

REVIEW ARTICLE

A review of melatonin as a suitable antioxidant against myocardial ischemia–reperfusion injury and clinical heart diseases

Abstract: Cardiac tissue loss is one of the most important factors leading to the unsatisfactory recovery even after treatment of ischemic heart disease. Melatonin, a circadian molecule with marked antioxidant properties, protects against ischemia–reperfusion (IR) injury. In particular, the myocardial protection of melatonin is substantial. We initially focus on the cardioprotective effects of melatonin in myocardial IR. These studies showed how melatonin preserves the microstructure of the cardiomyocyte and reduces myocardial IR injury. Thereafter, downstream signaling pathways of melatonin were summarized including Janus kinase 2/signal transducers and activators of transcription 3, nitric oxide-synthase, and nuclear factor erythroid 2 related factor 2. Herein, we propose the clinical applications of melatonin in several ischemic heart diseases. Collectively, the information summarized in this review (based on in vitro, animal, and human studies) should serve as a comprehensive reference for the action of melatonin in cardioprotection and hopefully will contribute to the design of future experimental research.

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Introduction

Cardiac tissue loss is one of the major factors leading to the unsatisfactory recovery from ischemic heart disease because it causes serious complications, unfavorable prognosis, and death [1, 2]. Effective drug therapy is the main strategy and an important research direction for the treatment of myocardial damage during hypoxia and reoxygenation [3]. However, exogenous drugs do not achieve the desired effects, so tests of potentially beneficial endogenous substances have become a field of active investigation. Among these endogenous substances, melatonin is of great interest.

Melatonin, a circadian hormone with marked antioxidant properties [4–8], has been shown to protect against ischemia–reperfusion (IR) injury in various organs including heart [9–12], liver [13–16], brain [17–19], kidney [20], intestine [21], lung [22], and testis [23]. Moreover, numerous studies suggest that melatonin plays a significant role in

hypertension [24, 25], heart failure [12, 26], drug-induced myocardial injury [27, 28], and atherosclerosis [29, 30]. A large amount of data published by a variety of investigations has demonstrated that melatonin can effectively reduce myocardial IR injury (Table 1). In a study using a working heart model, Dobsak et al. [31] document that the treatment with melatonin caused a significant improvement of hemodynamic parameters and a reduction of post-ischemic arrhythmias during reperfusion; the ability of melatonin to correct cardiac arrhythmias was also noted by Diez et al. [32]. A review by Dominguez-Rodriguez et al. [33] suggests that melatonin plays a key role in coronary heart disease; this is consistent with observations that melatonin reduces infarct size after experimental heart attack [34]. Vazan et al. [35] reported that melatonin significantly shortened the total duration of arrhythmia resulting from IR. We recently observed that melatonin pretreatment attenuated IR injury by reducing mitochondrial oxidative

Table 1. The effects of melatonin on some experimental models of IR injury

Model	Effects of melatonin	Reference
Perfused isolated rat heart and cultured neonatal rat cardiomyocytes	Reduced IR-induced mitochondrial oxidative damage	38
Langendorff's isolated rat heart	Recovered the ischemic tolerance and decreased the sensitivity of MPTP opening	39
Human cardiomyocytes	Counteracted the mitochondrial adaptive changes	40
Langerdoff isolated perfused rat heart	Attenuated reperfusion-induced mitochondrial alterations	41
Langerdoff isolated perfused rat heart	Inhibited MPTP opening	42
Rat heart mitochondria	Counteracted both the elevated release of cytochrome c and the increased susceptibility to Ca ²⁺ -induced MPTP opening	43
Rodent	Abrogated drug-mediated damage	44
Isolated perfused rat heart	Reduced the incidence of reperfusion arrhythmias	49
Adult Sprague-Dawley rat	Preserved SERCA expression and mitigated calcium handling	50
Isolated perfused rat heart	Reduced cAMP production	51

A summary of some of the numerous reports documenting the ability of melatonin to reduce cardiac damage resulting from IR. IR, ischemia-reperfusion; MPTP, mitochondrial permeability transition pore; SERCA, SR-Ca(2+) ATPase; cAMP, cyclic adenosine monophosphate.

damage via the activation of the Janus kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3) signaling pathway [36]. Collectively, these findings attest to melatonin being an important drug in the treatment of myocardial IR injury and provide encouragement for additional work in this area.

Herein, we focus on the cardioprotective effects of melatonin in myocardial IR. We initially introduce how melatonin changes the microstructure of the cardiomyocyte and thus prevents myocardial IR injury. Thereafter, we summarize some downstream signaling pathways that melatonin influences including JAK2/STAT3, nitric oxide (NO)-synthase (NOS), and nuclear factor erythroid 2 related factor 2 (Nrf2). Finally, we show the utility of melatonin in the clinical applications in several ischemic-related heart conditions. Taken together, the information compiled in this review should serve as a comprehensive reference to stimulate additional research on the cardioprotective role of melatonin and aid in experimental studies.

Cell biological actions of melatonin in the cardiomyocyte

Melatonin treatment causes microstructural changes in the cardiomyocyte (Fig. 1), and these morphological

alterations, so far as can be determined, contribute to the cardioprotective effect of melatonin. In 2006, Sahach et al. [37] studied the effect of melatonin on the ischemic tolerance and the sensitivity of the opening of the mitochondrial permeability transition pore (MPTP) in mature rat hearts. MPTP opening is an important event in cardiomyocyte cell death that occurs during IR and, therefore, it is a potential target for cardioprotection. The authors reported that melatonin administration contributed to the rehabilitation of the heart contractile function of the isolated heart during reperfusion and reduced the sensitivity of MPTP opening to Ca²⁺. These data suggested that the protective effect of melatonin on MPTP opening may be used to correct cardiac dysfunction during aging. Giacomo and Antonio [38] also demonstrated that melatonin plays a role in the mitochondrial adaptive changes and that cytochrome c (cyt c) is a significant mediator of this process. Almost a decade earlier, Petrosillo et al. [39] observed that reperfusion of the ischemic heart significantly altered several mitochondrial parameters, while melatonin treatment had a strong protective effect by attenuating these perturbations. The beneficial actions of melatonin in these situations appear to be due, at least in part, to melatonin's ability to limit reactive oxygen species (ROS) damage to cardiolipin, which plays a pivotal role in mitochondrial bioenergetics. The prevention of mitochondrial dysfunction was associated with an improvement in the postischemic hemodynamic function of the heart. In addition to cardiolipin, melatonin also had a strong protective effect against oxidative alterations to complex I and III in isolated mitochondria. In a later study, Petrosillo et al. [40] confirmed that melatonin protects the heart from reperfusion injury by inhibiting MPTP opening, most likely via the prevention of cardiolipin peroxidation. Most recently, this same group found that mitochondria from aged rats displayed an increased susceptibility to Ca²⁺-induced MPTP opening, which was associated with an elevated release of cyt c; melatonin treatment counteracted both of these processes [41]. These results emphasize that melatonin-induced mitochondrial adaptive changes are likely of great value for the cardioprotective actions of the indoleamine.

Studies have shown that increased levels of ROS, alterations in NOS, and elevated migration of neutrophils into the ischemic tissue play important roles in the pathophysiology of myocardial IR injury. There is little doubt that melatonin's cardioprotective properties relate its free radical scavenging activity. Melatonin and its metabolites efficiently interact with various ROS and reactive nitrogen species, and additionally they upregulate antioxidant enzymes and downregulate pro-oxidant enzymes [7, 42–45]. Reiter et al. [46] reported that, based on studies in rodents, melatonin, due to its multiple radical scavenging actions, is highly effective in abrogating drug-mediated damage to the heart.

Sahna et al. [47] examined the role of myeloperoxidase (MPO) activity in melatonin-induced cardioprotection. They found that L-NAME (a NOS inhibitor) treatment in nonischemic animals increased blood pressure and lipid peroxidation and depressed glutathione (GSH) levels in the myocardial tissue when compared to the non-L-NAME-treated animals. Melatonin reversed the L-NAME-induced

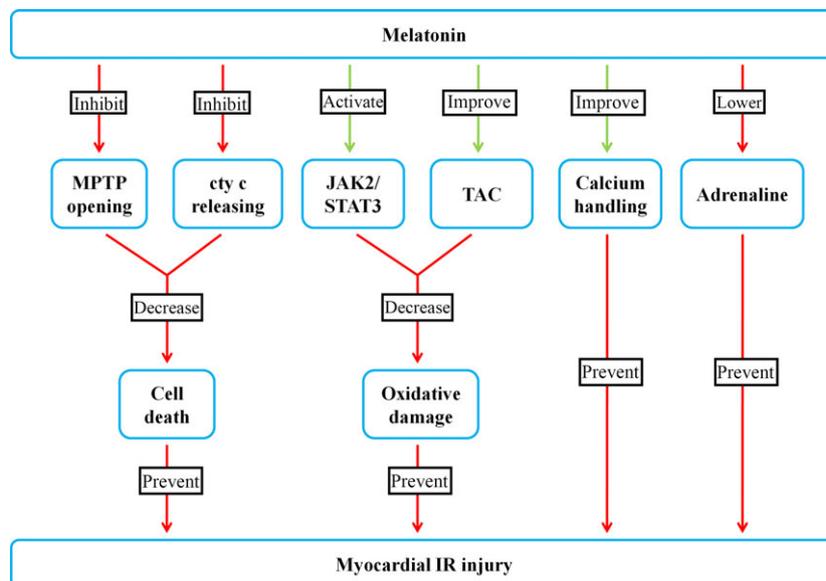


Fig. 1. Cell biological pathways by which melatonin is presumed to protect the cardiomyocyte from ischemia–reperfusion (IR) injury. MPTP, mitochondrial permeability transition pore; cyt c, cytochrome c; JAK2, Janus kinase 2; STAT3, signal transducers and activators of transcription 3; TAC, total antioxidant capacity.

blood pressure elevation and oxidative changes. Cardiac IR also increased malondialdehyde (MDA) levels and MPO activity and lowered GSH concentrations compared with the nonischemic animals. While L-NAME treatment did not change IR-induced MDA or GSH levels compared with the ischemic control animals, MPO activity was significantly higher than in the control ischemic hearts. MDA levels and MPO activity resulting from the ischemic injury were significantly lowered after melatonin treatment. These data indicate that neutrophil migration plays an important role in the development of ischemic injury in hypertensive rats. Chen et al. [48], however, demonstrated that the cardioprotective function of melatonin is independent of GSH peroxidase 1. We recently observed that melatonin pretreatment attenuated IR injury by reducing mitochondrial oxidative damage via an activation of the JAK2/STAT3 signaling pathway [36]. The published results collectively leave little doubt that the antioxidant actions of melatonin play a crucial role in its cardioprotective actions, and this property may have great clinical value for the prevention of myocardial IRI.

Electrophysiologically, the heart also benefits from melatonin [49]. Yeung et al. [50] suggested that melatonin is cardioprotective against chronic hypoxia-induced myocardial injury because it improves calcium handling in the sarcoplasmic reticulum (SR) of cardiomyocytes via an antioxidant mechanism. Furthermore, Genade et al. [51] showed that melatonin-induced cardioprotection may be receptor dependent and that its anti-adrenergic actions, mediated by NOS and guanylyl cyclase activation, are important contributors to its ability to forestall molecular damage in the cardiomyocyte due to IR.

Downstream signaling pathways of melatonin

Studies from several sources indicate that melatonin exerts cardioprotection via some downstream signaling pathways including JAK2/STAT3, NOS, and Nrf2. A brief review of this evidence follows (Fig. 2).

JAK2/STAT3

The JAK/STAT pathway is the signaling target of a number of pro-inflammatory cytokines including interleukin (IL)-6, which plays an important role in IR damage. To date, four mammalian JAKs (JAK1, 2, 3, and Tyk2) and seven mammalian STATs (STAT1, 2, 3, 4, 5a, 5b, and 6) have been identified [52–54]. JAK2/STAT3 signaling is a highly evolutionarily conserved pathway that is involved in growth and development; additionally, it controls communication among cells, signaling transduction in the cytoplasm, and gene transcription in the nucleus [55]. Recently, it is confirmed that the JAK2/STAT3 signaling pathway is hyperactivated in cellular and animal models of IR injury in a number of organs, including models of myocardial IR injury; this supports an important role of this signaling pathway in cardiac damage resulting from hypoxia and reoxygenation [42]. Hattori et al. [56] confirmed that the early phase of ischemic preconditioning potentiates JAK/STAT signaling by activating STAT3, which transmits a survival signal to the myocardium. Tian et al. [57] showed that IPostC may reduce myocardial apoptosis during prolonged reperfusion via a JAK2/STAT3/Bcl2 pathway. Some cardioprotective agents, including hydrogen sulfide and fasudil, can protect the myocardium against IR injury by activating the JAK2/STAT3 survival pathway [58, 59].

In mammals, some of melatonin's actions involve two high-affinity G protein-coupled receptors, MT1 and MT2, which are widely expressed in multiple tissues and organs, including the retina [60], brain [19], and cardiovascular system [61, 62]. The link between the melatonin receptor and JAK/STAT pathway has been proven in a few studies. For example, melatonin receptor/Ga coupling is capable of triggering the production of cytokines, including IL-6; this autocrine loop may account for the subsequent phosphorylation of STAT3 at Tyr705 [63]. Luzindole, a nonselective melatonin receptor antagonist, attenuates the promotion of astroglial cell survival and STAT3 phosphorylation resulting from melatonin treatment, suggesting

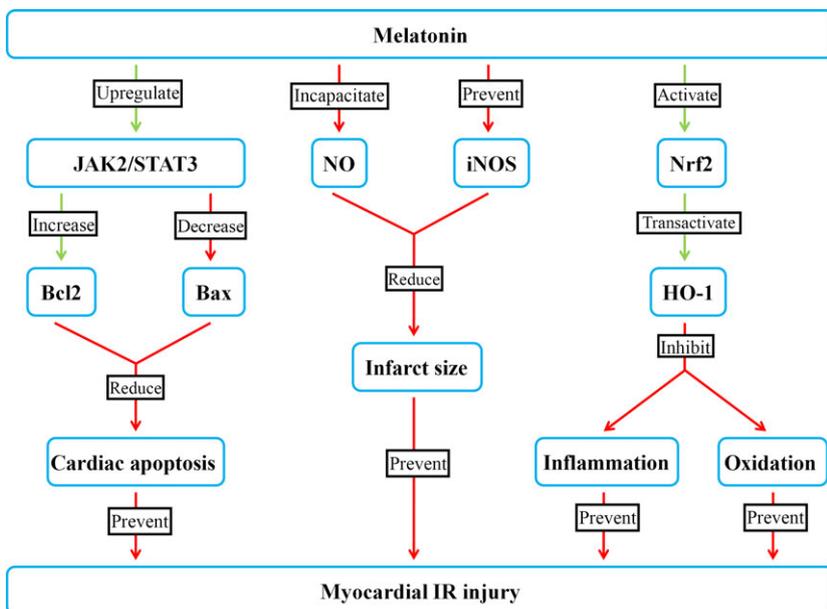


Fig. 2. Signaling pathways of melatonin when it limits ischemia–reperfusion (IR) damage to the cardiomyocyte. JAK2, Janus kinase 2; STAT3, signal transducers and activators of transcription 3; NO, nitric oxide; iNOS, inducible NO-synthase; Nrf2, nuclear factor erythroid 2 related factor 2; HO-1, heme oxygenase-1.

a direct relationship between cytoprotection and the phosphorylation of STAT and the melatonin receptors [64]. The MT1 receptor has also been shown to promote STAT3 phosphorylation in pancreatic islets [65]. These findings strongly suggest that at least some of the effects of melatonin are closely related to JAK2/STAT3 signaling. In a recent study by our group, melatonin treatment of normal hearts induced elevations in gene expression of both p-JAK2 and p-STAT3 [36]. Furthermore, melatonin pretreatment not only conferred functional cardiac recovery but also significantly increased p-JAK2 and p-STAT3 expressions, while these effects were abolished by AG490, a JAK2-specific inhibitor. Melatonin-induced upregulation of JAK2/STAT3 signaling was accompanied by an increase in the anti-apoptotic factor Bcl2 and a reduction in the pro-apoptotic factor Bax. There seems to be little doubt that the cardioprotection conferred by melatonin involves the activation of JAK2/STAT3 signaling and this may also promote anti-apoptotic processes in the heart.

NOS

NO is an important signaling molecule that is produced from L-arginine by three different synthesizing enzymes, namely, neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) [66, 67]. NO-mediated signaling influences a variety of normal physiological functions, including blood pressure and immunological defense processes [66–68]. Compared with the small amounts of nNOS- and eNOS-derived NO, an aberrant amount of NO is produced during the de novo synthesis via iNOS, which is closely associated with tissue injury or inflammatory processes, including septic shock and organ destruction in some inflammatory and autoimmune diseases [69–71].

Melatonin incapacitates NO [72, 73] and prevents NO-induced apoptosis [74] and induction of iNOS [75]. Melatonin may potentiate the effects of NOS augmentation

during beta-adrenergic stimulation. Evidence exists for beta-adrenergic mechanisms in the control of NO generation in cardiomyocytes; for example, isoproterenol has been demonstrated to upregulate NOS expression [76] and to activate eNOS via $G_{i\alpha}$, causing a rise in cGMP [77]. In a study by Genade et al. [51], forskolin caused a significant elevation in tissue cGMP, suggestive of prior NOS activation. In addition, inhibition of NOS activation with L-NAME before the onset of regional ischemia caused a significant decline in infarct size, suggesting a role for NO in the associated tissue damage. It has been noted that eNOS and nNOS attenuate the β_1/β_2 adrenergic-induced increase in inotropy and chronotropy, thereby protecting the heart against excessive stimulation by catecholamines [77, 78].

The effects of NO on IR, however, are still controversial. NOS inhibition has been reported to reduce myocardial infarct size [79] in the rabbit, improve functional recovery and reduce enzyme release [80, 81]. It has also been shown that NOS inhibitors had dual effects depending on the concentration: nonvasoactive inhibition had beneficial effects, while strong vasoactive inhibition exacerbated IR damage [81]. Taking together, the NO-mediated anti-adrenergic effects of melatonin may contribute to its cardioprotective actions in IR. Further investigations are needed to make the specific mechanisms clear.

Nrf2

Nrf2, also known as NFE2L2, is a transcription factor, which is responsible for the regulation and management of many antioxidant response genes in cells after binding with the DNA antioxidant response element (ARE) [82]. The Nrf2 pathway participates in the protection of a number of pathological developments, such as pancreatitis [83], hepatic failure [84], memory dysfunction [85], nephrotoxicity [86]. These studies all suggest that Nrf2 is a vital mediator in melatonin treatment.

Several recent experimental studies have linked the beneficial effects of melatonin in IR to Nrf2 pathway activation [86, 87]. Under normal conditions, Nrf2 is found mainly sequestered in the cytoplasm, tethered by a protein called Keap1; several stimuli can translocate Nrf2 from the cytoplasm to the nucleus. After binding to ARE, Nrf2 transactivates the expression of a group of cytoprotective enzymes including heme oxygenase-1 (HO-1), NADPH, quinone oxidoreductase-1 (NQO1), and GSH S-transferase α -1 (GST- α 1) [88]. Aparicio-Soto et al. [89] reported that melatonin reduces pro-inflammatory mediators and enhances the expression of HO-1 via the Nrf2 cascade signaling pathways. Moreover, it has been demonstrated that HO-1 plays a significant protective role against inflammatory processes and oxidative tissue injury [90–92], suggesting that melatonin may protect against myocardial IR by reducing inflammation and oxidation via the Nrf2–HO-1 pathway. Tao et al. [93] suggested a vasoprotective effect of melatonin by regulating the Keap1/Nrf2 antioxidative stress response. Nrf2–ARE pathway is considered to be a major protective pathway and may play an important role in IR injury [94]. Data accumulated in the studies of Haghjooy Javanmard et al. [95] provide preliminary data demonstrating that melatonin in patients undergoing coronary artery bypass grafting (CABG) can upregulate the activity of Nrf2–ARE pathway; this suggests that melatonin may play a significant role in the potentiation of antioxidant defense and attenuate cellular damage resulting from CABG surgery via the Nrf2 pathway. As a novel target in melatonin-induced cardioprotection against IR, the mechanisms of melatonin's effect in the activation of Nrf2 require further investigation.

Clinical administration of melatonin in heart diseases

Melatonin has been occasionally administered to patients in the clinic situation as a novel treatment strategy. Although these applications were experimental, melatonin exerted significant beneficial effects. Melatonin reportedly protects against myocardial infarction [96], hypertension [97], vascular endothelial dysfunction (VED) [29], arrhythmias [98], cardiotoxicity [10], etc. In addition, as noted above, recent research suggests that melatonin has a role in CABG [95].

Myocardial IR injury is always accompanied by myocardial infarction. Reducing the infarct size is of great importance in myocardial recovery after injury. Lee et al. [98] reported that melatonin caused a significant reduction in infarct size; they determined that the cardioprotective action of melatonin may be a result of its antioxidant activity and due to its capacity for neutrophil inhibition in myocardial tissue. In a case–control study of melatonin receptor type 1A polymorphisms and acute myocardial infarction (AMI) in a Spanish population, Samimi-Fard et al. [99] examined whether the expression of six single nucleotide polymorphisms (SNPs) of the melatonin receptor differed in AMI patients. It is the first study to report an association between a genetic polymorphism of the melatonin receptor 1A and coronary artery disease (CAD). Their findings suggested a synergistic effect

between the unfavorable genotype of the melatonin receptor 1A receptor SNP and vascular disease in this subgroup of patients.

As vasopressin and oxytocin secretion are known to be part of the neuroendocrine response to chronic heart failure evoked by myocardial infarction, Ciosek and Drobniak [96] evaluated the possible regulatory role of melatonin in the vasopressin and oxytocin release in rats with myocardial infarction. They found that coronary artery ligation-induced myocardial infarction was the basis for increased hypothalamo-neurohypophysial system activity in rats; thus, melatonin played an inhibitory neuromodulatory role on vasopressin and oxytocin release under these conditions. They also observed that myocardial infarction induced in pinealectomized rats was characterized by an inversion of the neurohumoral response pattern with respect to inhibited vasopressin release, while melatonin stimulated vasopressin (but decreased oxytocin) release in pinealectomized myocardial infarcted rats.

Dominguez-Rodriguez et al. [100] reported a reduced nocturnal elevation of melatonin in AMI patients. Their data showed that AMI is associated with a nocturnal serum melatonin deficit as well as elevated oxidative stress, suggesting that melatonin is, at least in part, depleted during the dark phase which enhances free radical damage resulting from the infarction. In another report, the same authors reported that the circulating ischemia-modified albumin is negatively correlated with melatonin levels in ST elevation myocardial infarction patients [101]. This indicates that melatonin might exert a beneficial effect as a radical scavenger in a human model of myocardial IR. They have demonstrated that melatonin attenuates molecular and cellular damage resulting from myocardial IR in which destructive free radicals are involved, thus protecting against the associated molecular destruction [102]. Moreover, they observed that patients with acute coronary syndrome and in those after myocardial infarction have reduced nighttime melatonin levels and 6-sulfatoxymelatonin urinary excretion [103]. These alterations might translate to increased cardiovascular risk observed in AMI patients who suffer with low melatonin levels. Also, a mutation in melatonin receptors might augment the risk for AMI. Because of these findings, it is expected that melatonin administration could play a clinically relevant role in the pharmacotherapy of ischemic heart disease, an assumption supported by the low toxicity and high safety of melatonin.

Several pathological conditions, including hypertension, atherosclerosis, diabetes, IR and nicotine-induced vasculopathy, are associated with VED characterized by altered secretory output of endothelial cells [104]. VED and inflammation contribute to the initiation and progression of atherosclerosis. Rodella et al. [104] reported that melatonin improved vascular function in experimental hypertension, reducing intimal infiltration and restoring NO production. Melatonin improved the NO pathway also in animal models of diabetes and prevented NO downregulation and adhesive molecule upregulation in nicotine-induced vasculopathy. The protection against endothelial damage, vasoconstriction, platelet aggregation, and leukocyte infiltration would likely contribute to the beneficial

effects of melatonin against the damage caused by IR. At the molecular level, Hu et al. [29] noted for the first time that suppression of the toll-like receptor (TLR) 4/nuclear factor κ B (NF- κ B) system in blood vessels with atherosclerotic damage is important for the protective effects of melatonin; they also found the indoleamine ameliorates lipid metabolism, VED, and inflammation and inhibits the progression of atherosclerosis in high-fat-fed rabbits. This group also observed melatonin reduced cyclophilin A (CyPA) mediated inflammatory cell extravasation and oxidative stress [105]; the authors suggested that melatonin treatment may represent a new atheroprotective approach that contributes to a reduction in the early phase of atherosclerosis, which involves the rolling of monocytes, their passage into the subendothelial space and inhibition of CyPA expression. Such findings support the conclusion that melatonin may protect against atherosclerosis.

CAD is a complex IR-induced disease, and experimentally, melatonin has been shown to reduce CAD. Incidence of sudden cardiac death is highest in the morning hours. It has been shown that melatonin levels are low at these times and with CAD patients even having lower values than normal individuals. With these observations as a basis, it would be of value to test melatonin for its possible inhibitory actions on IR [33, 106]. In a study aimed at assessing the effectiveness of melatonin monotherapy (MT) or combined treatment (CT) in aged patients with arterial hypertension and cardiovascular heart disease (CHD), Zaslavskaja et al. [107] reported that inclusion of melatonin in the CT for CHD produced marked anti-ischemic and anti-anginal effects and normalized oxidant/antioxidant balance. During and after CABG, oxidative stress is commonly measured. Finding an effective way to improve antioxidant response is important in CABG surgery. Guo et al. [108] pointed out that melatonin and cortisol secretion are disrupted during cardiac surgery and in the immediate postoperative period, suggesting that melatonin may have a role in CABG. That high plasma levels of melatonin may be directly related to low levels of IR markers was suggested by Sokullu et al. [109]; moreover, they proposed that melatonin may be protective against IR in CABG. This is consistent with preliminary data suggesting that melatonin may have a significant role in the potentiation of the antioxidant defense and attenuate cellular damage resulting from CABG surgery [95]; this beneficial action may involve the Nrf2 pathway. The general conclusion from the published reports is that melatonin may be a promising protective agent in clinical treatment of IR-induced myocardial diseases.

Prospective studies have shown that some drugs used for cancer treatment are cardiotoxic. The heart damage that they cause can manifest itself as arrhythmia, arterial hypertension, thromboembolism, angina pectoris, myocardial infarction, or heart failure [110, 111]. Due to its cardioprotective effects, melatonin has been administered during oncology treatment to protect against cardiotoxicity. Liu et al. [27] reported that melatonin protects against doxorubicin-induced cardiotoxicity without interfering with its antitumor effect. In a rat model of breast cancer, Zhang et al. [112] also observed that melatonin protects the myocardium by reducing doxorubicin-induced

myocardial oxidative damage. The property of melatonin to reduce cardiotoxicity due to chemotherapy (especially with anthracyclines) and radiotherapy is also noted by Sanchez-Barcelo et al. [113]. Although melatonin is an effective cardioprotective agent, further investigation is needed to expand its range of applications.

Important issues related to the use of melatonin

Melatonin has in fact been used for the treatment of several IR-induced myocardial conditions. However, melatonin seems to have different effects depending on the situation. Vazan et al. [35] found that melatonin significantly reduced the arrhythmia score and shorten the total duration of the arrhythmias, but it also lowered the post-ischemic recovery of contractility. These findings indicate that melatonin's actions may vary according to the end point measured. Subsequent work found that the effect of melatonin is dose dependent and associated with the time of administration.

In reference to melatonin's dose dependency, in the picomolar and micromolar range, melatonin significantly reduces infarct size and improves functional recovery during reperfusion [114]. Also, in a study by Dobsak et al. [31], melatonin exhibited a significant dose-dependent protective effect against the damage inflicted by the peroxy radical. In a review article authored by Sahna et al. [106], the authors claimed that total antioxidant capacity (TAC) of human serum is directly related to melatonin levels, as shown earlier by Benot et al. [115]. The incidence of sudden cardiac death is highest in the morning hours when melatonin levels are low; these values are maximally depressed at these times and patients with CHD have lower levels than normal individuals. In a review by Dominguez-Rodriguez et al. [33], the authors noted that patients with CHD generally have a low calculating melatonin levels; this is further magnified in patients with a higher risk of cardiac infarction and/or sudden death. These results suggest that supplementing melatonin to an appropriate level may benefit these patients.

Published reports suggest that the effect of melatonin is associated with the time when it is administered. Genade et al. [116] found that the specific action of melatonin on the perfused heart is related to the time at which it is administered. If added during reperfusion only, melatonin is cardioprotective, but when it is administered before and during an ischemic preconditioning protocol the protection disappears. Clearly, there are several issues that require attention in regard to the application of melatonin. This information is needed before melatonin will become a standard treatment strategy for cardiovascular diseases.

Concluding remarks

Melatonin, an endogenously produced molecule, is a new agent that may be useful for the treatment of myocardial IR. Giving melatonin to combat molecular damage to the heart becomes an interesting therapeutic strategy, not only because of its potent antioxidant effects, but also due to its high safety profile. Numerous studies have shown that

melatonin, given either acutely or chronically at pharmacological doses, is virtually without toxicity [117–120]. The impressive efficacy and safety of melatonin herald it as a promising prospect for protection of the myocardium from damage. However, the biological functions of melatonin remain only partially characterized. The new frontiers of melatonin study will include (i) the detailed information of melatonin-mediated signaling pathways in myocardial IR; (ii) clinical investigations of the cardioprotective effect of melatonin administration in CABG; (iii) defining whether melatonin is sufficiently safe for routine use in patients with a damaged heart [121, 122]. Further investigations into the targets and functions of melatonin will help develop new strategies for protection against and recovery from myocardial disease in general and IR injury specifically.

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Disclosures

The authors have no disclosures to declare.

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