Melatonin and cardiac pathophysiology

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Abstract

Melatonin, an indole produced in several organs but most notably in the pineal gland, has a variety of effects that influence cardiac pathophysiology. Herein, we summarize the findings that illustrate the ability of melatonin to attenuate the severity of hypertension, limit myocardial damage, improve the function of the ischemic-reperfused heart, protect the heart from the toxicity of anthracycline drugs and from an immunosuppressant drug (cyclosporine A), and reduce cardiac hypertrophy and the associated pathophysiology caused by hyperthyroidism. The protective actions of melatonin at the level of the heart probably involve membrane melatonin receptors that exist on cardiomyocytes, in addition functions of melatonin as an antioxidant that are not receptor mediated. Whereas studies to date have been performed primarily in experimental animals, the uncommonly low toxicity of melatonin warrants tests of its utility in humans in cases of cardiac pathophysiology.
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Introduction

Endogenously produced and exogenously administered melatonin may be of benefit to the cardiovascular system. Melatonin, *N*-acetyl-5-methoxytrypamine, is best known for its influence on circadian physiology. It was initially believed to be produced almost exclusively in the pineal gland [1], but recent data have indicated that it is likely to be produced in the heart also [2].

Melatonin may influence cardiovascular pathophysiology via both receptor-mediated [3] and receptor-independent [4] mechanisms. The classic melatonin membrane receptors (MT1 and MT2) are present in the heart and throughout the vascular system. Moreover, nuclear binding sites for melatonin exist [5]. The receptor-independent actions of melatonin relate to its ability, and that of its metabolites, to function as antioxidants [5–7].

Melatonin and hypertension

Removal of the pineal gland, a major source of circulating melatonin, causes a gradual, sustained increase in blood pressure. Moreover, melatonin treatment of spontaneously hypertensive rats decreases mean arterial pressure and heart rate, enhances relaxation of mesenteric arteries, and improves baroreflex responses [8]. Young healthy men and women have lower systolic, diastolic, and mean arterial pressure, and reduced blood norepinephrine (adrenaline) concentrations after taking melatonin.

The circadian rhythm of blood melatonin has a role in the normal daily fluctuation in blood pressure. Blood pressure is greatest during the daytime, when melatonin concentrations are least; these relative values are reversed at night [9]. Those individuals whose blood pressure decreases at night are referred to as ''dippers''. Individuals who lack a nocturnal increase in blood melatonin concentrations do not experience a decrease in night-time blood pressure – that is, they are ''non dippers''. Failure of a night-time reduction in blood pressure increases the 24 h mean pressure and exaggerates the strain on the cardiovascular system, which reportedly contributes to an increased risk of a cardiovascular accident and mortality [10].

In a double-blinded cross-over study, 16 men with essential hypertension given melatonin for 3 weeks, 1 h before sleep onset, exhibited reduced nocturnal systolic and diastolic blood pressures, by 6 and 4 mm Hg, respectively [11]. The mechanisms whereby melatonin influences blood pressure could involve any of the following: (i) a direct effect on neural centers governing cardiovascular status; (ii) reduction in catecholamine concentrations; (iii) relaxing smooth muscle in blood vessels; (iv) antioxidative actions. The ability of melatonin to modulate blood pressure may be a result of both receptor-mediated and receptor-independent processes.

Melatonin and cardiac ischemic-reperfusion injury

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are considered to be major contributors to cardiac damage during ischemia-reperfusion injury. Thus antioxidant strategies have often been considered in the prevention of ischemia-reperfusion damage. Of special interest in this regard are antioxidants that scavenge radicals at the mitochondrial level, which melatonin does [12]. Melatonin has frequently been tested for its ability to arrest cellular and molecular damage associated with a transitory interruption of the blood supply to the heart. These studies have uniformly shown that it is beneficial in reducing cardiac ischemia-reperfusion injury [4,13].

Several animal models have been used to document the protective actions of melatonin at the level of the heart. An isolated perfused heart model (Langendorff) in which the anterior descending coronary artery was temporarily ligated caused the heart to experience arrhythmias, including premature ventricular contraction and ventricular fibrillation upon reperfusion – alterations that often contribute to mortality [4]. When melatonin (1–250 μm) was infused during the ischemic and reperfusion episodes, the arrhythmias were prevented [14].

Not only cardiac pathophysiology, but also tissue destruction in the hypoxic-re-oxygenated heart is ameliorated by melatonin. Thus melatonin reduced infarct size, limited lipid peroxidation, reduced production of superoxide anion radical ($O_2^{\bullet-}$) and hydroxyl radical ($^{\bullet}OH$), decreased myeloperoxidase activity in hearts undergoing ischemia-reperfusion, and reduced the rate of death of the animals [4,13,15,16]. In an isolated working heart model, Dobsak et al [17] found that melatonin improved hemodynamic parameters, reduced postperfusion ventricular fibrillation, decreased apoptotic cardiomyocyte death, and reduced the formation of peroxyl radical ($LOO^{\bullet}$). In view of the reduction in tissue damage mediated by free radicals and the decrease in generation of ROS/RNS, the protective effects of melatonin in the ischemia-reperfusion heart were probably, at least in part, a result of the direct scavenging activity of melatonin or its stimulation of antioxidative enzymes, or both.

Melatonin and cardiotoxic drugs

Anthracyclines are chemotherapeutic drugs that cause irreversible myocardial damage, leading to life-threatening congestive heart failure. The cardiomyopathy associated with anthracycline usage is known to be mediated, in large part, by their ability to generate free radicals. As melatonin and its metabolites effectively reduce the oxidation of essential molecules [6,7], they would be expected to protect the heart from anthracycline-mediated toxicity.

When given to rats, doxorubicin alone (cumulative dose of 15 mg/kg) damaged the heart, as indicated by increased myocardial lipid peroxidation, ultrastructural damage to the heart musculature, reduced heart-to-body weight ratio, and decreased arterial pressure and left ventricular fractional shortening. Each of these changes was alleviated when melatonin was given in conjunction with the doxorubicin [18]. Subsequently, dozens of publications have confirmed the ability of melatonin to reduce the cardiotoxicity of doxorubicin [19]. It has also been shown to protect the heart from daunorubicin [20] and epirubicin [21].

Cyclosporine A (CsA) is a prototypic immunosuppressant drug commonly used to inhibit immune function in individuals receiving allotransplants, thereby reducing organ rejection. The toxicity of this molecule is most prominently manifested in the kidneys; however, collateral damage also occurs in the heart. When rats were treated for 21 days with subcutaneous CsA (15 mg/kg), increased concentrations of malondialdehyde, an oxidatively damaged lipid product, increased in the heart, whereas the activities of two antioxidative enzymes (superoxide dismutase

and catalase) and the cellular concentrations of reduced glutathione were diminished. Immunocytochemical evaluation of the cardiac tissue of CsA-treated rats confirmed high concentrations of heat-shock protein 70 (HSP70) and increased amounts of collagen. In addition, the number of apoptotic cells was increased [22,23]. The negative biochemical, morphological and immunocytochemical changes were reversed in the animals concurrently treated with melatonin (injected as a solution or in solid lipid nanoparticles). Because the protective effects of melatonin were diminished when the rats were given the membrane melatonin receptor blocker, luzindole, the authors presumed that the beneficial effects were receptor mediated [22], although this was less apparent when the indole was administered in nanoparticles [23].

Melatonin and hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a disease that causes a large number of deaths annually. Heart enlargement is normally a compensatory response, but the function of the hypertrophied cardiac muscle eventually becomes abnormal, leading to heart failure.

Hyperthyroidism is an endocrine condition that causes cardiac hypertrophy. Because the hyperthyroid state is associated with increased production of free radicals, Ghosh et al [24] compared the effects of two antioxidants, melatonin (2 mg/100 g body weight daily) and vitamin E (4 mg/100 g body weight daily), in potentially alleviating cardiac enlargement and the associated pathophysiology. When rats were treated with 3,5,3′-tri-iodo-L-thyronine (8 mg/100 g body weight daily) for 15 days, all the following changes were observed: cardiac enlargement, increased generation of lipid hydroperoxides and $^\bullet$OH, inhibition of copper/zinc superoxide dismutase, reduction in the glucose transporter GLUT4, downregulation of myocyte enhancer factor-2 (a regulator of GLUT4 expression), and increased B-type natriuretic peptide (a marker of heart failure). Each of these changes was reversed by concurrent administration of melatonin and partially prevented by vitamin E. Also, glucose uptake in the hypertrophic left ventricular cardiomyocytes was restored by both antioxidants.

These findings indicate that free radicals are a major contributor to cardiac pathophysiology under conditions of heart enlargement in hyperthyroidism. Vitamin E, at twice the dose of melatonin, was less effective in reversing the changes induced by 3,5,3′-tri-iodo-L-thyronine than was melatonin. The effects of melatonin may have been mediated by receptor-independent (free radical scavenging) or receptor-dependent processes [25].

Conclusions

Melatonin obviously has a variety of beneficial effects with reference to cardiovascular pathophysiology, including in the treatment of hypertension, ischemia-reperfusion injury, drug toxicity, and cardiac hypertrophy. Given the severity of these conditions and the uncommonly low toxicity of melatonin, clinical trials using this indole are highly justified. Unless the findings in animal investigations are totally misleading, it seems likely that melatonin will have similar protective effects at the level of the human heart. ■

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