Emerging role of melatonin in the alleviation of ischemic heart disease: A comprehensive review

Souradipta Chakraborty1, Razia Khatoon1, Aindrila Chattopadhyay2, Debasish Bandyopadhyay1

ABSTRACT
Melatonin, a circadian biomolecule, has potent cardioprotective properties. It exerts its effects via its well-established antioxidant properties and free-radical scavenging characteristics. This pineal-produced molecule has biological functions such as anti-apoptosis, anti-inflammation, antioxidant activity, mitochondrial protection, and controlling the production of cytokines by target cells. Melatonin also showed blood pressure lowering, normalizing lipid profiles, and anti-inflammatory characteristics. Melatonin plays critical roles in averting oxidative stress, enhancing autophagic cell repair, modulating immunological and inflammatory responses, improving mitochondrial function, and reducing endoplasmic reticulum stress in cardiomyocytes. The absence of these cardioprotective properties due to low melatonin levels may be linked to an array of cardiovascular diseases, including ischemic heart disease. As a result, melatonin administration is anticipated to have a clinically important role in managing ischemic heart disease, an assertion backed by melatonin’s low toxicity and high safety. Therefore, the evidence gathered in this review should provide comprehensive information on melatonin’s effect on cardioprotection and, perhaps, contribute to the planning of future experimental studies.

Keywords: Melatonin, Ischemic heart disease, Oxidative stress, Apoptosis, Cardioprotection.

INTRODUCTION
Cardiovascular disorders (CVDs) account for nearly one-third of all fatalities worldwide.1 It comprises heart failure, hypertensive heart disease, coronary artery disease, angina, myocardial infarction, congenital heart disease, valvulopathy, aortic aneurysm, venous thrombosis, carditis, rheumatic heart disease, peripheral vascular disease, and thromboembolic disease.2-5

Ischemic heart disease (IHD), also called coronary artery disease (CAD) or coronary heart disease (CHD), refers to cardiac disorders characterized by constricted coronary arteries, which distribute blood to the cardiac muscle.6 It contributes significantly to the disease burden in developing nations and is the leading cause of death in developed countries.7,8 If not diagnosed or treated, the condition will progress to ischemic heart failure (IHF), a condition defined by weak myocardium, and decreased cardiac output.9 Furthermore, it can also significantly worsen health conditions, reduce productivity and increase healthcare costs.9

Considering the pathophysiology of cardiovascular disorders, effective therapeutic interventions, and preventive measures will decrease the onset and progression of these diseases.10 Despite successful animal studies, cardioprotection has proven difficult to translate into clinical practice.11 Many pharmaceutical interventions have failed or produced inconsistent results.12

The pineal gland hormone, melatonin (N-acetyl-S-methoxy tryptamine), is a phylogenetically old molecule and a metabolite of serotonin.13 A receptor-dependent signaling pathway mediates its direct effects, and its indirect effects are mediated by its ability to scavenge free radicals.14,15 Melatonin functions as a natural synchronizer of seasonal and circadian rhythms to influence sleep patterns.16,17 The biological activities of melatonin also include antioxidant, anti-inflammatory, immunomodulatory, anti-excitatory, metabolic, and vasomotor properties.18,19 Studies showed that patients with ischemic heart disease have impaired nocturnal melatonin secretion.20,21

This review explores the current information available on ischemic heart disease and the potential therapeutic function of melatonin in alleviating such a dire disease and elevating the quality of life in populations suffering from IHD.

Ischemic Heart Disease
CAD is defined as the formation of atherosclerotic plaques within the coronary artery walls, which results in flow-limiting, obstructive lesions.22 The interruption of coronary flow results in myocardial ischemia, which is characterized clinically by discomfort or chest pain, breathlessness, reduced exercise tolerance, left ventricular dysfunction, arrhythmias, and eventually death.22 The onset and pathophysiology of IHD...
Cardioprotective properties of melatonin in the management of ischemic heart disease

determine whether it manifests as acute coronary syndromes or chronic stable angina; the latter is also known as chronic coronary syndromes. Acute coronary syndromes are characterized by abrupt limitation of coronary flow caused by acute reduction or occlusion of the vascular lumen, which is caused primarily by thrombosis superimposed on an atherosclerotic plaque, resulting in the initiation of ischemia leading to myocardial damage. Chronic stable angina is a condition in which the lumen of the coronary artery is chronically decreased by large atherosclerotic lesions, limiting coronary blood flow and leading to ischemia when metabolic needs of the myocardium are momentarily elevated, i.e., demand ischemia.

The preferred conventional strategy for the treatment of stable ischemic heart disease, generally known as chronic coronary syndrome, is undefined. There are two common approaches. The conservative strategy employs evidence-based medical therapy, such as disease-modifying agents and antianginal medicines like antithrombotic, hypolipidemic, angiotensin-converting enzyme inhibitors, and renin-angiotensin-blocking agents. The intrusive technique augments guideline-based therapy with coronary angiography, followed by either coronary artery bypass grafting or percutaneous coronary intervention. Significant breakthroughs in both treatments have occurred, resulting in a balance as to which method is more superior for individuals with stable ischemic heart disease.

Pathophysiological Mechanism of Ischemic Heart Disease

The heart requires an enormous amount of energy to function properly and is supplied by adenosine triphosphate (ATP), which is produced primarily via oxidative phosphorylation. Cardiomyocytes depend entirely on oxygen to satisfy their metabolic needs. A disruption in coronary blood flow strains cardiomyocytes rapidly, resulting in necrosis and apoptosis. As a result, the hemodynamic properties of the myocardium and signal propagation are altered, which causes dysfunction of cardiac systolic and diastolic pressure, dysrhythmia as well as ventricular remodeling and changes in the electrocardiogram (ECG).

Role of ROS in ischemic heart disease

Reactive oxygen species (ROS) are byproducts of normal cellular aerobic metabolism released during oxygen reduction. ROS production from multiple sources like lipoxygenase, nicotinamide adenine dinucleotide phosphate oxidase, xanthine oxidase, nNOS (Neuronal nitric oxide synthase), eNOS (endothelial NO synthase), and iNOS (Inducible nitric oxide synthase) causes the mitochondrial capacity to be damaged and mitochondrial dysfunction to occur. Mitochondrial failure increases ROS production and oxidative stress and, hence, plays a role in the onset, development, and progression of an atherosclerotic lesion. Several studies have demonstrated that reducing ROS from cells efficiently lowers the development and progression of atherosclerotic plaques. Endothelial dysfunction and coronary artery atherosclerosis are mediated by dyslipidemia, along with an imbalance between ROS generation and enzymatic and nonenzymatic antioxidant defense systems. Besides being linked to atherosclerosis, oxidative stress can cause oxidative alteration or damage to lipids or peroxidation at the level of proteins and DNA, which can have a negative impact on the structure and functionality of the vascular system. Elevated ROS levels, enhanced expression of ROS-producing enzymes (xanthine oxidase, P47phox), reduced expression of antioxidant enzymes (heme oxygenase-1, mitochondrial aldehyde dehydrogenase, and eNOS), and a rise in markers of inflammatory responses in right atrial myocardial tissue (CCL5/RANTES and sVCAM-1) and serum have been demonstrated in patients with an increased body mass index (BMI). In atherosclerotic plaques, fatty acids, high cholesterol, and oxidative stress may promote apoptosis of macrophages and endothelial cells induced by ERS (Endoplasmic reticulum stress).

Two major transcription factors, nuclear factor erythroid 2-related factor 2 (Nrf2) and peroxisome proliferator-activated receptor-β/δ (PPARβ/δ), have been found to protect coronary blood vessels against oxidative stress. These defensive transcription factors are believed to be activated primarily by oxidative damage and inflammation. Nrf2 activates genes that encode antioxidant and detoxifying enzymes, and it indirectly counteracts the proinflammatory effects of NF-B by eliminating ROS. PPARβ/δ is mostly found in the heart and has cardioprotective properties by inhibiting the activity of various transcription factors, like NF-κB.

Apoptosis in ischemic heart disease

Definition of apoptosis could have been stated here and then the facts of cardiac cell death

Cardiac cell death may happen through a variety of mechanisms in response to myocardial ischemia. Apoptosis contributes considerably to the death of myocyte cells in acute myocardial infarction (AMI) and occurs primarily in the peri-infarcted area. Apoptosis can be induced by the release of mitochondrial cytochrome C, which triggers the intrinsic apoptotic pathway mediated by caspase. In this situation, activation of death receptors on the cell surface (e.g., tumour necrosis factor receptor 1 (TNFR1)) may also trigger apoptosis. A proinflammatory cytokine, TNF-α has several biological activities. TNF-α may trigger apoptosis in cardiomyocytes after attaching to its receptor, in accordance with an in-vitro rat study. Research on heart failure patients shows that failing human myocardium expresses large quantities of TNF-α, suggesting a function for this protein in the development of heart failure.

Studies also reveal that cardiac-specific overexpression of Bcl-2, an apoptosis inhibitor, lowers infarct size following ischemia-reperfusion (I/R) injury. This decrease in I/R injury is associated with a decrease in cardiomyocyte apoptosis. Bcl-2 expression was also investigated in the hearts of MI patients who died.
Autophagy in ischemic heart disease

Autophagy is an intracellular catabolic mechanism that eliminates damaged cytoplasmic contents like whole organelles or senescent proteins.65–67 Cellular stress, such as nutrient deficiency, mitochondrial injury, oxidative stress, and endoplasmic reticulum stress generally activates autophagy. The mammalian target of rapamycin (mTOR) functions as an autophagy inhibitor, while glycogen synthase kinase-3 beta (GSK-3) and 5′-AMP-activated kinase (AMPK) are positive regulators of the process.68,70

AMPK activation and Ras homolog enriched in brain (Rheb)/mTOR complex 1 (mTORC1) inhibition increases autophagy during acute myocardial ischemia. Autophagy activation during myocardial ischemia appears to be an adaptive response that reduces heart injury, according to numerous sources of evidence. In reality, in acute myocardial ischemia models without reperfusion, genetic suppression of autophagy via mTORC1 stimulation or AMPK inactivation contributes to heart injury.71,72

The pro-apoptotic mammalian sterile 20-like kinase 1 (MST1) also regulates autophagy during chronic ischemia injury. Maejima and colleagues were the first to establish that MST1 activation decreases myocardial autophagy whereas MST1 inhibition enhances cardiac function and decreases size of infarcts in a chronic MI model.73

Melatonin

Chemically characterized in 1959, melatonin is an amphiphilic molecule derived from tryptophan (232.2 molecular weight). It has significant antioxidant properties because of its ability to enhance the activity of antioxidant enzymes in various tissues and its free radicals scavenging capacity.74,75 Melatonin and its metabolites [N1-acetyl-N2-formyl-5-methoxyquinuramine and cyclic 3-hydroxymelatonin] are scavengers of free radicals.76 In mammals, melatonin production in the pineal gland is synchronized to the light/dark cycle by the hypothalamic suprachiasmatic nucleus (SCN).77

The receptors for melatonin are G-protein coupled receptors, such as membrane receptors type 1 (MT1, Mel1A, MTNR1A) and type 2 (MT2, Mel1B, MTNR1B), along with the retinoid-related orphan nuclear receptors RZR and RORα.74,78 In accordance with the dosage of exogenous or endogenous melatonin, melatonin acts either via receptor-independent or receptor-dependent pathways.76

Melatonin and its Cardioprotective Properties

Endogenous melatonin, in particular, plays a crucial role in a variety of CVDs and metabolic diseases that can lead to heart failure.79 Several prior investigations have looked into the effects of melatonin on the cardiovascular system.80 In a clinical study reported in 2016, Melatonin (10 and 20 mg/day) was administered orally to 45 ischemic heart disease patients before an elective coronary artery bypass graft (CABG) surgical procedure. Patients undergoing CABG surgery were shown to have decreased perioperative myocardial injury when pre-treated with melatonin for five days, compared to pre-treatment with placebo. It has been proposed that melatonin may serve better as a cardioprotective agent if it is administered before index ischemia (as in CABG surgery) rather than during reperfusion (as in STEMI (ST-segment elevation myocardial infarction)).81

Many of melatonin’s potential benefits on the cardiovascular system are due to its anti-inflammatory and antioxidant properties.82 In addition to effectively interacting with different ROS and RNS, melatonin and its metabolites
also regulate antioxidant enzymes and pro-oxidant enzymes.\textsuperscript{83,84} Free radical scavenging and antioxidant function are accomplished via two distinct pathways.\textsuperscript{85} Melatonin interacts with the MT3 receptor and functions as an antioxidant by decreasing the electron transfer events of quinones via the first pathway.\textsuperscript{86} They scavenge free radicals through the second pathway.\textsuperscript{87} It can exhibit modulatory effects on the heart and blood vessels after it binds to these receptors.\textsuperscript{14}

It also effectively reduces oxidative alterations of lipids in heart tissue.\textsuperscript{88} According to Lee et al.,\textsuperscript{89} this molecule significantly reduced the size of infarcts. They suggested that this effect may have been mediated by melatonin’s antioxidant activity as well as its ability to suppress neutrophils in cardiac tissue.

This indolamine inhibits NO and also inhibits NO from inducing iNOS and apoptosis.\textsuperscript{90-93} A study by Ortiz et al. showed that treatment with melatonin prevented iNOS (inducible nitric oxide synthase) and I-mtNOS (inducible mitochondrial nitric oxide synthase) production, restored cardiac mitochondrial homeostasis, and retained nNOS (neuronal nitric oxide synthase) and c-mtNOS (constitutive mitochondrial nitric oxide synthase) function.\textsuperscript{94}

It has also been demonstrated that several signaling pathways, including adenylate cyclase, protein kinase C (PKC), phospholipase C, guanylate cyclase, potassium channels, and phospholipase A2, regulate the downstream effects of melatonin. A few of these mediate melatonin’s anti-adrenergic effects.\textsuperscript{14,95,96}

Furthermore, melatonin may act as an effective cardiovascular system protector, reducing the likelihood of developing reperfusion injury following myocardial infarction.\textsuperscript{97} After a myocardial infarction, melatonin receptors are also crucial in lowering the risk of heart failure and cardiomyopathy.\textsuperscript{80-101} According to Yeung et al., melatonin was found to be protective against CIH-induced myocardial fibrosis, inflammation, and ischemia-reperfusion injury. Melatonin administration considerably reduced the expression of inflammatory cytokines (IL-6 and tumor necrosis factor (TNF)) as well as fibrosis markers [transforming growth factor (TGF) and PC1] in this experimental study.\textsuperscript{102} Melatonin also acts as a potentially significant metabolic regulator in pathologically impaired cardiac energy homeostasis.\textsuperscript{103}

The activation of NLRP3 results in the production of IL-1, which triggers the inflammatory cascade. Melatonin inhibits NLRP3 expression at the location of atherosclerotic plaques.\textsuperscript{104,105} The findings of Xie et al. showed that melatonin modulates autophagy-regulated apoptosis and the adenosine monophosphate-activated protein kinase pathway, resulting in reduced CIH-induced hypertrophy of the myocardium and cardiomyocyte apoptosis.\textsuperscript{106}

It enhances autophagy and reduces inflammation via downregulation of Gal-3 (galectin-3), suggesting that it could be utilized for the treatment of atherosclerosis.\textsuperscript{107} The positive effects of melatonin in IR have also been attributed to the activation of the Nrf2 pathway in a number of current experimental studies.\textsuperscript{108,109} Melatonin is known to decrease pro-inflammatory mediators and increase the production of HO-1 through the Nrf2 cascade signaling pathways, according to Aparicio-Soto et al.\textsuperscript{110}

A distinct over-action of the renin-angiotensin system also influences cardiac damage. The cardioprotective benefits of melatonin are interrupted due to a significant decrease in overall pineal melatonin levels. This, in turn, increases the overall stress scenario in the cardiovascular tissue, resulting in a vicious, never-ending cycle of stress formation. Exogenous administration of melatonin may be able to break this vicious cycle.\textsuperscript{111}

Melatonin also has electrophysiological advantages for the heart.\textsuperscript{112} According to Yeung et al., melatonin protects the myocardium from damage caused by chronic hypoxia by enhancing the handling of calcium in the sarcoplasmic reticulum (SR) of cardiomyocytes through an antioxidant mechanism.\textsuperscript{113}

Mitochondrial dysfunction has also been linked to cardiovascular disorders.\textsuperscript{114} Stabilizing mitochondrial structure and function effectively prevents injury and necrosis in cardiomyocytes.\textsuperscript{115,116} Melatonin also has mitochondrial-protective properties.\textsuperscript{117-120} Its effective free radical scavenging and antioxidant qualities help reduce the oxidative burden on mitochondria.\textsuperscript{86} Melatonin inhibits cell death while preserving mitochondrial activity.\textsuperscript{16}

**Summary and Conclusion**

Circadian rhythms have been disturbed in the present generations due to a multitude of reasons. As a result, melatonin secretion and release are disrupted. It may prove beneficial to use melatonin supplementation as a therapeutic intervention in disorders associated with stress and other external factors, including ischemic heart disease.

According to experimental findings, melatonin is one of the important components of the antioxidant defense mechanisms of an organism. Melatonin’s identification either as a direct free radical scavenger or an indirect antioxidant through its stimulating actions upon antioxidative enzymes has heightened interest in this indoleamine’s possible cardioprotective properties.
Melatonin has minimal or no negative effects and is inexpensive. Its lipophilic nature enables it to easily permeate cell membranes and reach cell compartments containing free radicals. The capacity of this molecule and its metabolites to engage in radical detoxification considerably boosts their potential to reduce oxidative damage at various levels within cells.

Despite the numerous clinical and experimental studies that support its usage, larger population-based studies are needed before recommending melatonin as part of conventional treatment for myocardial ischemia.

Melatonin alone may not be adequate; it should be combined with lifestyle changes such as a regular sleep-wake cycle, a healthy diet, measures for stress reduction, and so on. Clinical outcomes like mortality, the existence of symptoms (like angina), and possibly the duration of stay for patients administered with this molecule should also be assessed in future trials.

REFERENCES


Cardioprotective properties of melatonin in the management of ischemic heart disease

Med. 1977;297(12):661-663. DOI:10.1056/NEJM197709222971209
47. Liu Q. Lentinivirus mediated interference of Caspase-3 expression
Cardioprotective properties of melatonin in the management of ischemic heart disease


**Peer-reviewed Certification**

During the review of this manuscript, a double-blind peer-review policy has been followed. The author(s) of this manuscript received review comments from a minimum of two peer-reviewers. Author(s) submitted revised manuscript as per the comments of the assigned reviewers. On the basis of revision(s) done by the author(s) and compliance to the Reviewers’ comments on the manuscript, Editor(s) has approved the revised manuscript for final publication.