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REVIEW ARTICLE

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Melatonin and age-related cardiovascular diseases

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Abstract

The pineal gland is a neuroendocrine gland closely related to human aging. Melatonin is a kind of indole neuroendocrine hormone secreted by the pineal gland, which is essential for maintaining physiological function. Many researches found that melatonin plays a key role in anti-aging-related cardiovascular diseases. In this paper, the latest advances in the study of melatonin and aging-related cardiovascular diseases are reviewed, and their related physiological functions and mechanisms are discussed.

KEYWORDS
aging, cardiovascular diseases, melatonin, pineal gland

1 | INTRODUCTION

With an increase in the average life expectancy, the world will irreversibly enter an aging society. As the largest developing country, China is entering a period of high-speed aging. Cardiovascular disease and its risk factors are one of the main causes of death, accounting for nearly one-third of the world's deaths,[1] and the incidence of cardiovascular disease increased significantly with age. Aging is the phenomenon of natural decline in the structure and physiological function of the human body. It involves the immunoregulatory system and the progressive decline of the endocrine and nervous system, leading to an imbalance of its own homeostasis. Among so many mechanisms of aging is the free radical-induced aging hypothesis that the pineal gland and its secreted melatonin play an important role. This article reviews the recent domestic and international advances in the researches about melatonin and aging-related cardiovascular diseases, with the intention to provide theoretical basis and research ideas for further revealing melatonin and age-related cardiovascular diseases.

2 | PINEAL GLAND AND AGING

The pineal gland is a multifunctional organ that is closely related to aging process and is considered to be the initial factor of aging. The morphology and function of the pineal gland are closely related to age. With age, the glands will gradually appear calcified, and the size of it will decrease. This will then lead to a reduction in the synthesis and secretion of melatonin and a disorder in the biological rhythm. As a consequence, the gland's internal regulatory function and coordination ability declined, and showed the gradual degenerative changes in the gland, manifested as aging. Pierpoli transplanted the pineal gland of 3- to 4-month-old rats into the thymus of 16- to 22-month-old rats, which demonstrated that the survival time of the rats[2] prolonged significantly.[2] The experiments on animal showed that the pinealectomy shortens the lifespan of rats. Once the gland is removed, there would be a series of aginglike symptoms in rats, such as elevated blood cholesterol, high blood pressure, skin pigment deposition and reduced anticancer capacity.[3] In the gland transplantation experiment, it is shown that the aged rats receiving the pineal glands of the young rats had increased activity, thickened and shiny fur, strong muscles, and a longer survival time than the control group, and were less susceptible to infection. On the contrary, the young rats receiving pineal glands in aged rats developed cataracts, decreased activity, atrophy of the spirit, muscle relaxation, and symptoms such as progressive leukoplakia. Therefore, the pineal gland plays an important role in the aging process.

3 | THE PHYSIOLOGICAL FUNCTION AND MECHANISM OF MELATONIN

Melatonin (*N*-acetyl-5-methoxytryptamine), secreted mainly by the pineal gland in mammals, is a potent free radical scavenger widely

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found in the body. It is also an important enzyme in the human body that regulates redox activity.[4] The existence of melatonin in many plants,[5] in Chinese herbal medicine[6] and in single-celled organisms is also confirmed.[7,8] The secretion of melatonin has a circadian rhythm, in which light has the most obvious effect on its rhythm. It can influence the synthesis of melatonin in the pineal gland by acting on mammalian eyes and can also directly affect the lower levels of vertebrates and birds. The pineal gland exerts an influence on its rhythm of secretion, and exposure to light at night can rapidly inhibit the synthesis of melatonin. In addition to the pineal body and the retina, many organs (gastrointestinal tract, testis, thymus, bone marrow, cochlea, and harderian gland) or cells (immune system cells, astrocytes, and glial cells) can also have the capacity of synthesizing melatonin.[9,10] Melatonin released from these sites is less or only released on specific stimuli (eg, postprandial gastrointestinal motility).[11,12] In addition to melatonin in the pineal gland and circulation, melatonin in the pineal tissue should not be ignored.[12]

Once melatonin is synthesized, it is not stored in the pineal gland but diffused in capillary blood and cerebrospinal fluid.[13] The junction of the pineal tissue does not prevent melatonin from spreading in the cerebrospinal fluid. The same amount of cerebrospinal fluid reaches the third ventricle earlier than the lateral ventricle. Since melatonin is easy to pass through all biofilms, its level is higher in brain than any other tissues in the body.[14] In fact, the level of melatonin from pineal recess in the third ventricle cerebrospinal fluid is 5-10 times higher than that in the blood at the same time.[15] However, the concentration of melatonin in most ventricles and spinal canal is relatively low. Since the level of melatonin is quite different between cerebrospinal fluid and brain tissue, it is not clear that melatonin is absorbed or rapidly metabolized by brain tissue.[16]

Melatonin participates in many biological processes of the body through two G protein-coupled membrane receptors, the melatonin receptor 1 (MT1) and melatonin receptor 2, such as controlling the biological cycle rhythm, regulating sleep, immunity, blood pressure, adjusting human mood and behavior, protecting the retina from injury, clearing oxygen free radicals, inhibiting tumor growth, and so on. Therefore, MT1 and MT2 are very essential to maintain the normal physiological function of the body.[17] MT1 and MT2 exist in cell membranes as dimers and heterodimers. As a representative of the G protein-coupled receptor family, they eventually lead to specific physiological effects through many signal transduction mechanisms.[17]

In addition to binding the M1 and M2 receptors, melatonin also has an affinity for another binding site, originally thought to be membrane-bound receptor (MT3), but was eventually identified as a quinone reductase (QR2 or NQO2).[18] Anthraquinone reductase protects against oxidative stress caused by the electron transfer reaction of terpenoids. It has been reported that homogeneous QR2 promoter region in humans associated with Parkinson's disease[19] and decreased cognitive function during aging[20] However, the specific role of subform QR2 is still poorly understood.

In addition, melatonin also binds to transcription factors that are members of the retinoic acid receptor superfamily, particularly RORa splicing variants (RORa1, RORa2, and RORa isomer D) and RZRb.[21,22] Retinoic acid receptor subtypes are widely expressed in mammalian tissues, especially in lymphocytes, neutrophils, and monocytes.[21] Although the activity of these nuclear binding proteins is still controversial and they have low affinity for melatonin compared to MT1, they can be identified as nuclear receptors.[23] Electrophoretic mobility shift assay analysis showed that the upregulation of the anti-oxidase glutamylcysteine synthase involved in nuclear transcription can increase the DNA binding of melatonin and AP-1, RZR/RORa, indicating that nuclear receptors are involved.[24]

Melatonin may also act directly on cells by binding to calmodulin,[25] tubulin,[26] calreticulin, or other calcium-binding proteins.[27] These studies found that the affinity of mammalian cells for melatonin mainly depends on their binding sites to melatonin, which may be regulated by the interaction between CaM and CaM-activating enzymes.

The secretion of melatonin gradually decreases with age and decreases significantly after 50 years old. Along with this, humans show the signs of aging. Mocchegian et al[28] added melatonin to drinking water to feed mice and found that the average lifespan of the mice was 20% longer than that of the control group (6 months). It indicated that aging can be delayed by supplementing exogenous melatonin to maintain normal melatonin levels in the body. In conclusion, melatonin plays an important role in correcting circadian clock, antioxidation, immunity enhancement, antistress, and neuroendocrine regulation by binding to these receptors, thereby delaying aging.

4 | MELATONIN AND AGE-RELATED CARDIOVASCULAR DISEASES

Melatonin may protect the cardiovascular system[29-31] not only via its direct free radical scavenging and indirect antioxidant activity[32] but also its obvious anti-inflammatory properties.[33] It regulates blood pressure[31,34] and has a significant anti-atherosclerotic effect.[29,31] The essential structure of synthetic melatonin may exist in the heart. Sánchez-Hidalgo[35,36] found that rat myocardial tissue had the key synthetases of age-associated melatonin, namely aryl *N*-acetyltransferase (AA-NAT) and hydroxyanthraquinone-*O*-methyltransferase (HIOMT). The activity of NAT enzyme showed little change with increasing age, while the function of HIOMT decreased significantly and participated in the physiological aging process of the heart. What's more, human cardiovascular system contains melatonin receptors, mainly located in the ventricular wall, coronary arteries, aorta, and peripheral arteries.[37]

4.1 | Melatonin and human aging

In recent years, humans have changed natural light periods by increasing nighttime light and spending most of their time indoors. These changed lifestyles cause circadian rhythm disorders, including the melatonin rhythm disorders.[38] Epidemiological studies indicate that interruption of circadian rhythm can increase the incidence of

heart disease, diabetes, premature aging, cognitive and affective disorders, obesity, and some types of cancer.[39] Moreover, many studies have shown that there is a close relationship between the decrease in melatonin levels in the circulation and severe circadian rhythm-related cardiovascular events including ischemic heart disease, acute myocardial infarction, and cardiac X syndrome.[40-44] Domínguez-Rodríguez[45] found that the area of infarct after percutaneous coronary intervention was significantly narrowed in patients with ST-segment elevation myocardial infarction (STEMI) after melatonin treatment. The changes in the circadian rhythm of melatonin may affect light/dark variation, thus producing the endogenous soluble vascular cell adhesion molecule-1 in the patients with STEMI.[46] Interestingly, VCAM-1 was expressed in the coronary artery of the patients with fibrous atherosclerotic lesions after 20-70% heart transplantation, while it was rarely expressed in normal coronary arteries.[47] Adhesion molecules are also elevated in acute myocardial infarction[47] as well as unstable angina pectoris, probably due to the activation of endothelial cells and platelets after myocardial ischemia.[46] Notably, melatonin can reduce the adhesion molecules that inhibit migration and edema of endothelial cells.[48]

As an antioxidant and anti-inflammatory agent, melatonin seems to play an important role in protecting various cardiovascular functions.[42,49] Gubin[50] studied the effect of oral administration of 1.5 mg of melatonin on elderly hypertensive volunteers (63-91 years old). Some drugs, especially nonselective beta-blockers, may help to obtain the ultimate benefits in clinical trials. However, the recent studies show that a long-term use of melatonin makes no significant difference in the response to insomnia and blood pressure in the elderly patients treated with beta-blockers or placebo.[50,51] Meanwhile, changing medications or treatments during the study may cause more problems. In this clinical trial, oral melatonin treatment for 2 weeks had significant antihypertensive effects on both systolic and diastolic blood pressure. Gubin et al speculated that melatonin binds to melatonin receptors around the artery, leading to vasodilation along with a decrease in arterial blood pressure. In addition, the independent role of the receptor cannot be ruled out because melatonin cannot be used only as a direct diastolic factor, and it plays an antihypertensive role via the influence on the suprachiasmatic nucleus.[50,52,53] Due to the insufficient production of exogenous melatonin to supplement self-indole amines, older people can gain more benefits from it. In addition, melatonin may provide a new strategy for the treatment of hypertension by improving the circadian rhythm of pacemakers.[50]

Melatonin can prevent injury after ischemia-reperfusion and reduce the development of ventricular arrhythmia and infarction.[31,54,55] Melatonin can prevent ventricular arrhythmias in the process of ischemia-reperfusion by regulating excess lipid peroxidation and nitration stress.[51,56] Dwaich et al[57] found that in patients receiving selective coronary artery bypass surgery, melatonin can improve myocardial ischemia-reperfusion injury by interfering with oxidative stress, inflammation, and apoptosis markers in a dose-dependent manner (10 mg vs 20 mg daily). Melatonin can significantly reduce the arrhythmia score and shorten the rhythm duration, but it also reduces the recovery of postischemic contractility.[55]

4.2 | Melatonin and animal aging

Animal studies have shown that the dual effect of melatonin on blood vessels depends on the type of specific G protein-coupled activated melatonin membrane receptors, combined with MT1 promotes vasoconstriction and promotes vascular relaxation after binding to MT2.[53] Melatonin also plays a role in binding to the retinoid's small receptor/retinol Z nuclear receptor (ROR/RZR) family.[53] Therefore, melatonin-induced cardioprotection may depend on the receptor and may not depend on the receptor or even on the adrenergic effect.[58]

It has been reported that exogenous melatonin lowers blood pressure through a variety of mechanisms, including direct hypothalamic effects, and may also diastole smooth muscle walls by lowering catecholamine levels through its antioxidant effects.[40] In the spontaneously hypertensive rats, the antioxidation of melatonin can reduce their nocturnal hypertension, inflammatory cytokines, left ventricular hypertrophy, and remodeling.[59,60] Rezzani et al[61] found that melatonin treatment can improve vascular function, and reduce arterial remodeling and intimal infiltration in spontaneous hypertensive rats, as well as restore vasoactive factors and collagen fiber production. Melatonin can improve recovery from heart, kidney, and brain disease in renovascular hypertensive rats, which indicates that melatonin can be used in the prevention and treatment of oxidative stress damage caused by hypertension.[30]

Melatonin can reduce oxidative stress in the heart of hypoxia rats and increase the expression of a variety of antioxidant enzymes, which can reduce the level of chronic intermittent hypoxia induced by oxidative stress at the cell level.[56] In addition, melatonin alleviates myocardial fibrosis and inhibits the activation of nuclear factor-kappa beta (NF-kappa beta) in ischemic and anoxic rats significantly by reducing the mRNA expression of cardiac hypertrophy-related genes, such as tumor growth factor-beta (TGF-beta).[56] Due to the formation of excessive fibrous connective tissue, especially type I collagen, myocardial fibrosis is evident in pinealectomized rats.[62] Myocardial fibrosis caused by myocardial cell necrosis and inflammation is always accompanied by cardiac damage, resulting in hypertrophy of cardiac myocytes. In vivo, melatonin can also reduce the accumulation of type I collagen and fibrosis markers, such as TGF-beta in cardiac fibroblasts.[63]

The antifibrotic effect of melatonin may be connected with its antioxidant properties, and its most beneficial effect at the heart level may depend on the role of mitochondrial bioenergetics. Melatonin exerts antioxidant effects through various mechanisms, including electron transport chain dysfunction, electron leakage, and mitochondrial oxidative damage, and its direct effect on the opening of mitochondrial permeability transition pores (MPTP).[64] The myocardial mitochondria of old rats are more easily released by Ca^{2+} activation of MPTP and cytochrome *C*, which probably is of great significance to the necrosis associated with myocardial ischemia-reperfusion injury, death of apoptotic cardiomyocytes, and other age-related cardiovascular diseases. Melatonin may help to improve these age-related cardiovascular changes,[65] which reduces the irregularity of the endothelial cells and their nuclei, the differentiation of the basement membrane and adjacent cells to the endothelial cells and the fragmentation of the elastic

fibers.[66] In these cases, the effect of melatonin depends on its ability to scavenge active oxygen to destroy a unique phospholipid in the mitochondrial membrane, which is an important factor in the regulation of more mitochondrial bioenergy.

Due to its serious complications, poor prognosis, and death risk, myocardial tissue loss is one of the main reasons for the poor recovery of ischemic heart disease. After hypoxia, blood flows into the heart, which has additional negative effects on cardiac muscle cells and cardiac physiology. This ischemia-reperfusion injury can lead to myocardial dysfunction and irreversible damage, characterized by excessive myocardial contracture, lower left ventricular pressure, and increased incidence of ventricular fibrillation.[65] Therefore, it is crucial to find a therapeutic strategy for myocardial injury during hypoxia/reoxygenation. Sahna et al[67] reported that the size of myocardial infarct area produced by ischemia-reperfusion after pinealectomy was significantly increased, while exogenous melatonin could attenuate this significant increase, indicating that physiological concentrations of melatonin are important in protecting the heart from ischemia-reperfusion-induced myocardial infarction. In addition, the authors demonstrated that the administration of melatonin immediately before reperfusion also has protective effects on the tissue damage which is induced by pineal gland-induced ischemia-reperfusion in rats, whereas most drugs are only used to prevent ischemia-reperfusion injury before ischemia.

Observing ischemia-reperfusion injury in rat's heart, melatonin can reduce lipid peroxidation and prevent the loss of mitochondrial complex I and III activity. Inhibitory melatonin on mitochondrial phospholipid peroxidation during reperfusion is thought to take effect through cardiolipin inhibition of the main components of the heart cardiolipin linoleic acid fatty acid oxidation.[64] Some studies about the heart of aged rats have shown that melatonin protects the heart from ischemia-reperfusion injury and necrosis, as well as inhibiting the mitochondrial permeability transition pore opening calcium channel, which is a key event of cardiac reperfusion injury. It is also a potential target for myocardial protection.[56]

Since melatonin protects endothelial cells from injury, vasoconstriction, platelet aggregation, leukocyte infiltration, and inflammatory processes, medical treatment focused on it improves hemodynamics apparently and helps prevent injury caused by ischemia-reperfusion.[65] A suitable model of isolated rat heart was used to determine the direct effect of various substances on the heart. Tan et al[68] found that both ventricular premature beat and ventricular fibrillation were significantly reduced after reopening of the blood vessel if melatonin was injected during coronary artery occlusion. Sallinen et al[69] confirmed that the ligation of the anterior descending coronary artery in rats increased the synthesis of endogenous melatonin and altered the expression levels of MT1 and MT2 receptors in the heart. This research suggests that cardiac ischemia-reperfusion injury results in a compensatory increase in melatonin, probably to protect the heart from myocardial infarction. Nduhirabandi et al[70] demonstrated that melatonin protects rat pre-ischemic heart by activating mitochondrial STAT3 against ischemic injury. In contrast, the simultaneous use of melatonin and TLR4 inhibitors attenuates the protective effect of guanamine on the heart. Diez et al[71] found that melatonin antiarrhythmic effects can be maintained until the onset of reperfusion injury, which is related to the delay in recovery caused by a shortening of the action potential. This mechanism can reduce Ca^{2+} overload at the onset of reperfusion and help reduce ventricular fibrillation and other forms of sustained arrhythmias, probably through melatonin's anti-adrenergic effects.

Melatonin treatment significantly reduces infarct area and improves cardiac function recovery during reperfusion, which is related to dose and time.[65] In some cases, melatonin at a dose of 10 mg/kg/d showed a significant effect on inflammation, oxidative stress, and apoptotic pathways compared with the low-dose group (1 mg/kg/d). However, it has also been demonstrated that low doses protect against age-related changes in heart disease of aging animal models. Forman et al observed that administration of 1 mg/kg/d of melatonin can delay and restore several processes associated with aging in rats.[72] Age-related inflammation and oxidative stress can be observed in these accelerated aging animals.[73] In a rat model of myocardial ischemia-reperfusion injury, 5 mg/kg of melatonin was more effective than 1 mg/kg, and 0.5 mg/kg had no significant effect. To confirm the results, Lochner et al[74] found that cardiac perfusion buffers containing 50 μmol/L melatonin exerted the greatest protection against cardiac output, peak systolic pressure, and work performance compared to untreated hearts, whereas concentrations of 25 μm melatonin are ineffective. In another 10-minute study of coronary artery ligation, 10 μmol/L melatonin reduced ventricular premature beats and ventricular fibrillation.[68]

In conclusion, melatonin is worthy of attention as a drug that potentially protects the heart, especially considering its low toxicity and cheapness and its advantages over other antioxidants in improving oxygen and reoxygenation injury.[68]

4.3 | Melatonin and cell aging

Melatonin has a strong protective effect on the changes of mitochondrial energy metabolism associated with ischemia-reperfusion induced by lipid peroxide production and nitrosation.[64,65] Mitochondria are thought to be involved in the process of cell death following ischemia-reperfusion. These are important targets for melatonin protection interventions. Melatonin reduces mitochondrial oxidative damage through the Janus kinase 2/signal transduction and transcription activator 3 (JAK2/STAT3) pathway to reduce ischemia-reperfusion injury.[75] The JAK2/STAT3 signaling pathway is involved in the regulation of cell growth and intercellular communication, signal transduction in the cytoplasm, and gene transcription in the nucleus. In recent years, many studies have confirmed that the ischemia-reperfusion cell model can activate the JAK2/STAT3 signaling pathway and subsequently transmit a survival signal to the myocardium,[76] which is important for reducing ischemia-reperfusion injury.[75] Melatonin induces JAK2/STAT3 signaling pathway upregulation, along with anti-apoptotic factor Bcl-2 upregulation and pro-apoptotic factor BAX downregulation, thereby prolonging the heart's survival.[65] Heart progenitor cells are a promising tool for the

treatment of aging-related cardiovascular diseases. However, due to the pathological stimuli, the senescence of myocardium progenitors leads to a decline in their function and regeneration. Notably, melatonin binds to its membrane receptors to fight premature aging caused by oxidative stress in the myocardium progenitor cell through the H19/miR-675/USP10 pathway.[77]

The two main cells of the blood vessel wall, vascular smooth muscle cells and endothelial cells, which are closely related to the aging-related cardiovascular diseases, play an indispensable role in maintaining vascular structure and function stability. The literature reports that an antioxidant melatonin can restore nicotine-induced changes in vascular smooth muscle cells, inhibit the formation of neointima, and increase the expression of thrombospondin-1. This suggested that it may be an effective drug to maintain homeostasis of the blood vessel wall.[78] In human vascular endothelial cells, melatonin induces the expression of γ-glutamylcysteine synthetase and rate-limiting enzyme of glutathione synthesis, protects endothelial cells from damage caused by oxidative stress, and regulates cell proliferation.[24] Excessive concentrations of vascular endothelial growth factor (VEGF) cause angiogenesis, which results in the instability of atherosclerotic plaque. Significantly, melatonin has been reported to inhibit VEGF-induced activation of human endothelial cells and subsequent angiogenesis.[79] In addition, melatonin reduces endothelial cell apoptosis by activating the AMPK/SERCA2a signaling pathway.[80] A study on melatonin combined with atorvastatin calcium tablets for endothelial cell damage caused by inflammation and oxidative stress damage found that melatonin, rather than atorvastatin calcium tablets, reduces lipopolysaccharide-induced endothelial cell free radical production, lipid peroxidation, and interleukin-6 levels. In the presence of atorvastatin calcium tablets, the effect of melatonin can be maintained or even improved. This combination can also reduce the side effects of atorvastatin calcium tablets on endothelial cells under inflammatory and oxidative stress conditions.[81] Kostovski et al[82] found that melatonin stimulated vascular endothelial cells to secrete tissue factor pathway inhibitors but did not change their gene transcription. If melatonin increases the release of similar tissue factor pathway inhibitors in vivo, it may have clinical significance for preventing thromboembolic events.

5 | CONCLUSIONS

With the improvement of medical conditions and living standards, the aging population has increased year by year, and the incidence and mortality rate of cardiovascular diseases have also increased. It is urgent to study how to delay aging process and reduce the occurrence of cardiovascular diseases. Melatonin is involved in many biological behaviors, such as controlling the rhythm of the biological cycle, regulating sleep, immunity, blood pressure, adjusting human emotions and behaviors, protecting the retina from damage, scavenging oxygen free radicals, and inhibiting tumor growth. It is very important to maintain the normal physiological function of the body.[83] As a circadian rhythm regulator of the body, an antioxidant, an anti-inflammatory agent, and a protective agent for mitochondrial function, supplementing melatonin is beneficial for delaying aging and reducing the occurrence of cardiovascular disease in aging conditions.[84] With the deeper research on pineal gland and melatonin, it will provide new insights into delaying aging and preventing and treating senile cardiovascular diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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