Effects of melatonin on cardiovascular diseases: progress in the past year

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Purpose of review
Melatonin is a neuroendocrine hormone synthesized primarily by the pineal gland. Numerous studies have suggested that melatonin plays an important role in various cardiovascular diseases. In this article, recent progress regarding melatonin’s effects on cardiovascular diseases is reviewed.

Recent findings
In the past year, studies have focused on the mechanism of protection of melatonin on cardiovascular diseases, including myocardial ischemia-reperfusion injury, myocardial hypoxia-reoxygenation injury, pulmonary hypertension, hypertension, atherosclerosis, valvular heart diseases, and other cardiovascular diseases.

Summary
Studies have demonstrated that melatonin has significant effects on ischemia-reperfusion injury, myocardial chronic intermittent hypoxia injury, pulmonary hypertension, hypertension, valvular heart diseases, vascular diseases, and lipid metabolism. As an inexpensive and well tolerated drug, melatonin may be a new therapeutic option for cardiovascular disease.

Keywords
cardiovascular diseases, melatonin, myocardial ischemia-reperfusion injury

INTRODUCTION
Melatonin (N-acetyl-5-methoxytryptamine) is a neuroendocrine hormone, which is synthesized primarily by the pineal gland [1]. The synthesis and secretion of melatonin are regulated by light intensity [2]. It was found that melatonin functions to regulate the sleep cycle in the early study [3]. Further investigation revealed that melatonin also has antioxidant and anti-inflammatory functions [4]. It has also been shown to regulate lipid and glucose metabolism [5,6]. Importantly, recent research suggests that melatonin plays an important role in various cardiovascular diseases, including myocardial ischemia-reperfusion injury [7,8], atherosclerosis [9,10], hypertension [11,12], heart failure [13,14], and drug-induced myocardial injury [15,16]. In the past year, several studies have focused on the mechanism of the protection of melatonin on cardiovascular diseases. In this article, we review the recent progress in the understanding of melatonin’s effects on cardiovascular disease.

MELATONIN AND MYOCARDIAL ISCHEMIA-REPERFUSION INJURY
Melatonin confers profound protective effects against ischemia-reperfusion injury in various organs, including the heart [7,8], liver [17], and kidney [18]. However, the mechanisms by which it affords protection remain incompletely understood. Ghaeli et al. [19] reported that in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, administration of melatonin plus standard treatment significantly reduced the level of creatine kinase-MB compared with the control group, receiving only standard therapy. However, in a porcine closed-chest reperfusion infarct model, intracoronary or intravenous melatonin administration did not reduce myocardial reperfusion injury [20]. The
Studies have demonstrated that melatonin has significant effects on ischemia-reperfusion injury and myocardial chronic intermittent hypoxia (CIH) injury.

Studies suggest that melatonin also plays an important role in pulmonary hypertension, hypertension, vascular diseases, valvular heart diseases, and lipid metabolism.

Another study showed that melatonin significantly inhibited myocardial apoptosis during myocardial ischemia-reperfusion in rats [25]. Melatonin also preserves the structural integrity of mitochondria in myocardiocytes, promoting ATP synthesis and preserving cardiac function [25]. In a rat model of ischemia/reperfusion injury, administration of melatonin reduced infarct size by inhibiting the mitochondrial permeability transition pore [26]. In a model of diet-induced obesity utilizing Wistar rats, melatonin treatment reduced serum insulin levels, homeostatic model assessment index and myocardial infarct volume, while increasing serum adiponectin levels and activating baseline myocardial extracellular signal-regulated kinases 42/44 (ERK42/44), glycogen synthase kinase-3 beta (GSK-3β), signal transducer and activator of transcription 3 (STAT-3), and Protein Kinase B (PKB/Akt) during reperfusion [27]. In another rat model of high-fat diet-fed streptozotocin induced diabetes [28], treatment with melatonin suppressed protein kinase ribonucleic acid-like endoplasmic reticulum kinase (PERK)/eukaryotic initiation factor 2 alpha kinase (eIF2α)/activating transcription factor 4 (ATF4) signaling, reduced myocardial oxidative damage, and up-regulated SIRT1 expression. Endoplasmic reticulum stress is considered to be an important contributing factor in cardiovascular diseases [29]. Melatonin was also found to modulate endoplasmic reticulum stress by suppressing PERK/eIF2α/ATF4 signaling after ischemia reperfusion in H9C2 cardiomyocytes [28]. A recent study also implicated Toll-like receptor 4 (TLR4) signaling in the protective effects of melatonin [30]. In isolated hearts, melatonin treatment was shown to protect against ischemia/reperfusion injury through increased TLR4 signaling and also increased mitochondrial STAT-3 expression, leading to subsequent activation of the survivor activating enhancement pathway [30].

MELATONIN AND MYOCARDIAL CHRONIC INTERMITTENT HYPOXIC INJURY

Obstructive sleep apnea is associated with CIH and increases myocardial injury contributing to ischemic heart disease [31]. Yeung et al. [32] reported that melatonin protected against CIH-induced myocardial inflammation, fibrosis, and ischemia-reperfusion injury. In this study, treatment with melatonin significantly reduced the expression of inflammatory cytokines [tumor necrosis factor-α (TNF-α) and IL-6] and markers of fibrosis [PC1 and transforming growth factor β (TGFβ)]. Furthermore, melatonin treatment decreased infarct size in isolated hearts with regional ischemia reperfusion by mitigating sarcoplasmic reticulum calcium (2+) release.
Melatonin and Pulmonary Hypertension

Pulmonary hypertension is a disease characterized by elevated pulmonary arterial pressure, which leads to right ventricular hypertrophy and failure [38]. Maarman et al. [39] reported that treatment with melatonin alleviated right ventricular hypertrophy and dysfunction, and also reduced interstitial fibrosis and plasma oxidative stress in a rat model of pulmonary hypertension. Torres et al. [40] found that melatonin reduced pulmonary artery pressure and resistance and improved vasodilation of small pulmonary arteries in newborn sheep with pulmonary hypertension. In addition, melatonin increased nitric oxide bioavailability and reduced markers of pulmonary oxidative stress. Jin et al. [41] reported that melatonin attenuated hypoxic pulmonary hypertension. Chronic hypoxia elevates the ratio of the weights of the right ventricle to left ventricle plus intraventricular septum (RV/LV+S), right ventricular systolic pressures (RVSP), and median width of pulmonary arterioles. Treatment with melatonin reduced the elevation of RV/LV+S and RVSP and also inhibited pulmonary vascular remodeling. Additionally, melatonin reduced levels of hypoxia-inducible factor-1α, proliferating cell nuclear antigen, and nuclear factor-kB (NF-kB). In an in-vitro study, it was found that melatonin inhibited the proliferation of pulmonary artery smooth myocytes and reduced the expression of extracellular signal-regulated kinases1/2 (ERK1/2) and phosphorylation of Akt.

Melatonin and Vascular Diseases

Recent studies have shown that melatonin is associated with atherosclerosis [48,49]. Cheng et al. [50] reported that melatonin reduced the number and area of atheromatous plaques in a rabbit model of atherosclerosis by modulating mitogen-activated protein kinase (MAPK) pathway signal transduction. In addition to MAPK signaling, a recent study showed that melatonin decreased aortic endothelial permeability and atherosclerosis in a mouse model of diabetes by decreasing the expression of myosin light chain kinase (MLCK), myosin phosphatase-targeting subunit phosphorylation, and myosin light-chain phosphorylation. Melatonin also decreased upstream expression of extracellular signal-related kinase (ERK) and p38 [51]. Zhu et al. [52] found that micro ribonucleic acid-29b (miR-29b) promotes endothelial permeability and apoptosis in high-fat diet-fed apoE knock-out mice by down-regulating the expression of MT1, which is a melatonin receptor. Yang et al. [53] reported that...
the anti-inflammatory effects of melatonin improved cigarette smoke-induced restenosis in rat carotid arteries after balloon injury. Melatonin may improve vascular dysfunction by affecting epigenetic regulation. In mice generated with assisted reproductive technologies, treatment with melatonin resulted in decreased arterial hypertension, which was thought to be due to its effects on normalizing nitric oxide levels by preventing impaired methylation of endothelial nitric oxide synthase [54]. It was also shown that melatonin may improve macrovascular and microvascular diseases [55–58]. Melatonin administration to high-fat diet and streptozotocin-induced diabetic rats restored endothelial function and vascular responses [59].

| Table 1. The effects of melatonin on various cardiovascular diseases |
|--------------------------|----------------------------------|----------------------------------|
| **Function**             | **Factor/pathway/action**        | **References**                  |
| Melatonin and myocardial ischemia-reperfusion injury | Induce/activate | SIRT1 | [21,22*] |
|                         |                                 | NOTCH1, NICD, HES1, p-Akt/Akt ratio | [24] |
|                         |                                 | BCL-2 | [22*] |
|                         |                                 | SOD-1, HFG | [23] |
|                         |                                 | Adiponectin, ERK42/44, GSK-3β, STAT-3, PKB/Akt | [27] |
|                         |                                 | TLR4, STAT3, SAFE | [30*] |
| Reduce/inhibit          |                                 | CK-MB | [19] |
|                         |                                 | BAX | [21,22*] |
|                         |                                 | Ac-FoxO1, Ac-p53, Ac-NF-kB | [22*] |
|                         |                                 | Caspase, ROS | [23] |
|                         |                                 | Caspase-3, PTEN, | [24] |
|                         |                                 | Serum insulin, HOMA index | [27] |
|                         |                                 | PERK/eIF2α/ATF4 signaling pathway | [28*] |
| Melatonin and myocardial chronic intermittent hypoxia injury | Reduce/inhibit | TNF-α, IL-6, COX-2, PC1, TGF-β, P22, NOX2, CAT, MnSOD | [32*] |
|                         |                                 | CK, IDH, MDA | [35] |
|                         |                                 | iNOS/mtNOS, nNOS, c-mtNOS | [36] |
| Melatonin and pulmonary hypertension | Induce/activate | Nitric oxide | [41*] |
| Reduce/inhibit          |                                 | RV hypertrophy and dysfunction, interstitial fibrosis | [39] |
|                         |                                 | Pulmonary artery pressure and resistance | [40] |
|                         |                                 | RV/LV+S, RVSP, HIF-1α, PCNA, NF-κb, ERK1/2, p-Akt | [41*] |
| Melatonin and hypertension | Reduce/inhibit | Oxidative load in the LV, aorta and LV hypertrophy, LV fibrosis | [44] |
|                         |                                 | Renal oxidative stress and vascular reactivity | [45] |
| Melatonin and vascular diseases | Reduce/inhibit | Number and areas of atheromatous plaques | [50] |
|                         |                                 | MLCK, p-MYPT, p-MLC, ERK, p-38 | [51] |
|                         |                                 | eNOS | [54] |
| Melatonin and valvular heart disease | Induce/activate | bFGF, BCL-2, PDGF | [60*] |
| Reduce/inhibit          |                                 | Caspase 3, PUMA, BAX | [60*] |
| Melatonin and lipid metabolism | Reduce/inhibit | TG, LDL-C | [61,63] |
|                         |                                 | FFA | [62] |
|                         |                                 | TC, oxidized LDL-C, apoB100 | [63] |

BCL-2, B-cell lymphoma 2; bFGF, basic fibroblast growth factor; CK-MB, creatine kinase-MB; HIF-1α, hypoxia-inducible factor-1α; NICD, NOTCH1 intracellular domain; PCNA, proliferating cell nuclear antigen; PUMA, p53 upregulated modulator of apoptosis; PDGF, platelet-derived growth factor; RV/LV+S, right ventricle to left ventricle plus intraventricular septum; ROS, reactive oxygen species; SOD-1, superoxide dismutase; STAT-3, signal transducer and activator of transcription 3; TLR4, toll-like receptor 4; TGF-β, transforming growth factor β; TG, triglycerides. A summary of the mechanistic effects of melatonin on myocardial ischemia-reperfusion injury, myocardial hypoxia-reoxygenation injury, pulmonary hypertension, hypertension, and vascular diseases. [original].
MELATONIN AND VALVULAR HEART DISEASE

It has been demonstrated that melatonin reduces flow shear stress-induced bone marrow mesenchymal stem cells injury by acting on melatonin receptors and the adenosine monophosphate-activated protein kinase/acyetyl-CoA carboxylase signaling pathway [60*]. In this study, melatonin reduced the expression of caspase 3, p53 upregulated modulator of apoptosis, and BAX, while inducing the expression of basic fibroblast growth factor, TGFβ, vascular endothelial growth factor, (BCL-2), and platelet-derived growth factor [60*]. These findings suggest that targeting melatonin relating signaling in tissue-engineered heart valves may be an effective strategy in treating valvular heart disease.

MELATONIN AND LIPID METABOLISM

Early experiments showed that treatment with melatonin can improve dyslipidemia [4]. In patients with nonalcoholic fatty liver disease, treatment with melatonin (2 x 5 mg/day) for 14 months significantly reduced levels of triglycerides and LDL cholesterol (LDL-C) compared with controls treated with Essentielle [61]. Treatment with melatonin for 2 weeks significantly reduced free fatty acids compared with placebo in cigarette smokers [62]. A study on aluminum-induced toxicity in a rat model found that melatonin protected against toxic dyslipidemia by alleviating the aluminum induced increase in total cholesterol, LDL-C, triglycerides, oxidized LDL and apolipoprotein B100 [63]. In unpublished results, we have demonstrated that melatonin administration can improve lipid metabolism and reduce weight. Melatonin treatment reduced body weight, body fat, and waist circumference in obese patients with acanthosis nigricans. We also found that melatonin could decrease LDL and body weight in high-fat diet-induced non-alcoholic fatty liver disease mice. Dyslipidemia is an important risk factor of cardiovascular diseases [64], and melatonin’s beneficial effects on lipid metabolism may reduce the incidence of cardiovascular diseases.

CONCLUSION

In conclusion, studies have demonstrated that melatonin has significant effects on ischemia-reperfusion injury, myocardial CIH injury, pulmonary hypertension, hypertension, vascular diseases, valvular heart diseases, and lipid metabolism (Table 1). As an inexpensive and well tolerated drug, melatonin may be a new therapeutic option for cardiovascular disease.

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Conflicts of interest

There are no conflicts of interest.

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