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REVIEW

Myocardial ischemia-reperfusion injury: Possible role of melatonin

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Abstract

Our knowledge and understanding of the pathophysiology of coronary atherosclerosis has increased enormously over the last 20 years. Reperfusion through thrombolysis or percutaneous coronary angioplasty is the standard treatment for preventing acute myocardial infarction. Early reperfusion is an absolute prerequisite for survival of the ischemic myocardium, but reperfusion itself may lead to accelerated and additional myocardial injury beyond that generated by ischemia alone. These outcomes, in a range of reperfusion-associated pathologies, are collectively termed "reperfusion injuries". Reactive oxygen species are known to be produced in large quantities in the first few minutes of the post-ischemia reperfusion process. Similarly, scientific evidence from the last 15 years has suggested that melatonin has beneficial effects on the cardiovascular system. The presence of vascular melatoninergic receptor binding sites has been demonstrated; these receptors are functionally linked to vasoconstrictor or vasodilatory effects of melatonin. It has been shown that patients with coronary heart disease have a low melatonin production rate, especially those with higher risk of cardiac infarction and/or sudden death. Melatonin attenuates molecular and cellular damage resulting from cardiac ischemia-reperfusion in which destructive free radicals are involved.

Key words: Ischemia-reperfusion injury; Melatonin; Acute myocardial infarction; Reactive oxygen species; Primary percutaneous coronary intervention

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INTRODUCTION

Acute coronary occlusion is the leading cause of morbidity and mortality in the Western world. According to the World Health Organisation, it will be the major cause of death in the world by the year 2020[1]. Despite effective reperfusion of epicardial coronary arteries by percutaneous coronary intervention or thrombolysis in acute ST-segment elevation myocardial infarction, substantial morbidity and mortality remain elevated[2]. Infarct size is an important determinant of the short- and long-term outcome after acute myocardial infarction[3].

Although beneficial in terms of myocardial salvage,

reperfusion itself may contribute to additional damage of the myocardium, due to the combined processes known as "ischemia-reperfusion injury"[4]. The pathogenesis of myocardial ischemia-reperfusion injury is a multifactorial process involving the interaction of multiple mechanisms. Partially reduced oxygen species, including the superoxide anion radical, hydroxyl radical, and hydrogen peroxide, are generated intracellularly as products of oxygen metabolism[4].

These reactive oxygen species cause peroxidation of membrane lipids, denaturation of proteins, and modification of DNA, all of which can ultimately lead to cell death. In mammals, cell damage induced by reduced oxygen species can also initiate local inflammatory responses, which then lead to further oxidant-mediated tissue injury[4]. Because there is strong evidence that free radicals contribute to postischemic injury, antioxidant therapy could be extremely effective in reducing the cellular damage. However, the usefulness of this therapy is limited by a number of factors, in particular the ability of the antioxidants to penetrate the cell membrane and to scavenge free radicals *in situ*. Recent publications present evidence that the newly discovered antioxidant melatonin has significant protective actions against the cardiac damage occurring during ischemia-reperfusion injury[5].

CIRCADIAN RHYTHM AND CARDIOVASCULAR EVENTS

Almost all living organisms have developed biological rhythms linked to the day/night or light/dark cycles of the sun. The impact of these rhythms on a variety of physiological functions in humans has been recognized for a long time[6]. The internal oscillator, or control station regulating the body's circadian clock, is the suprachiasmatic nucleus, a tiny structure located in the hypothalamus above the optic chiasm[7]. The suprachiasmatic nucleus processes external signals such as ambient light, and internal signals from the brain to regulate a variety of cyclic functions, including body temperature, sleep/wake cycles, and secretion of hormones such as melatonin[6].

Evidence gathered over the past 15 years suggests that melatonin influences several functions of the cardiovascular system. Similar to other organs and systems, the cardiovascular system exhibits diurnal and seasonal rhythms in heart rate, blood pressure, and platelet and endothelial function, which are likely to be modulated by the suprachiasmatic nucleus and, possibly, by the melatoninergic system[8]. The circadian pacemaker within the suprachiasmatic nucleus stimulates the pineal gland to produce melatonin at night[6].

The amount of melatonin produced by the pineal gland of mammals changes with the age of the animal. The production of melatonin wanes with the aging process[9]. In humans, melatonin production not only diminishes with age, but it is also significantly lower in many age-related diseases, including cardiovascular disease[10,11]. Mounting evidence reveals that the rhythmicity of melatonin has a crucial role in a variety of cardiovascular pathophysiological processes including antiinflammatory, antioxidant, antihypertensive and, possibly, antilipidemic functions[12]. In addition, we have demonstrated that light/dark variations in the production of endogenous inflammatory markers in patients with coronary artery disease may be related, at least in part, to day/night fluctuations in circulating melatonin levels[13-15].

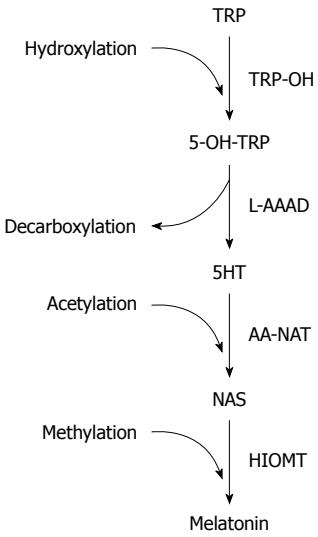

Figure 1 Biosynthetic pathways of melatonin. TRP: Tryptophan; TRP-OH: Tryptophan hydroxylase; L-AAAD: L Aromatic amino acid decarboxylase; 5HT: 5-Hydroxy tryptamine (Serotonin); AA-NAT: Aryl alkyl-amine-n-acetyl-transferase; NAS: *N*-acetyl-serotonin; HIOMT: Hydroxyindole *O*-methyltransferase.

MELATONIN SYNTHESIS

L-tryptophan circulating in the blood is taken up by pinealocytes. Via several enzymatic steps including tryptophan 5-hydroxylation, decarboxylation, *N*-acetylation and *O*-methylation, in that sequence, *N*-acetyl-5-methoxytryptamine (melatonin) is synthesized[16] (Figure 1). During melatonin synthesis, two enzymes play important roles in its production, namely arylalkylamine *N*-acetyl-transferase and hydroxyindole *O*-methyltransferase (HIOMT). The former *N*-acetylates serotonin to produce *N*-acetyl serotonin which is then *O*-methylated by HIOMT to generate *N*-acetyl-5-methoxytryptamine (melatonin)[17].

The melatonin is then secreted by the pineal gland following a circadian rhythm in response to environmental light/dark cycles. The amplitude of the diurnal melatonin cycle is attenuated by age. The diurnal/nocturnal levels of blood melatonin can range between 8 ± 2 pg/mL (light phase) and 81 ± 11 pg/mL (dark phase). The distribution of melatonin in the human being is very broad. As a result of being a non polar molecule, the melatonin is released upon biosynthesis into the extracellular fluid to the general circulation from which it easily crosses the membranes of various cells and is excreted in saliva, bile, cerebrospinal fluid, milk, urine, *etc*[18].

Melatonin mediates a variety of physiological responses through membrane and nuclear binding sites. Two mammalian receptor subtypes have been cloned and designated as MT_1 and MT_2[19]. Animal studies suggest that melatonin

has dual effects on the vasculature, depending on the specific receptor type activated[9] with vasoconstriction occurring after MT_1 activation and vasorelaxation after MT_2 activation. The likely mechanisms of melatonin's actions are *via* a modulation of the noradrenergic and/or nitric oxide effects in the system[20]. MT_1 and MT_2 receptors have also been identified in human coronary arteries from pathological samples and also from healthy controls. The functional relevance of melatonin receptors in human coronary arteries requires additional study[21-23].

MELATONIN AND REPERFUSION INJURY

The results of many publications suggest a decrease in circulating melatonin concentration at different stages of the coronary heart disease in humans. Furthermore, experimental and clinical data suggest that melatonin is involved in normal cardiovascular physiology[5]. Melatonin is known to be a powerful scavenger of the hydroxyl radical and to protect against cardiac tissue damage mediated by oxidative stress[5]. Also, metabolites of melatonin including N^1-acetyl-N^2-formyl-5-methoxykynuramine and *N*-acetyl-5-methoxykynuramine are direct free radical scavengers and also upregulate antioxidant enzymes and downregulate pro-oxidative and pro-inflammatory enzymes. In many disease states which reportedly involve reactive oxygen and/or nitrogen species, endogenous melatonin levels are significantly lower than in healthy subjects[24]. In comparison to the majority of antioxidant compounds that act on a single reactive species (Vitamin C, Vitamin E), melatonin is the most potent endogenous free radical acting on both reactive oxygen species, such as the hydroxyl radical, superoxide anion, hydrogen peroxide and singlet oxygen, and reactive nitrogen species, such as nitric oxide and the peroxynitrite anion[25]. Our group analyzed serum levels of melatonin and parameters of oxidative stress in a cohort of 25 patients diagnosed with acute myocardial infarction and 25 subjects with no evidence of coronary artery disease as controls. We demonstrated that acute myocardial infarction is associated with a nocturnal serum melatonin deficit as well as increased oxidative stress[11]. However, it is uncertain whether low melatonin levels in these patients are the result of melatonin consumption caused by scavenging of the elevated free radical production, or represent lower melatonin production, and hence less protection against oxidative stress[24].

Recently, the role of mitochondrial ATP-sensitive K^+ channel opening was further revealed by melatonin-mediated protection against heart ischemia-reperfusion injury[26]. The regulatory mechanism is related to inhibition of cardiolipin peroxidation in mitochondria and prevention of mitochondrial permeability transition and cytochrome c release[27]. Melatonin seems to have antiapoptotic actions in normal cells *via* the regulation of a permeability transition pore and cytochrome c release[28]; opposite regulation has been observed in different cell types, such as tumor cells[29]. This suggests that there exists considerable variability in the permeabilization of the outer membrane in different cell types treated with melatonin. Therefore, the role of mitochondrial ATP-sensitive K^+ channels in the regulation of cytochrome c release and reactive oxidative stress-induced cell death needs to be studied carefully[30].

In a recent study in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, we observed a relationship between melatonin concentration and ischemia-modified albumin, a marker of myocardial ischemia[31]. On the basis of this finding, our data suggested that melatonin acts as a potent antioxidant, reducing myocardial damage induced by ischemia-reperfusion[31]. We are currently assessing, in a prospective trial, The Melatonin Adjunct in acute myocaRdial Infarction treated with Angioplasty trial, whether pharmacological doses of melatonin confers cardioprotection against ischemia-reperfusion injury in ST-elevation myocardial infarction patients[32]. The importance of this study is emphasized by the fact when, exogenously administered, melatonin is quickly distributed throughout the organism. It crosses all morphophysiologic barriers and it enters cardiac cells with ease. The highest intracellular concentrations of melatonin appear to be in the mitochondria. This is especially important as the mitochondria are a major site of free radical generation and oxidative stress. Melatonin is a molecule with low toxicity. Its administration in a broad range of concentrations by oral and intravenous routes has proven to be safe in human studies[24].

CONCLUSION

Many aspects of cardiovascular physiology are subject to diurnal variations, and serious adverse cardiovascular events, including myocardial infarction and sudden cardiac death, appear to be conditioned by the time of day.

Neurohormones such as melatonin, which are particularly relevant to the cardiovascular system, exhibit a diurnal variation and they may play a role in the synchronization of molecular circadian clocks in the suprachiasmatic nucleus. Furthermore, mounting evidence indicates that the blood melatonin rhythm has a crucial role in several cardiovascular functions. Melatonin has antioxidant, anti-inflammatory, and chronobiotic regulatory functions.

We recognize that melatonin is of special interest, being an endogenous molecule that can be used in humans, and which is also safe. We will await the results of our phase Ⅱ study of melatonin with great interest.

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