

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.

Yang Yang^{1,2,*}, Yang Sun^{3,*}, Wei Yi¹, Yue Li⁴, Chongxi Fan⁵, Zhenlong Xin⁴, Shuai Jiang⁴, Shouyin Di⁵, Yan Qu⁴, Russel J. Reiter⁶ and Dinghua Yi¹

¹Department of Cardiovascular Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China; ²Department of Biomedical Engineering, The Fourth Military Medical University, Xi'an, China; ³Departments of Geriatrics, Xijing Hospital, The Fourth Military Medical University, Xi'an, China; ⁴Department of Neurosurgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China; ⁵Department of Thoracic Surgery, Tangdu Hospital, The Fourth Military Medical University, Xi'an, China; ⁶Department of Cellular and Structural Biology, UT Health Science Center, San Antonio, TX, USA

Key words: cardioprotection, clinical heart diseases, melatonin, myocardial ischemia–reperfusion injury

Address reprint requests to Dinghua Yi, Russel J. Reiter and Yan Qu, Department of Cardiovascular Surgery, Xijing Hospital, The Fourth Military Medical University, 127 Changle West Road, Xi'an 710032, China.
E-mails: dinghuayi210@126.com (DY), reiter@uthscsa.edu (RJR), and yanqu1974@126.com (YQ)

*These authors contributed equally to this work.

Received August 16, 2014;

Accepted September 12, 2014.

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

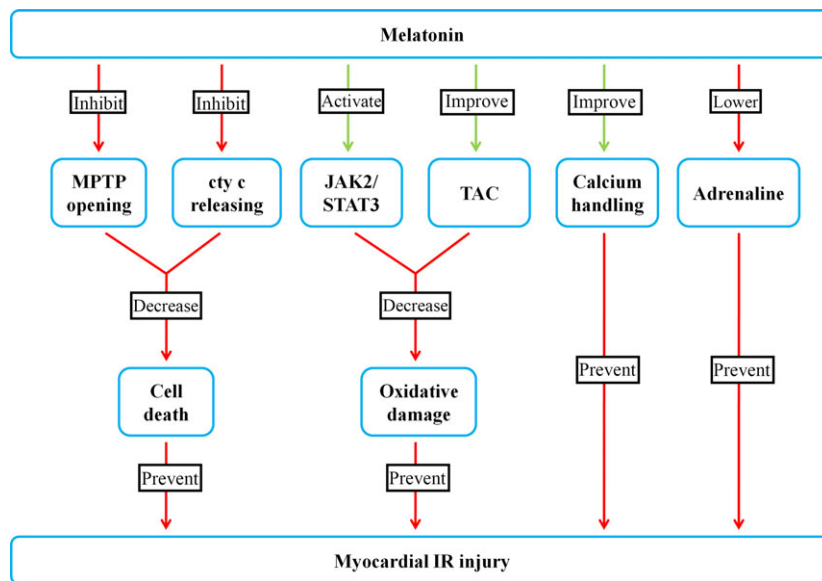


Fig. 1. Cell biological pathways by which melatonin is presumed to protect the cardiomyocyte from ischemia–reperfusion (IR) injury. MPTP, mitochondrial permeability transition pore; cyt c, cytochrome c; JAK2, Janus kinase 2; STAT3, signal transducers and activators of transcription 3; TAC, total antioxidant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

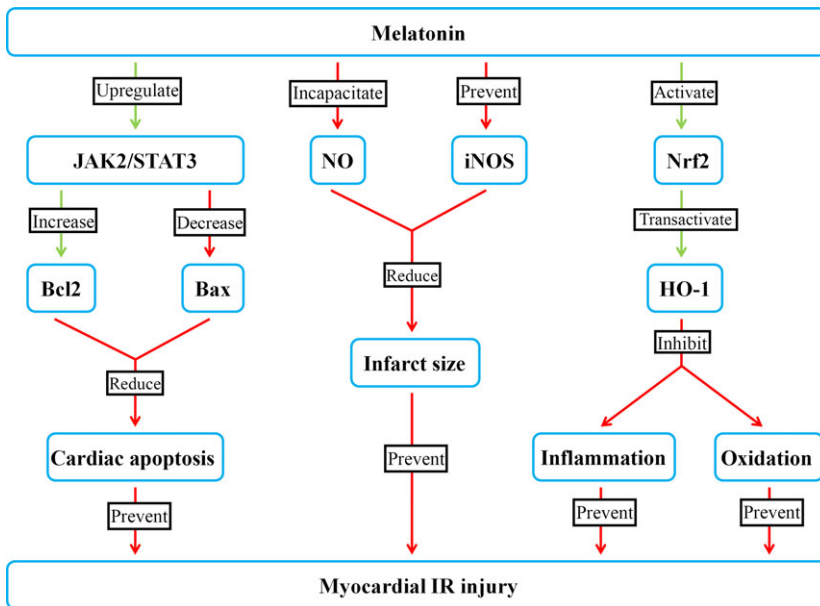


Fig. 2. Signaling pathways of melatonin when it limits ischemia–reperfusion (IR) damage to the cardiomyocyte. JAK2, Janus kinase 2; STAT3, signal transducers and activators of transcription 3; NO, nitric oxide; iNOS, inducible NO-synthase; Nrf2, nuclear factor erythroid 2 related factor 2; HO-1, heme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

Acknowledgements

This study was supported by grants from the Excellent Doctoral Support Project of the Fourth Military Medical University (2013D01), the National Natural Science Foundation of China (81070951, 81222015, 81273100, 81100843, 81000938, 81170213, 81102091), and the New Century Talent Supporting Project by Chinese Education Ministry (NCET-12-1004).

Disclosures

The authors have no disclosures to declare.

References

1. YANG Y, DUAN W, LI Y et al. Novel role of silent information regulator 1 in myocardial ischemia. *Circulation* 2013; **128**:2232–2240.
2. RAINS MG, LANEY CA, BAILEY AL et al. Biomarkers of acute myocardial infarction in the elderly: troponin and beyond. *Clin Interv Aging* 2014; **9**:1081–1090.
3. CHU LM, LASSALETTA AD, ROBICH MP et al. Effects of red wine and vodka on collateral-dependent perfusion and cardiovascular function in hypercholesterolemic swine. *Circulation* 2012; **126**:S65–S72.
4. ZIEGLER M, ELVERS M, BAUMER Y et al. The bispecific SDF1-GPVI fusion protein preserves myocardial function after transient ischemia in mice. *Circulation* 2012; **125**:685–696.
5. YANG Y, DUAN W, LIN Y et al. SIRT1 activation by curcumin pretreatment attenuates mitochondrial oxidative damage induced by myocardial ischemia reperfusion injury. *Free Radic Biol Med* 2013; **65**:667–679.
6. TAN DX, CHEN LD, POEGGELER B et al. Melatonin: a potent, endogenous hydroxyl radical scavenger. *Endocr J* 1993; **1**:57–60.
7. GALANO A, TAN DX, REITER RJ. On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK. *J Pineal Res* 2013; **54**:245–257.
8. HARDELAND R. Melatonin and the theories of aging: a critical appraisal of melatonin's role in antiaging mechanisms. *J Pineal Res* 2013; **55**:325–356.
9. TAN DX, MANCHESTER LC, REITER RJ et al. Ischemia/reperfusion-induced arrhythmias in the isolated rat heart: prevention by melatonin. *J Pineal Res* 1998; **25**:184–191.
10. TENGATTINI S, REITER RJ, TAN DX et al. Cardiovascular diseases: protective effects of melatonin. *J Pineal Res* 2008; **44**:16–25.
11. NDUHIRABANDI F, DU TOIT EF, BLACKHURST D et al. Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of diet-induced obesity. *J Pineal Res* 2011; **50**:171–182.
12. ŞEHİRLİ AÖ, KOYUN D, TETİK Ş et al. Melatonin protects against ischemic heart failure in rats. *J Pineal Res* 2013; **55**:138–148.
13. SEWERYNEK E, REITER RJ, MELCHIORRI D et al. Oxidative damage in the liver induced by ischemia–reperfusion: protection by melatonin. *Hepatogastroenterology* 1996; **43**:898–905.
14. ZAOUALÍ MA, REITER RJ, PADRISSA-ALTÉS S et al. Melatonin protects steatotic and nonsteatotic liver grafts against cold ischemia and reperfusion injury. *J Pineal Res* 2011; **50**:213–221.
15. KANG JW, LEE SM. Melatonin inhibits type 1 interferon signaling of toll-like receptor 4 via heme oxygenase-1 induction in hepatic ischemia/reperfusion. *J Pineal Res* 2012; **53**:67–76.
16. KANG JW, KOH EJ, LEE SM. Melatonin protects liver against ischemia and reperfusion injury through inhibition of toll-like receptor signaling pathway. *J Pineal Res* 2011; **50**:403–411.
17. REITER RJ, TAN DX, LEON J et al. When melatonin gets on your nerves: its beneficial actions in experimental models of stroke. *Exp Biol Med (Maywood)* 2005; **230**:104–117.
18. TAI SH, CHEN HY, LEE EJ et al. Melatonin inhibits postischemic matrix metalloproteinase-9 (MMP-9) activation via dual modulation of plasminogen/plasmin system and endogenous MMP inhibitor in mice subjected to transient focal cerebral ischemia. *J Pineal Res* 2010; **49**:332–341.
19. KILIC U, YILMAZ B, UGUR M et al. Evidence that membrane-bound G protein-coupled melatonin receptors MT1 and MT2 are not involved in the neuroprotective effects of melatonin in focal cerebral ischemia. *J Pineal Res* 2012; **52**:228–235.
20. LI Z, NICKKHOLGH A, YI X et al. Melatonin protects kidney grafts from ischemia/reperfusion injury through inhibition of NF-κB and apoptosis after experimental kidney transplantation. *J Pineal Res* 2009; **46**:365–372.
21. ATES B, YILMAZ I, GECKIL H et al. Protective role of melatonin given either before ischemia or prior to reperfusion on intestinal ischemia–reperfusion damage. *J Pineal Res* 2004; **37**:149–152.
22. YIP HK, CHANG YC, WALLACE CG et al. Melatonin treatment improves adipose-derived mesenchymal stem cell therapy for acute lung ischemia–reperfusion injury. *J Pineal Res* 2013; **54**:207–221.
23. KOKSAL M, OĞUZ E, BABA F et al. Effects of melatonin on testis histology, oxidative stress and spermatogenesis after experimental testis ischemia–reperfusion in rats. *Eur Rev Med Pharmacol Sci* 2012; **16**:582–588.
24. BENOVA T, VICZENCZOVA C, RADOSINSKA J et al. Melatonin attenuates hypertension-related proarrhythmic myocardial maladaptation of connexin-43 and propensity of the heart to lethal arrhythmias. *Can J Physiol Pharmacol* 2013; **91**:633–639.

25. HUNG MW, KRAVTSOV GM, LAU CF et al. Melatonin ameliorates endothelial dysfunction, vascular inflammation, and systemic hypertension in rats with chronic intermittent hypoxia. *J Pineal Res* 2013; **55**:247–256.
26. DOMINGUEZ-RODRIGUEZ A, ABREU-GONZALEZ P, REITER RJ. The potential usefulness of serum melatonin level to predict heart failure in patients with hypertensive cardiomyopathy. *Int J Cardiol* 2014; **174**:415–417.
27. LIU X, CHEN Z, CHUA CC et al. Melatonin as an effective protector against doxorubicin-induced cardiotoxicity. *Am J Physiol Heart Circ Physiol* 2002; **283**:H254–H263.
28. MUKHERJEE D, GHOSH AK, BANDYOPADHYAY A et al. Melatonin protects against isoproterenol-induced alterations in cardiac mitochondrial energy-metabolizing enzymes, apoptotic proteins, and assists in complete recovery from myocardial injury in rats. *J Pineal Res* 2012; **53**:166–179.
29. HU ZP, FANG XL, FANG N et al. Melatonin ameliorates vascular endothelial dysfunction, inflammation, and atherosclerosis by suppressing the TLR4/NF- κ B system in high-fat-fed rabbits. *J Pineal Res* 2013; **55**:388–398.
30. FAVERO G, RODELLA LF, REITER RJ et al. Melatonin and its atheroprotective effects: a review. *Mol Cell Endocrinol* 2014; **382**:926–937.
31. DOBSAK P, SIEGLOVA J, EICHER JC et al. Melatonin protects against ischemia–reperfusion injury and inhibits apoptosis in isolated working rat heart. *Pathophysiology* 2003; **9**:179–187.
32. DIEZ ER, RENNA NF, PRADO NJ et al. Melatonin, given at the time of reperfusion, prevents ventricular arrhythmias in isolated hearts from fructose-fed rats and spontaneously hypertensive rats. *J Pineal Res* 2013; **55**:166–173.
33. DOMINGUEZ-RODRIGUEZ A, ABREU-GONZALEZ P, REITER RJ. Clinical aspects of melatonin in the acute coronary syndrome. *Curr Vasc Pharmacol* 2009; **7**:367–373.
34. SAHNA E, PARLAKPINAR H, TURKOZ Y et al. Protective effects of melatonin on myocardial ischemia–reperfusion induced infarct size and oxidative changes. *Physiol Res* 2005; **54**:491–495.
35. VAZAN R, PANCZA D, BÉDER I et al. Ischemia–reperfusion injury–antiarrhythmic effect of melatonin associated with reduced recovering of contractility. *Gen Physiol Biophys* 2005; **24**:355–359.
36. YANG Y, DUAN W, JIN Z et al. JAK2/STAT3 activation by melatonin attenuates the mitochondrial oxidative damage induced by myocardial ischemia/reperfusion injury. *J Pineal Res* 2013; **55**:275–286.
37. SAHACH VF, RUDYK OV, VAVILOVA HL et al. Melatonin recovers ischemic tolerance and decreases the sensitivity of mitochondrial permeability transition pore opening in the heart of aging rats. *Fiziol Zh* 2006; **52**:3–14.
38. GIACOMO CG, ANTONIO M. Melatonin in cardiac ischemia/reperfusion-induced mitochondrial adaptive changes. *Cardiovasc Hematol Disord Drug Targets* 2007; **7**:163–169.
39. PETROSILLO G, DI VENOSA N, PISTOLESE M et al. Protective effect of melatonin against mitochondrial dysfunction associated with cardiac ischemia–reperfusion: role of cardiolipin. *FASEB J* 2006; **20**:269–276.
40. PETROSILLO G, COLANTUONO G, MORO N et al. Melatonin protects against heart ischemia–reperfusion injury by inhibiting mitochondrial permeability transition pore opening. *Am J Physiol Heart Circ Physiol* 2009; **297**:H1487–H1493.
41. PETROSILLO G, MORO N, PARADIES V et al. Increased susceptibility to Ca(2+)-induced permeability transition and to cytochrome c release in rat heart mitochondria with aging: effect of melatonin. *J Pineal Res* 2010; **48**:340–346.
42. RODRIGUEZ C, MAYO JC, SAINZ RM et al. Regulation of antioxidant enzymes: a significant role for melatonin. *J Pineal Res* 2004; **36**:1–9.
43. REITER RJ, PAREDES SD, MANCHESTER LC et al. Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. *Crit Rev Biochem Mol Biol* 2009; **44**:175–200.
44. GALANO A, TAN DX, REITER RJ. Melatonin as a natural ally against oxidative stress: a physicochemical examination. *J Pineal Res* 2011; **51**:1–16.
45. ZHANG HM, ZHANG Y. Melatonin: a well-documented antioxidant with conditional pro-oxidant actions. *J Pineal Res* 2014; **57**:131–146.
46. REITER RJ, TAN DX, PAREDES SD et al. Beneficial effects of melatonin in cardiovascular disease. *Ann Med* 2010; **42**:276–285.
47. SAHNA E, DENIZ E, BAY-KARABULUT A et al. Melatonin protects myocardium from ischemia–reperfusion injury in hypertensive rats: role of myeloperoxidase activity. *Clin Exp Hypertens* 2008; **30**:673–681.
48. CHEN ZY, CHUA CC, GAO J et al. Prevention of ischemia/reperfusion-induced cardiac apoptosis and injury by melatonin is independent of glutathione peroxidase 1. *J Pineal Res* 2009; **46**:235–241.
49. DIEZ ER, PRADOS LV, CARRIÓN A et al. A novel electrophysiologic effect of melatonin on ischemia/reperfusion-induced arrhythmias in isolated rat hearts. *J Pineal Res* 2009; **46**:155–160.
50. YEUNG HM, HUNG MW, FUNG ML. Melatonin ameliorates calcium homeostasis in myocardial and ischemia–reperfusion injury in chronically hypoxic rats. *J Pineal Res* 2008; **45**:373–382.
51. GENADE S, GENIS A, YTREHUS K et al. Melatonin receptor-mediated protection against myocardial ischaemia/reperfusion injury: role of its anti-adrenergic actions. *J Pineal Res* 2008; **45**:449–458.
52. BOENGLER K, HILFIKER-KLEINER D, DREXLER H et al. The myocardial JAK/STAT pathway: from protection to failure. *Pharmacol Ther* 2008; **120**:172–185.
53. BOENGLER K, HILFIKER-KLEINER D, HEUSCH G et al. Inhibition of permeability transition pore opening by mitochondrial STAT3 and its role in myocardial ischemia/reperfusion. *Basic Res Cardiol* 2010; **105**:771–785.
54. McCORMICK J, BARRY SP, SIVARAJAH A et al. Free radical scavenging inhibits STAT phosphorylation following in vivo ischemia/reperfusion injury. *FASEB J* 2006; **20**:2115–2117.
55. DUAN W, YANG Y, YAN J et al. The effects of curcumin posttreatment against myocardial ischemia and reperfusion by activation of the JAK2/STAT3 signaling pathway. *Basic Res Cardiol* 2012; **107**:263.
56. HATTORI R, MAULIK N, OTANI H et al. Role of STAT3 in ischemic preconditioning. *J Mol Cell Cardiol* 2001; **33**:1929–1936.
57. TIAN Y, ZHANG W, XIA D et al. Postconditioning inhibits myocardial apoptosis during prolonged reperfusion via a JAK2-STAT3-Bcl-2 pathway. *J Biomed Sci* 2011; **18**:53.
58. LI Y, ZHU W, TAO J et al. Fasudil protects the heart against ischemia–reperfusion injury by attenuating endoplasmic reticulum stress and modulating SERCA activity: the differential role for PI3K/Akt and JAK2/STAT3 signaling pathways. *PLoS ONE* 2012; **7**:e48115.

59. LUAN HF, ZHAO ZB, ZHAO QH et al. Hydrogen sulfide postconditioning protects isolated rat hearts against ischemia and reperfusion injury mediated by the JAK2/STAT3 survival pathway. *Braz J Med Biol Res* 2012; **45**:898–905.
60. KAUR C, SIVAKUMAR V, ROBINSON R et al. Neuroprotective effect of melatonin against hypoxia-induced retinal ganglion cell death in neonatal rats. *J Pineal Res* 2013; **54**:190–206.
61. GROSSINI E, MOLINARI C, UBERTI F et al. Intracoronary melatonin increases coronary blood flow and cardiac function through β -adrenoreceptors, MT1/MT2 receptors, and nitric oxide in anesthetized pigs. *J Pineal Res* 2011; **51**:246–257.
62. SLOMINSKI RM, REITER RJ, SCHLABRITZ-LOUTSEVITCH N et al. Melatonin membrane receptors in peripheral tissues: distribution and functions. *Mol Cell Endocrinol* 2012; **351**:152–166.
63. LAU WW, NG JK, LEE MM et al. Interleukin-6 autocrine signaling mediates melatonin MT1/2 receptor-induced STAT3 Tyr (705) phosphorylation. *J Pineal Res* 2012; **52**:477–489.
64. WANG Z, LIU D, WANG J et al. Cytoprotective effects of melatonin on astroglial cells subjected to palmitic acid treatment in vitro. *J Pineal Res* 2012; **52**:253–264.
65. PICINATO MC, HIRATA AE, CIPOLLA-NETO J et al. Activation of insulin and IGF-1 signaling pathways by melatonin through MT1 receptor in isolated rat pancreatic islets. *J Pineal Res* 2008; **44**:88–94.
66. BOGDAN C. Nitric oxide and the immune response. *Nat Immunol* 2001; **2**:907–916.
67. MONCADA S, PALMER R, HIGGS E. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991; **43**:109–142.
68. PALMER R, FERRIGE A, MONCADA S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987; **327**:524–526.
69. MACMICKING J, XIE Q, NATHAN C. Nitric oxide and macrophage function. *Annu Rev Immunol* 1997; **15**:323–350.
70. HIBBS JB, TAINTOR RR, VAVRIN Z. Macrophage cytotoxicity: role for L-arginine deiminase and imino nitrogen oxidation to nitrite. *Science* 1987; **235**:473–476.
71. GRISHAM MB, JOURD'HEUIL D, WINK DA. Nitric oxid. I. Physiological chemistry of nitric oxide and its metabolites: implications in inflammation. *Am J Physiol* 1999; **276**:G315–G321.
72. MAHAL HS, SHARMA HS, MUKHERJEE T. Anti-oxidant properties of melatonin: a pulse radiolysis study. *Free Radic Biol Med* 1999; **26**:557–565.
73. BLANCHARD B, POMPON D, DUCROQ C. Nitrosation of melatonin by nitric oxide and peroxynitrite. *J Pineal Res* 2000; **29**:184–192.
74. CHOI SI, JOO SS, YOO YM. Melatonin prevents nitric oxide-induced apoptosis by increasing the interaction between 14-3-3 β and β -Bad in Sk-N-MC cells. *J Pineal Res* 2008; **44**:95–100.
75. ESPOSITO E, IACONO A, MUIÀ C et al. Signal transduction pathways involved in protective effects of melatonin in C6 glioma cells. *J Pineal Res* 2008; **44**:78–87.
76. BUCHWALOW IB, SCHULZE W, KARCZEWSKI P et al. Cellular control of nitric oxide synthase expression and activity in rat cardiomyocytes. *Antioxid Redox Signal* 2004; **6**:345–352.
77. BALLIGAND JL. Regulation of cardiac β -adrenergic response by nitric oxide. *Cardiovasc Res* 1999; **43**:607–620.
78. MASSION PB, PELAT M, BELGE C et al. Regulation of the mammalian heart function by nitric oxide. *Comp Biochem Physiol A Mol Integr Physiol* 2005; **142**:144–150.
79. WOOLFSON RG, PATEL VC, NEILD GH et al. Inhibition of nitric oxide synthesis reduces infarct size by an adenosine-dependent mechanism. *Circulation* 1995; **91**:1545–1551.
80. DEPREE C, VANOVERSCHELDE JL, GOUEMANT JF et al. Protection against ischemic injury by nonvasoactive concentrations of nitric oxide synthase inhibitors in the perfused rabbit heart. *Circulation* 1995; **92**:1911–1918.
81. TATSUMI T, TAKEDA M, MANO A et al. The dual effects of nitric oxide inhibitors on ischemia–reperfusion injury in rat hearts. *Basic Res Cardiol* 2003; **98**:319–328.
82. LI W, KONG AN. Molecular mechanisms of Nrf2-mediated antioxidant response. *Mol Carcinog* 2009; **48**:91–104.
83. JUNG KH, HONG SW, ZHENG HM et al. Melatonin ameliorates cerulein-induced pancreatitis by the modulation of nuclear erythroid 2-related factor 2 and nuclear factor- κ B in rats. *J Pineal Res* 2010; **48**:239–250.
84. CRESPO I, MIGUEL BS, LALIENA A et al. Melatonin prevents the decreased activity of antioxidant enzymes and activates nuclear erythroid 2-related factor 2 signaling in an animal model of fulminant hepatic failure of viral origin. *J Pineal Res* 2010; **49**:193–200.
85. DWIVEDI S, NAGARAJAN R, HANIF K et al. Standardized extract of bacopa monniera attenuates okadaic acid induced memory dysfunction in rats: effect on Nrf2 pathway. *Evid Based Complement Alternat Med* 2013; **2013**:294501.
86. KILIC U, KILIC E, TUZCU Z et al. Melatonin suppresses cisplatin-induced nephrotoxicity via activation of Nrf2/HO-1 pathway. *Nutr Metab (Lond)* 2013; **10**:7.
87. WANG Z, MA C, MENG CJ et al. Melatonin activates the Nrf2-ARE pathway when it protects against early brain injury in a subarachnoid hemorrhage model. *J Pineal Res* 2012; **53**:129–137.
88. GIUDICE A, ARRA C, TURCO MC. Review of molecular mechanisms involved in the activation of the Nrf2-ARE signaling pathway by chemopreventive agents. *Methods Mol Biol* 2010; **647**:37–74.
89. APARICIO-SOTO M, ALARCÓN-DE-LA-LASTRA C, CÁRDENO A et al. Melatonin modulates microsomal prostaglandin E synthase 1 and nuclear factor-E2-related factor-2-regulated antioxidant enzyme expressions in LPS-induced murine peritoneal macrophages. *Br J Pharmacol* 2014; **171**:134–144.
90. FAN W, HUANG F, ZHU X et al. The heme oxygenase system and oral diseases. *Oral Dis* 2011; **17**:252–257.
91. ZHU X, FAN WG, LI DP et al. Heme oxygenase-1 system and gastrointestinal inflammation: a short review. *World J Gastroenterol* 2011; **17**:4283–4288.
92. BAE GS, KIM MS, PARK KC et al. Effect of biologically active fraction of *Nardostachys jatamansi* on cerulein-induced acute pancreatitis. *World J Gastroenterol* 2012; **18**:3223–3234.
93. TAO RR, HUANG JY, SHAO XJ et al. Ischemic injury promotes Keap1 nitration and disturbance of antioxidative responses in endothelial cells: a potential vasoprotective effect of melatonin. *J Pineal Res* 2013; **54**:271–281.
94. LEONARD MO, KIERAN NE, HOWELL K et al. Reoxygenation-specific activation of the antioxidant transcription factor Nrf2 mediates cytoprotective gene expression in ischemia–reperfusion injury. *FASEB J* 2006; **20**:2624–2626.

95. HAGHJOY JAVANMARD S, ZIAEI A, ZIAEI S et al. The effect of preoperative melatonin on nuclear erythroid 2-related factor 2 activation in patients undergoing coronary artery bypass grafting surgery. *Oxid Med Cell Longev* 2013; **2013**:676829.
96. CIOSEK J, DROBNIK J. Function of the hypothalamo-neurohypophysial system in rats with myocardial infarction is modified by melatonin. *Pharmacol Rep* 2012; **64**:1442–1454.
97. HUBER M, TRESZL A, REIBIS R et al. Genetics of melatonin receptor type 2 is associated with left ventricular function in hypertensive patients treated according to guidelines. *Eur J Intern Med* 2013; **24**:650–655.
98. LEE YM, CHEN HR, HSIAO G et al. Protective effects of melatonin on myocardial ischemia/reperfusion injury in vivo. *J Pineal Res* 2002; **33**:72–80.
99. SAMIMI-FARD S, ABREU-GONZALEZ P, DOMINGUEZ-RODRIGUEZ A et al. A case-control study of melatonin receptor type 1A polymorphism and acute myocardial infarction in a Spanish population. *J Pineal Res* 2011; **51**:400–404.
100. DOMINGUEZ-RODRIGUEZ A, ABREU-GONZÁLEZ P, GARCÍA MJ et al. Decreased nocturnal melatonin levels during acute myocardial infarction. *J Pineal Res* 2002; **33**:248–252.
101. DOMINGUEZ-RODRIGUEZ A, ABREU-GONZALEZ P, GARCIA-GONZALEZ MJ et al. Association of ischemia-modified albumin and melatonin in patients with ST-elevation myocardial infarction. *Atherosclerosis* 2008; **199**:73–78.
102. DOMINGUEZ-RODRIGUEZ A, ABREU-GONZALEZ P. Myocardial ischemia-reperfusion injury: possible role of melatonin. *World J Cardiol* 2010; **2**:233–236.
103. DOMINGUEZ-RODRIGUEZ A, ABREU-GONZALEZ P, AVANZAS P. The role of melatonin in acute myocardial infarction. *Front Biosci* 2012; **17**:2433–2441.
104. RODELLA LF, FAVERO G, FOGGIO E et al. Vascular endothelial cells and dysfunctions: role of melatonin. *Front Biosci (Elite Ed)* 2013; **5**:119–129.
105. REZZANI R, FAVERO G, STACCHIOTTI A et al. Endothelial and vascular smooth muscle cell dysfunction mediated by cyclophillin A and the atheroprotective effects of melatonin. *Life Sci* 2013; **92**:875–882.
106. SAHNA E, DENIZ E, AKSULU HE. Myocardial ischemia-reperfusion injury and melatonin. *Anadolu Kardiyol Derg* 2006; **6**:163–168.
107. ZASLAVSKAIA RM, SHCHERBAN' EA, LILITSA GV et al. Melatonin in the combined treatment of cardiovascular diseases. *Klin Med (Mosk)* 2010; **88**:26–30.
108. GUO XY, LUO AL, REN HZ et al. Perioperative melatonin secretion rhyme in patients undergoing coronary artery bypass grafting surgery. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2003; **25**:594–598.
109. SOKULLU O, SANIOĞLU S, KURÇ E et al. Does the circadian rhythm of melatonin affect ischemia-reperfusion injury after coronary artery bypass grafting? *Heart Surg Forum* 2009; **12**:E95–E99.
110. EWER MS, SWAIN SM, CARDINALE D et al. Cardiac dysfunction after cancer treatment. *Tex Heart Inst J* 2011; **38**:248–252.
111. SCHLITT A, JORDAN K, VORDERMARK D et al. Cardiotoxicity and oncological treatments. *Dtsch Arztebl Int* 2014; **111**:161–168.
112. ZHANG Y, LI L, XIANG C et al. Protective effect of melatonin against Adriamycin-induced cardiotoxicity. *Exp Ther Med* 2013; **5**:1496–1500.
113. SANCHEZ-BARCELO EJ, MEDIIVILLA MD, ALONSO-GONZALEZ C et al. Melatonin uses in oncology: breast cancer prevention and reduction of the side effects of chemotherapy and radiation. *Expert Opin Investig Drugs* 2012; **21**:819–831.
114. LOCHNER A, HUISAMEN B, NDUHIRABANDI F. Cardioprotective effect of melatonin against ischaemia/reperfusion damage. *Front Biosci (Elite Ed)* 2013; **5**:305–315.
115. BENOT S, GOBERNA R, REITER RJ et al. Physiological levels of melatonin contribute to the antioxidant capacity of human serum. *J Pineal Res* 1999; **27**:59–64.
116. GENADE S, YTREHUS K, LOCHNER A. Melatonin prevents cardioprotection induced by a multi-cycle ischaemic preconditioning protocol in the isolated perfused rat heart. *Cardiovasc J S Afr* 2006; **17**:239–244.
117. NORLUND JJ, LERNER AB. The effects of melatonin on skin color and on the release of pituitary hormones. *J Clin Endocrinol Metab* 1977; **45**:768–774.
118. SEABRA MDLV, BIGNOTTO M, PINTO LR Jr et al. Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. *J Pineal Res* 2000; **29**:193–200.
119. JAN JE, HAMILTON D, SEWARD N et al. Clinical trials of controlled- released melatonin in children with sleep-wake cycle disorders. *J Pineal Res* 2000; **29**:34–39.
120. JAHNKE G, MARR M, MYERS R et al. Maternal and developmental toxicity evaluation of melatonin administration orally to pregnant Sprague-Dawley rats. *Toxicol Sci* 1999; **50**:271–279.
121. CHEUNG RTF, TIPOE GL, TAM S et al. Preclinical evaluation of pharmacokinetics and safety of melatonin in propylene glycol for intravenous administration. *J Pineal Res* 2006; **41**:337–343.
122. MORERA AL, HENRY M, de LA VARGA M. Safety in melatonin use. *Actas Esp Psiquiatr* 2001; **29**:334–337.