

The role of melatonin in acute myocardial infarction

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1. ABSTRACT

Melatonin, a circadian hormone with marked antioxidant properties, has been shown to protect against ischemia-reperfusion myocardial damage, especially when administered during reperfusion period. Melatonin has cardioprotective properties via its direct free radical scavenging and its indirect antioxidant activity. Melatonin efficiently interacts with various reactive oxygen and reactive nitrogen species and it also upregulates antioxidant enzymes and downregulates pro-oxidant enzymes. In addition, melatonin demonstrated blood pressure lowering, lipid profile normalizing and anti-inflammatory properties. The lack of these cardioprotective effects due to insufficient melatonin levels might be associated with several cardiovascular pathologies including ischemic heart disease. Patients with acute coronary syndrome or after myocardial infarction were shown to have reduced nighttime melatonin levels and 6-sulfatoxymelatonin urinary excretion. These alterations might translate to increased cardiovascular risk observed in acute myocardial infarction patients with low melatonin levels; and a mutation in melatonin receptors might augment the risk for acute myocardial infarction. Therefore, it is expected that melatonin administration could play a clinically relevant role in the pharmacotherapy of ischemic heart disease; an assumption supported by low toxicity and high safety of melatonin.

2. INTRODUCTION

Acute coronary occlusion is the leading cause of morbidity and mortality in the Western World and, according to the World Health Organisation, it will be the major cause of death in the world by the year 2020 (1). The recognition that thrombotic occlusion of a coronary artery results in a wave front of irreversible myocardial cell injury, extending from the subendocardium to the subepicardium in a time-dependent fashion, led to the introduction of reperfusion therapy for AMI (2,3). Modalities for reperfusion include thrombolysis, percutaneous coronary intervention and coronary bypass grafting. Ischemia/reperfusion injury has been observed in each one of these situations (4).

The underlying pathophysiological mechanisms of ischemia/reperfusion injury have not been fully elucidated (Figure 1). It has been suggested that an over consume of oxygen (5) and intracellular calcium overload or redistribution (6) during the first minutes of reflow might be involved. However, oxygen-derived free radicals and hypercontracture, due to calcium-overload, are not the only candidates responsible for ischemia/reperfusion injury. Other factors of importance in the pathogenesis of ischemia/reperfusion injury include platelet- and neutrophil-mediated injury, the renin-angiotensin system and the complement activation (7-9). In general, there are

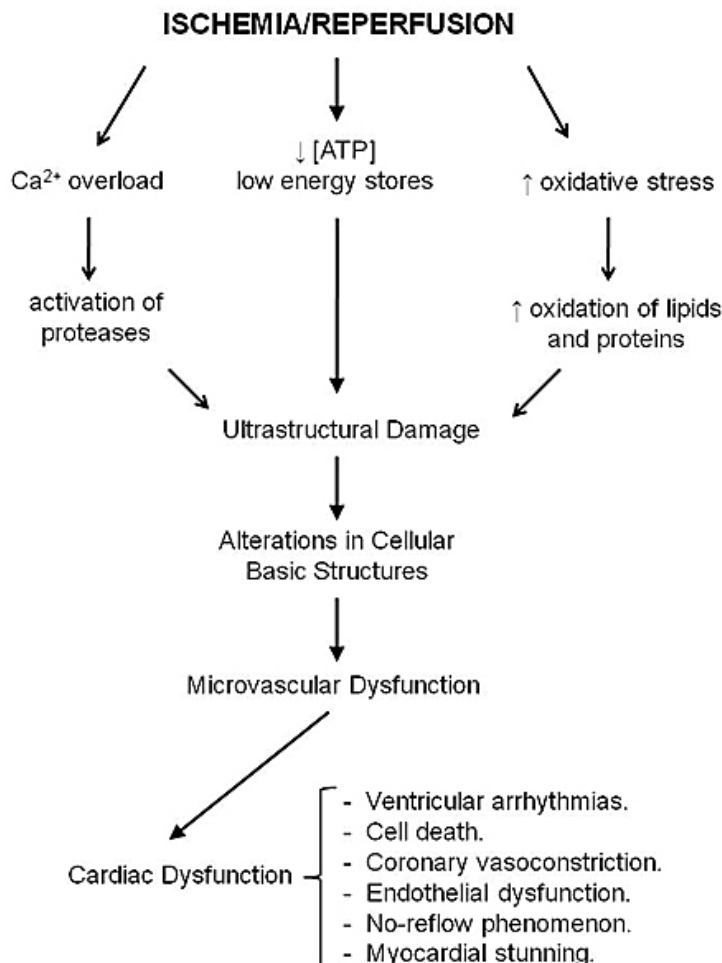


Figure 1. Biological process of an episode of ischemia/reperfusion in a damaged coronary artery by occlusion of it.

three moments to prevent ischemia/reperfusion injury. The acute reperfusion therapy is given in the first minutes. In the first hours, the therapy has anti-inflammatory and anti-apoptotic targets. In the days and months after an AMI, the therapy has an anti-remodeling effect (4).

The evidence from the last 20 years documents that melatonin influences the cardiovascular system (10-12). Melatonin mediates a variety of physiological responses through membrane and nuclear binding sites. Two mammalian receptor subtypes have been cloned and designated as MT₁ and MT₂ (12). These receptors have been identified in human coronary arteries from pathological samples and also from healthy controls. Animal studies suggest that melatonin has dual effects on the vasculature, depending on the specific receptor type activated, with vasoconstriction occurring after MT₁-activation and vasorelaxation after MT₂-activation (13). It has been observed that patients with coronary artery disease have a low melatonin production rate, which correlates with the stage of the disease, e.g. greater reductions are observed in patients with a higher risk of cardiac infarction and/or sudden death (12,13). The current brief survey provides an overview on the role of melatonin in AMI.

We performed a comprehensive literature search by using electronic bibliographic databases (MEDLINE, EMBASE and The Cochrane Library) and combinations of the following keywords: melatonin AND human AND ST-elevation myocardial infarction OR non-ST-elevation myocardial infarction OR acute coronary syndrome OR AMI. Bibliographies of all selected articles and review were handled for other relevant article.

2.1. Circulating melatonin levels in patients with coronary artery disease

The pineal gland is a photoneuroendocrine organ that converts external luminic stimuli into a hormone secretion, being responsible for the synchronization between internal homeostasis and the environment. The circadian activity of the suprachiasmatic nucleus (SCN) is synchronised to the light/dark cycle mainly by light perceived by the retina. The photic signal generated in the retina is transmitted to the SCN through the retino-hypothalamic tract (RHT) that has its origin in the ganglion cell layer of the retina. In the absence of light (during the night), an increase of melatonin biosynthesis in the pineal gland is stimulated by electrical signals from neurons in the SCN. These neurons receive inputs from the retina and they

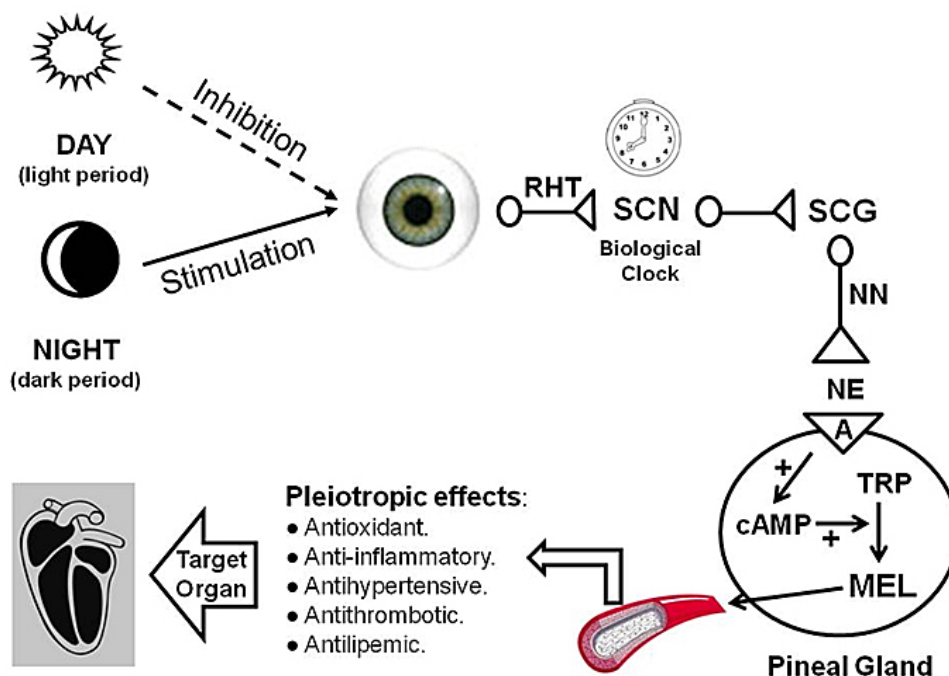


Figure 2. Physiological regulation of circadian melatonin (MEL) production. In the pineal gland, MEL synthesis follows a rhythm driven by the suprachiasmatic nucleus (SCN), the biological clock. Neural signals from the SCN follow a multisynaptic pathway to the superior cervical ganglia (SCG). The noradrenaline released from postganglionic fibers activates adrenoceptors (A) in the pinealocyte, leading to increases in a second messengers (cAMP) increasing the enzymatic activity of AA-NAT, the rate-limiting step in MEL biosynthesis. The system is dramatically inhibited by light (day), the external signal allows entrainment to the environmental light/dark cycle. The photic signal received by the retina is transmitted to the SCN via the retinohypothalamic tract (RHT), which originates in a subset of retinal ganglion cells. Abbreviations: AA-NAT= Aryl-Alkylamine-N-acetyl transferase; NA= Noradrenaline; TRP= L-Tryptophan; A= Adrenoceptor; NN= Noradrenergic neuron.

send inputs via para-ventricular nucleus (PVN) and then make synaptic connections with the intermediolateral column of the cervical spinal cord to the superior cervical ganglia (SCG) (14-16). The post-ganglionic sympathetic fibers coming from SCG terminate adjacent to the pinealocytes. The neurotransmitter at the post-ganglionic sympathetic nerve terminal is noradrenaline (NA). Activation of the β -adrenoceptors present on the pinealocytes results an increases in cAMP concentration that promotes the biosynthesis of melatonin. During the day, NA release from the sympathetic fibers is suppressed by an increased in electrical activity in the SCN. At night, when SCN is inhibited, the release of NA is enhanced (17,18) (Figure 2).

Several studies show that humans with cardiovascular disease have noticeably lower circulating melatonin levels than age-matched subjects without significant cardiovascular deterioration (13). The reports that have investigated the circulating melatonin levels in subjects with coronary artery disease are summarized in Table 1.

The first clinical study in humans that demonstrated a relationship between melatonin and coronary artery disease was published by Brugger *et al* (19). They reported reduced levels of plasma melatonin

measured at 02:00 h in coronary artery disease patients. Moreover, other investigators studied nocturnal urinary excretion of 6-sulfatoxymelatonin, major melatonin metabolite, in patients with coronary artery disease and they demonstrated a low melatonin production rate (20-22). Moreover, Yaprak *et al* (23) demonstrated in patients with angiographically documented coronary artery disease, a decreased nocturnal melatonin synthesis and release. Similarly, patients suffering cardiac syndrome X have an attenuated nocturnal rise in serum melatonin levels related to that of age-matched individuals with no cardiac pathology (24). Likewise, our group analyzed serum levels of melatonin and parameters of oxidative stress in a cohort of 25 AMI patients and 25 subjects with no evidence of coronary artery disease as controls. We demonstrated that AMI is associated with a nocturnal serum melatonin deficit as well as increased oxidative stress (25).

Coronary atherosclerosis is characterized by a complex multifactorial pathophysiology. Inflammation in the vessel wall plays an essential role in the initiation, progression and development of thrombotic complications of atherosclerosis, namely normally plaque destabilization and eventually plaque rupture (26). Previous studies from our group have reported a relationship between melatonin and light/dark variations in the production of inflammatory systemic molecules, such as interleukin-6, C-reactive

Table 1. Publications about the circulating melatonin levels in humans with coronary artery disease

First Author (Ref)	Population	Measures	Outcome/Conclusion
Brugger et al. (19)	15 patients with CAD and 10 controls	Serum melatonin concentrations at night (0200 h)	Melatonin was significantly lower in the patients with CAD
Sakotnik et al. (20)	48 patients with CAD and 18 controls	6-sulfatoxymelatonin was measured radioimmunologically from overnight urine.	Urinary 6-sulfatoxymelatonin concentration was significantly decreased in patients with CAD
Girotti et al. (21)	3 groups of individuals: a) 32 patients with stable angina; b) 27 patients with unstable angina; and c) 24 controls	For 6-sulphatoxymelatonin measurement, urine was collected from 18:00 to 06:00 hr.	Urinary 6-sulphatoxymelatonin excretion was significantly lower in unstable angina patients than in healthy subjects or in patients with stable angina.
Vijayasathya et al. (22)	21 patients with unstable angina and 30 controls	Serum malondialdehyde, oxidized LDL and 6-sulphatoxymelatonin in 24 h urine sample	Decreased excretion of 6-Sulphatoxymelatonin in patients with unstable angina
Yaprak et al. (23)	16 patients with angiographically documented CAD and 9 controls	Blood samples were collected every 2 h between 22:00 and 08:00 h. to determine melatonin levels	Patients with CAD secreted less nocturnal melatonin at 02:00, 04:00 and 08:00 h than control subjects
Altun et al. (24)	5 patients with cardiac syndrome X and 9 controls	Blood samples were collected every 2 h between 22:00 and 08:00 h. to determine melatonin levels	Patients with cardiac syndrome X secreted less nocturnal melatonin at 02:00 h than control subjects
Dominguez-Rodriguez et al. (25)	25 patients with AMI and 25 controls	Blood samples were obtained at 10:00 and 03:00 h to determine melatonin	AMI is associated with a nocturnal serum melatonin deficit

CAD = coronary artery disease; AMI = acute myocardial infarction.

protein, matrix metalloproteinase-9 and soluble vascular cell adhesion molecule-1 (27-30). On this basis of a large amount of data, it is clear that melatonin inhibits the production of inflammatory mediators, adhesion molecules, growth and chemotactic factors of cells of the immune system, thereby likely limiting the local inflammatory response in the atherosclerotic plaque (31).

Of particular interest, it is the emerging prognostic role of melatonin in patients with coronary artery disease. At this respect, Dominguez-Rodriguez *et al* (32) demonstrated in patients with AMI that low nocturnal melatonin levels predict cardiac adverse events (heart failure or death) during 6-month follow up. The results of many publications suggest an impending decrease in circulating melatonin concentration at different stages of the coronary heart disease in humans (33).

3. EFFECTS OF MELATONIN ON MYOCARDIAL INFARCTION

Re-introduction of abundant oxygen at the onset of reperfusion evokes, within the first few minutes of reflow, a burst of potent free radicals, including superoxide anion, hydroxyl radical and peroxynitrite, have been demonstrated in experimental settings as well as in human with AMI undergoing thrombolysis (34) or percutaneous coronary intervention (35). The production of free radicals in the early phase of reperfusion, in combination with the ischemia-reperfusion induced loss of antioxidant activity, renders the myocardium extremely vulnerable to molecular damage (4). Membranes are composed mostly of phospholipids and proteins. Alterations in membrane proteins by free radicals are among the important factors in the evolution of myocardial ischemia-reperfusion damage. Large quantities of free radicals drain off endogenous antioxidant defenses. This leads to peroxidation of lipid membranes and loss of membrane integrity and results in necrosis and cell death (4).

Several recent publications present convincing evidence for the protective actions of melatonin against cardiac damage occurring during ischemia-reperfusion injury (10, 36, 37). Thus far, these beneficial actions have been attributed to the anti-oxidant and free radical scavenging actions of the hormone (10, 11, 18). Sallinen *et al*, examined the time course of changes in the synthesis and levels of endogenous melatonin and in the expression of MT₁ and MT₂ melatonin receptors 1 day, 2 and 4 week after AMI in rats. AMI was produced by ligation of the left anterior descending coronary artery. They demonstrated that the melatonin synthesis in the pineal gland increased rapidly in response to the AMI, supporting an important role for endogenous melatonin in protecting the heart after AMI (38). These observations of increased melatonin synthesis may indicate that the decreased plasma melatonin levels in humans with coronary artery disease (19-21). In AMI (25) these levels are the result of melatonin consumption caused by scavenging of the elevated free radical production, or they represent lower melatonin production, and hence less protection against oxidative stress (33).

Ischemia-reperfusion injury causes an increase in oxygen free radicals; it alters calcium signaling in platelets (39), and stimulates platelet aggregation (40). Melatonin synthesis is not restricted to the pineal gland but also takes place in megakaryocytes and platelets (41, 42). A recent study from our group showed in AMI patients undergoing primary percutaneous coronary intervention a relationship between intraplatelet melatonin and the “no-reflow” phenomenon (specific type of vascular damage, occurring when complete removal of coronary occlusion does not lead to restoration of coronary flow) (43). Our data suggest that these patients have low intraplatelet melatonin levels as the result of consumption because “no-reflow” patients have higher oxidative stress (44).

Melatonin has shown to have a scavenging effect on the hydroxyl radical and it may have a protective effect on tissue injury mediated by oxidative stress. Melatonin

metabolites, such as N¹-acetyl-N²-formyl-5-methoxykynuramine and N-acetyl-5-methoxykynuramine, up-regulate antioxidant enzymes and down-regulate the pro-oxidative and proinflammatory enzymes (18). Recent investigations in patients with AMI undergoing primary percutaneous coronary intervention confirmed a relationship between melatonin concentrations and ischemia-modified albumin, a marker of myocardial ischemia. Thus our data suggest that melatonin acts as a potent antioxidant agent, reducing myocardial damage induced by ischemia-reperfusion (45).

Growing evidence has become available supporting a crucial role of mitochondrial permeability transition in cardiomyocyte cell death occurring during ischemia-reperfusion process (46-48). Permeability transition is caused by the opening of the mitochondrial permeability transition pore, a multiprotein megachannel connecting the mitochondrial matrix compartment with the cytosol. Massive mitochondrial permeability transition pore opening results in mitochondrial depolarization, swelling and rupture of the external mitochondrial membrane, uncoupling of the respiratory chain and efflux of cytochrome c and other proapoptotic factors that may lead to either apoptosis or necrosis (49). Recent data suggest that some of the cell protective effect of melatonin may be produced at a mitochondrial level (50). Petrosillo *et al* have demonstrated that melatonin protects against heart ischemia-reperfusion injury by inhibiting mitochondrial permeability transition pore opening. Melatonin treatment significantly improves the functional recovery of Langendorff hearts on reperfusion; it reduces the infarct size and decreases necrotic damage, as shown by the reduced release of lactate dehydrogenase (51).

Taking into account that free radicals are involved in the inflammatory process, melatonin is a good candidate as an anti-inflammatory agent, which complements its antioxidant and free radical scavenging features (10-13). Anti-inflammatory actions of melatonin are related to the inhibition of PGE₂ effects, and in particular, COX-2 down regulation (31, 33). The variety of biologically activate metabolites explains why melatonin exhibits a variety of physiological functions. As the oxidative status of organisms can modify melatonin metabolism, the ratio of different melatonin metabolites could serve as an indicator of oxidative status of organisms and can also serve as signals to trigger *in vivo* responses of organisms (18).

The marked variability of melatonin production by the pineal gland may be due to mutations in genes encoding critical enzymes involved in melatonin biosynthesis (13). Two G protein-coupled membrane receptors for melatonin have been cloned and they are identified as MT₁ and MT₂ (52). In mammals, these melatonin receptors are expressed in the majority of the central neural system and peripheral tissues, including the cardiovascular system (53, 54). These receptors share a high degree of sequence homology with an orphan receptor also named G protein-coupled receptor 50 (GPR50), which plays a pivotal role in mediating the intracellular effects of

numerous neurotransmitters and hormones, including melatonin (55). There are nine coding single nucleotide polymorphisms in the MT₁ gene (5 missenses, 3 synonymous and 1 insertion) and another nine coding single nucleotide polymorphisms in the MT₂ gene (7 missenses and 2 synonymous) (13). Recently, we have performed a case-control study in 300 consecutive AMI patients and 250 healthy controls. In this study, a mutation in the MT₁ receptor (polymorphism rs2838653), may be associated with less-effective melatonin receptor and specific pattern of expression, emphasizing the possibility to predispose a higher incidence of AMI (56).

4. PERSPECTIVE FUTURE ON THE UTILIZATION OF MELATONIN IN THE ACUTE MYOCARDIAL INFARCTION

The administration of melatonin has been reported to reduce blood pressure as a consequence of various mechanisms including a direct hypothalamic effect, a lowering of catecholamine levels, relaxation of the smooth muscle wall and, most importantly, as a result of its antioxidant properties (11). Likewise, melatonin treatment of peri- and post-menopausal women causes a significant elevation of high-density lipoprotein cholesterol without influencing total cholesterol levels (12, 33).

Studies in animals have confirmed the ameliorative effects of melatonin on abnormal function and cardiac tissue destruction resulting from ischemia-reperfusion after the administration of pharmacologic doses of melatonin prior to ischemia and/or during reperfusion (36, 57-59). Additional studies showed that melatonin also markedly reduced the superoxide anion radical production and lowered myeloperoxidase activity induced by ischemia-reperfusion (10).

A report by Dobsak *et al* (60) documents the pivotal role of melatonin in limiting myocardial pathophysiology in the ischemia-reperfusion rat heart. In this case, an isolated working heart model was used to test melatonin's ability to reduce myocardial damage after transient ischemia followed by reoxygenation. The results of Kacmaz *et al* (61) also confirmed that melatonin has a protective effect on ischemia-reperfusion induced oxidative cardiac damage. Moreover, Genade *et al* have demonstrated in animal studies, that melatonin's actions on the perfused heart are dependent on the time of administration. If it is added during reperfusion only, melatonin is cardioprotective, while it is when administered before and during an ischemic preconditioning protocol; it abolishes protection (62).

The available scientific evidence has led our group to carry out a phase II clinical trial (ClinicalTrials.gov no. NCT00640094). We attempt to demonstrate inhibition of I/R damage after administration of intravenous melatonin in patients with ST-elevation myocardial infarction immediately before primary percutaneous coronary intervention (63). Moreover, other authors are testing whether intracoronary injection of melatonin can reduce the myocardial damage sustained by

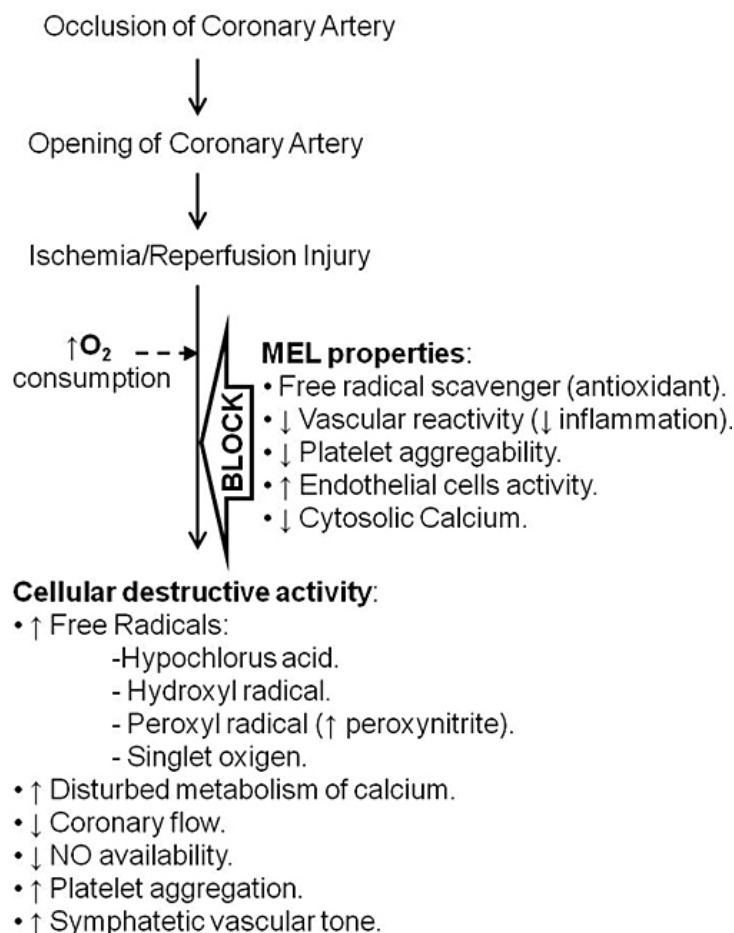


Figure 3. Participation of melatonin (MEL) in the reperfusion process of coronary artery post-occlusion of it. Melatonin treats to block the destructive activity, at cellular level (ischemia), produced by the high consume of oxygen post re-opening of the artery occluded (reperfusion).

I/R (ClinicalTrials.gov no. NCT01172171). The importance of these studies is emphasized by the fact when, exogenously administered, melatonin is quickly distributed throughout the organism. It crosses all morphophysiologic barriers and it enters into cardiac cells with great ease. Highest intracellular concentrations of melatonin are found at a mitochondrial level. This is especially important, as the mitochondria is a major site of free radical generation and oxidative stress (33, 64-66) (Figure 3).

It is clear that melatonin could potentially become an ideal agent for clinical treatment of patients with ischemic heart diseases (13). Based on surface area [$M^2 = \text{weight (g)}^{2/3} \times K \times 10^{-4}$, where the constant specific for each animal species (K) = 10.5 for mice] the dose used for mice (150 $\mu\text{g/kg}$) is equivalent to 0.8 mg/1.8 m^2 for humans (67). Since the melatonin is a natural endogenous substance, even at pharmacological doses (10 mg/day, \approx 25000 times the nocturnal physiological levels), it showed very low toxicity in clinical practice. The reported adverse effects, such as, nightmares and hypotension were rare and mild. The somnolence is the principal physiological effect and not a side effect of it (68,69).

5. CONCLUSIONS

Experimental results have contributed to solid evidence to consider melatonin to be one of the essential components of the organism's antioxidant defense system. This review shows data from studies that confirm the cardioprotective actions of melatonin, particularly during ischemia-reperfusion process in the ischemic heart. The discovery of melatonin as a direct free radical scavenger and as an indirect antioxidant via its stimulatory actions on antioxidative enzymes has greatly increased interest in the potential cardioprotective of this indoleamine. Furthermore, melatonin's ability to inhibit the pro-oxidative enzyme, nitric oxide synthase, is mediated by a tertiary metabolite of melatonin, N^1 -acetyl- N^2 -formyl-5-methoxykynuramine (70). The ability of the patent molecule melatonin as well as its metabolites to function in radical detoxification greatly increases its ability to limit oxidative abuse at many levels within cells.

Melatonin is an endogenous molecule with few side effects and a low monetary cost. Its lipophilic nature allows crossing cell membranes with ease to reach cell

compartments where oxygen-derived free radicals can be found. We will await the results of the phase II studies of melatonin with great interest.

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7. REFERENCES

1. AD Lopez, CC Murray: The global burden of disease: 1990-2020. *Nat Med* 4,1241-1243 (1998)
2. MA DeWood, J Spores, R Notske, LT Mouser, R Burroughs, MS Golden, HT Lang: Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction: *N Engl J Med* 303,897-902 (1980)
3. KA Reimer, JE Lowe, MM Rasmussen, RB Jennings: The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 56,786-794 (1977)
4. AL Moens, MJ Claeys, JP Timmermans, CJ Vrints: Myocardial ischemia/reperfusion-injury, a clinical view on a complex pathophysiological process. *Int J Cardiol* 100,179-190 (2005)
5. JL Zweier: Measurement of superoxide-derived free radicals in the reperfused heart. Evidence for a free radical mechanism of reperfusion injury. *J Biol Chem* 263,1353-1357 (1988)
6. WW Brooks, CH Conrad, JP Morgan: Reperfusion induced arrhythmias following ischaemia in intact rat heart: role of intracellular calcium. *Cardiovasc Res* 29,536-542 (1995)
7. LA Neves, AP Almeida, MC Khosla, MJ Campagnole-Santos, RA Santos: Effect of angiotensin-(1-7) on reperfusion arrhythmias in isolated rat hearts. *Braz J Med Biol Res* 30,801-809 (1997)
8. PR Hansen: Role of neutrophils in myocardial ischemia and reperfusion. *Circulation* 91,1872-1885 (1995)
9. CY Xiao, A Hara, K Yuhki, T Fujino, H Ma, Y Okada, O Takahata, T Yamada, T Murata, S Narumiya, F Ushikubi: Roles of prostaglandin I(2) and thromboxane A(2) in cardiac ischemia-reperfusion injury: a study using mice lacking their respective receptors. *Circulation* 104,2210-2215 (2001)
10. RJ Reiter, DX Tan: Melatonin: a novel protective agent against oxidative injury of the ischemic/reperfused heart. *Cardiovasc Res* 58,10-19 (2003)
11. S Tengattini, RJ Reiter, DX Tan, MP Terron, LF Rodella, R Rezzani: Cardiovascular diseases: protective effects of melatonin. *J Pineal Res* 44,16-25 (2008)
12. A Dominguez-Rodriguez, P Abreu-Gonzalez, RJ Reiter: Clinical aspects of melatonin in the acute coronary syndrome. *Curr Vasc Pharmacol* 7,367-373 (2009)
13. A Dominguez-Rodriguez, P Abreu-Gonzalez, JJ Sanchez-Sanchez, JC Kaski, RJ Reiter: Melatonin and circadian biology in human cardiovascular disease. *J Pineal Res* 49,14-22 (2010)
14. RJ Reiter: Pineal melatonin: cell biology of its synthesis and of its physiological interactions. *Endocr Rev* 12,151-180 (1991)
15. RJ Reiter: Melatonin: the chemical expression of darkness. *Mol Cell Endocrinol* 79,C153-C158 (1991)
16. FW Turek, C Dugovic, PC Zee: Current understanding of the circadian clock and the clinical implications for neurological disorders. *Arch Neurol* 58,1781-1787 (2001)
17. RY Moore: Neural control of the pineal gland. *Behav Brain Res* 73,125-130 (2001)
18. DX Tan, LC Manchester, MP Terron, LJ Flores, RJ Reiter: One molecule, many derivatives: a never-ending interaction of melatonin with reactive oxygen and nitrogen species? *J Pineal Res* 42,28-42 (2007)
19. P Brugger, W Marktl, M Herold: Impaired nocturnal secretion of melatonin in coronary heart disease. *Lancet* 345,1408 (1995)
20. A Sakotnik, PM Liebmann, K Stoschitzky, P Lercher, K Schauenstein, W Klein, B Eber: Decreased melatonin synthesis in patients with coronary artery disease. *Eur Heart J* 20,1314-1347 (1999)
21. L Girotti, M Lago, O Ianovsky, J Carbajales, MV Elizari, LI Brusco, DP Cardinali: Low urinary 6-sulphatoxymelatonin levels in patients with coronary artery disease. *J Pineal Res* 29,138-142 (2000)
22. K Vijayasarathy, K Shanthi Naidu, BK Sastry: Melatonin metabolite 6-Sulfatoxymelatonin, Cu/Zn superoxide dismutase, oxidized LDL and malondialdehyde in unstable angina. *Int J Cardiol* 144,315-317 (2010)
23. M Yaprak, A Altun, A Vardar, M Aktoz, S Ciftci, G Ozbay: Decreased nocturnal synthesis of melatonin in patients with coronary artery disease. *Int J Cardiol* 89,103-107 (2003)
24. A Altun, M Yaprak, M Aktoz, A Vardar, UA Betul, G Ozbay: Impaired nocturnal synthesis of melatonin in patients with cardiac syndrome X. *Neurosci Lett* 327,143-145 (2002)
25. A Dominguez-Rodríguez, P Abreu-Gonzalez, MJ Garcia, J Sanchez, F Marrero, D de Armas-Trujillo: Decreased nocturnal melatonin levels during acute myocardial infarction. *J Pineal Res* 33,248-252 (2002)

26. W Koenig, N Khuseynova: Biomarkers of atherosclerotic plaque instability and rupture. *Arterioscler Thromb Vasc Biol* 27,15-26 (2007)
27. A Dominguez-Rodriguez, P Abreu-Gonzalez, M Garcia, J Ferrer, A de la Rosa, M Vargas, RJ Reiter: Light/dark patterns of interleukin-6 in relation to the pineal hormone melatonin in patients with acute myocardial infarction. *Cytokine* 26,89-93 (2004)
28. A Dominguez-Rodriguez, M Garcia-Gonzalez, P Abreu-Gonzalez, J Ferrer, JC Kaski: Relation of nocturnal melatonin levels to C-reactive protein concentration in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 97,10-12 (2006)
29. A Dominguez-Rodriguez, P Abreu-Gonzalez, MJ Garcia-Gonzalez, RJ Reiter: Relation of nocturnal melatonin levels to serum matrix metalloproteinase-9 concentrations in patients with myocardial infarction. *Thromb Res* 120,361-366 (2007)
30. A Dominguez-Rodriguez, P Abreu-Gonzalez, MJ Garcia-Gonzalez, S Samimi-Fard, JC Kaski, RJ Reiter: Light/dark patterns of soluble vascular cell adhesion molecule-1 in relation to melatonin in patients with ST-segment elevation myocardial infarction. *J Pineal Res* 44,65-69 (2008)
31. RJ Reiter, JR Calvo, M Karbownik, W Qi, DX Tan: Melatonin and its relation to the immune system and inflammation. *Ann N Y Acad Sci* 917,376-386 (2000)
32. A Dominguez-Rodriguez, P Abreu-Gonzalez, M Garcia-Gonzalez, RJ Reiter: Prognostic value of nocturnal melatonin levels as a novel marker in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 97,1162-1164 (2006)
33. A Dominguez-Rodriguez, P Abreu-Gonzalez P: Myocardial ischemia-reperfusion injury: Possible role of melatonin. *World J Cardiol* 2,233-236 (2010)
34. T Béard, D Carrié, MJ Boyer, B Boudjemaa, J Ferrières, M Delay, P Bernadet, JP Thouvenot: Production of oxygen free radicals in myocardial infarction treated by thrombolysis. Analysis of glutathione peroxidase, superoxide dismutase and malondialdehyde]. *Arch Mal Coeur Vaiss* 87,1289-1296 (1994)
35. MJ Roberts, IS Young, TG Trouton, ER Trimble, MM Khan, SW Webb, CM Wilson, GC Patterson, AA Adgey: Transient release of lipid peroxides after coronary artery balloon angioplasty. *Lancet* 336,143-145 (1990)
36. YM Lee, HR Chen, G Hsiao, JR Sheu, JJ Wang, MH Yen: Protective effects of melatonin on myocardial ischemia/reperfusion injury *in vivo*. *J Pineal Res* 33,72-80 (2002)
37. A Lochner, S Genade, A Davids, K Ytrehus, JA Moolman: Short- and long-term effects of melatonin on myocardial post-ischemic recovery. *J Pineal Res* 40,56-63 (2006)
38. P Sallinen, S Mänttari, H Leskinen, M Ilves, O Vakkuri, H Ruskoaho, S Saarela: The effect of myocardial infarction on the synthesis, concentration and receptor expression of endogenous melatonin. *J Pineal Res* 42,254-260 (2007)
39. PC Redondo, GM Salido, JA Rosado, JA Pariente: Effect of hydrogen peroxide on Ca²⁺ mobilisation in human platelets through sulphhydryl oxidation dependent and independent mechanisms. *Biochem Pharmacol* 67,491-502 (2004)
40. N Alexandru, I Jardín, D Popov, M Simionescu, J García-Estaño, GM Salido, JA Rosado: Effect of homocysteine on calcium mobilization and platelet function in type 2 diabetes mellitus. *J Cell Mol Med* 12,2015-2026 (2008)
41. L Di Bella, L Gualano: Key aspects of melatonin physiology: thirty years of research. *Neuro Endocrinol Lett* 27,425-432 (2006)
42. AL Morera, P Abreu: Existence of melatonin in human platelets. *J Pineal Res* 39,432-433 (2005)
43. A Dominguez-Rodriguez, P Abreu-Gonzalez, A Jimenez-Sosa, P Avanzas, F Bosa-Ojeda, JC Kaski: Usefulness of intraplatelet melatonin levels to predict angiographic no-reflow after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 106,1540-1544 (2010)
44. Y Xu, Y Huo, MC Toufektsian, SI Ramos, Y Ma, AD Tejani, BA French, Z Yang: Activated platelets contribute importantly to myocardial reperfusion injury. *Am J Physiol Heart Circ Physiol* 290,H692-H699 (2006)
45. A Dominguez-Rodriguez, P Abreu-Gonzalez, MJ Garcia-Gonzalez, S Samimi-Fard, RJ Reiter, JC Kaski: Association of ischemia-modified albumin and melatonin in patients with ST-elevation myocardial infarction. *Atherosclerosis* 199,73-78 (2008)
46. M Crompton: Mitochondrial intermembrane junctional complexes and their role in cell death. *J Physiol* 529,11-21 (2000)
47. AP Halestrap: Mitochondria and preconditioning: a connexin connection? *Circ Res* 99,10-12 (2006)
48. DJ Hausenloy, DM Yellon: The mitochondrial permeability transition pore: its fundamental role in mediating cell death during ischaemia and reperfusion. *J Mol Cell Cardiol* 35,339-341 (2003)
49. AP Halestrap, SJ Clarke, SA Javadov: Mitochondrial permeability transition pore opening during myocardial

reperfusion--a target for cardioprotection. *Cardiovasc Res* 61,372-385 (2004)

50. J Leon, D Acuña-Castroviejo, G Escames, DX Tan, RJ Reiter: Melatonin mitigates mitochondrial malfunction. *J Pineal Res* 38,1-9 (2005)

51. G Petrosillo, G Colantuono, N Moro, FM Ruggiero, E Tiravanti, N Di Venosa, T Fiore, G Paradies: Melatonin protects against heart ischemia-reperfusion injury by inhibiting mitochondrial permeability transition pore opening. *Am J Physiol Heart Circ Physiol* 297,H1487-H1493 (2009)

52. ML Dubocovich, K Markowska: Functional MT1 and MT2 melatonin receptors in mammals. *Endocrine* 27,101-110 (2005)

53. C Ekmekcioglu, P Haslmayer, C Philipp, MR Mehrabi, HD Glogar, M Grimm, T Thalhammer, W Marktl: 24h variation in the expression of the mt1 melatonin receptor subtype in coronary arteries derived from patients with coronary heart disease. *Chronobiol Int* 18,973-985 (2001)

54. C Ekmekcioglu, T Thalhammer, S Humpeler, MR Mehrabi, HD Glogar, T Hölzenbein, O Markovic, VJ Leibetseder, G Strauss-Blasche, W Marktl: The melatonin receptor subtype MT2 is present in the human cardiovascular system. *J Pineal Res* 35,40-44 (2003)

55. R Jockers, P Maurice, JA Boutin, P Delagrèze: Melatonin receptors, heterodimerization, signal transduction and binding sites: what's new? *Br J Pharmacol* 154,1182-1195 (2008)

56. S Samimi-Fard, P Abreu-Gonzalez, A Dominguez-Rodriguez, A Jimenez-Sosa: A case-control study of melatonin receptor type 1A polymorphism and acute myocardial infarction in a Spanish population. *J Pineal Research* 51,400-404 (2011)

57. O Szárszoi, G Asemu, J Vanecek, B Ost'adal, F Kolár: Effects of melatonin on ischemia and reperfusion injury of the rat heart. *Cardiovasc Drugs Ther* 15,251-257 (2001)

58. E Sahna, A Acet, MK Ozer, E Olmez: Myocardial ischemia-reperfusion in rats: reduction of infarct size by either supplemental physiological or pharmacological doses of melatonin. *J Pineal Res* 33,234-238 (2002)

59. E Sahna, H Parlakpinar, MK Ozer, F Ozturk, F Ozugurlu, A Acet: Melatonin protects against myocardial doxorubicin toxicity in rats: role of physiological concentrations. *J Pineal Res* 35,257-261 (2003)

60. P Dobsak, J Siegelova, JC Eicher, J Jancik, H Svacinova, J Vasku, S Kuchtickova, M Horky, JE Wolf: Melatonin protects against ischemia-reperfusion injury and inhibits apoptosis in isolated working rat heart. *Pathophysiology* 9,179-187 (2003)

61. A Kaçmaz, EY User, AO Sehirli, M Tilki, S Ozkan, G Sener: Protective effect of melatonin against ischemia/reperfusion-induced oxidative remote organ injury in the rat. *Surg Today* 35,744-750 (2005)

62. S Genade, K Ytrehus, A Lochner: Melatonin prevent cardioprotection induced by a multi-cycle ischaemic preconditioning protocol in the isolated perfused rat heart. *Cardiovasc J S Afr* 17,239-244 (2006)

63. A Dominguez-Rodriguez, P Abreu-Gonzalez, MJ Garcia-GonzalezJ, JC Kaski, RJ Reiter, A Jimenez-Sosa: A unicenter, randomized, double-blind, parallel-group, placebo-controlled study of Melatonin as an Adjunct in patients with acute myocardiAl Infarction undergoing primary Angioplasty The Melatonin Adjunct in the acute myocardiAl Infarction treated with Angioplasty (MARIA) trial: study design and rationale. *Contemp Clin Trials* 28,532-539 (2007)

64. A Dominguez-Rodriguez, P Abreu-Gonzalez: Melatonin: Still a forgotten antioxidant. *Int J Cardiol* 149,382 (2011)

65. A Korkmaz, RJ Reiter, T Topal, LC Manchester, S Oter, DX Tan: Melatonin: an established antioxidant worthy of use in clinical trials. *Mol Med* 15,43-50 (2009)

66. RJ Reiter, F Gultekin, LJ Flores, MP Terron, DX Tan: Melatonin: potencial utility for improving public health. *TAF Prev Med Bull* 5,131-158 (2006)

67. Z Chen, CC Chua, J Gao, RC Hamdy, BH Chua: Protective effect of melatonin on myocardial infarction. *Am J Physiol Heart Circ Physiol* 284,H1618-H1624 (2003)

68. MLV Seabra, M Bignotto, LR Pinto, S Tufik: Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. *J Pineal Res* 29,193-200 (2000)

69. PD Penev, PC Zee: Melatonin: A clinical perspective. *Ann Neurol* 42,545-553 (1997)

70. J Leon, G Escames, MI Rodríguez, LC López, V Tapias, A Entrena, E Camacho, MD Carrión, MA Gallo, A Espinosa DX, Tan, RJ Reiter, D Acuña-Castroviejo: Inhibition of neuronal nitric oxide synthase activity by N1-acetyl-5-methoxykynuramine, a brain metabolite of melatonin. *J Neurochem* 98,2023-2033 (2006)

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