carotid Arterial Stenosis. Molecules. 2021; 26 (4).
52. Zhang Y., Liu X., Bai X. et al. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. J Pineal Res. 2018; 64 (2).