Chapter

Melatonin in Cardiovascular Diseases

Hülya Kara and Adem Kara

Abstract

Melatonin is an endocrine product released from the gland known as the pineal gland and is predominantly secreted during the night. Light exerts an inhibitory effect on melatonin secretion in the pineal gland. The suprachiasmatic nucleus controls pineal melatonin synthesis and its release *via* the peripheral sympathetic nervous system, which includes synapses in the intermediolateral cell column of the thoracic cord and its projection toward the superior cervical ganglia. Melatonin regulates many physiological functions in the body through membrane receptors and nuclear binding sites. In a chick study, the presence of melatonin receptors in cardiomyocytes was reported and, in another study, MT1 and MT2 membrane receptors were identified in left ventricular cardiomyocytes of the human heart. For this reason, it is suggested that melatonin has some regulatory effects on the cardiovascular system. Ischemic heart disease and myocardial infarctions are the main cause of cardiovascular death. Studies have shown that melatonin applications reduce the amount of blood cholesterol, LDL, and triglyceride and increase the amount of HDL. In light of these data, it can be said that melatonin is an important cardiovascular system protector. In this chapter, the protective effects and mechanisms of melatonin on the cardiovascular system will be discussed.

Keywords: melatonin, cardiovascular diseases, heart, antioxidant, anti-inflammatory

1. Introduction

Melatonin [N-acetyl-5-methoxytryptamine] is a neuroendocrine hormone and was firstly isolated from the bovine pineal gland in 1958 by Lerner et al. [1]. The pineal gland is originating from the prosencephalon and was first identified by Herophilus in 325–280 BC. Photic data is received by photoreceptors in the retina and transmitted to the superior cervical ganglion via sympathetic preganglionic adrenergic neurons. Melatonin is synthesized from tryptophan through a number of enzymatic reactions in pinealocytes [2]. Melatonin secretion is regulated by the day/night events. In addition, while norepinephrine stimulates beta1-adrenoreceptors synthesis and secretion of melatonin, stimulation of alpha1-adrenoreceptors increases the reaction [3, 4]. While melatonin is mainly secreted from the pineal gland, melatonin is also secreted from the retina, gastrointestinal tract tissues, skin, platelets, and bone marrow. Melatonin production is described in **Figure 1**.

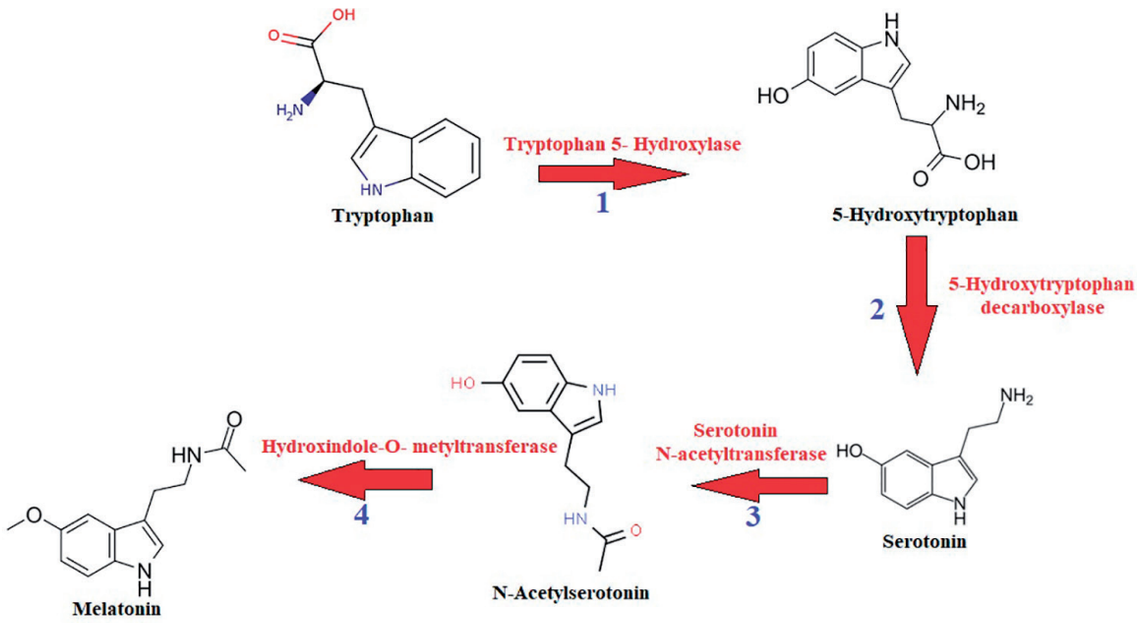

Figure 1.
Synthesis of melatonin from tryptophan.

Melatonin is given to the body by oral or intravenous which is rapidly absorbed and metabolized mainly in the liver and secondarily in the kidneys. Two types of membrane receptors [MT1 and MT2] and one type of cytoplasmic receptor [MT3] for melatonin were determined in humans [5]. Melatonin is both a lipid- and water-soluble hormone, with three types of high-affinity G-protein-coupled receptors mainly MT1, MT2, and MT3. MT1 is a receptor located mainly in the suprachiasmatic nucleus (SCN) and to a lesser extent in the pituitary and cerebral vascular systems (CVSs). MT2 is found in the retina. In addition, melatonin receptors in coronary arteries have been demonstrated [5]. Besides CVSs, melatonin receptors are found in multiple tissues. MT3 receptors are nuclear binding sites of melatonin located in the cytosol [6], acting as an enzyme and responsible for the detoxification of harmful agents. MT1 receptors are mainly found in the cardiovascular system. It can also be found in the immune system, placenta, retina, spleen, liver, breast, kidney, skin, testis, ovary, pancreas, adrenal cortex, retina, and brain [4]. MT2 is found in the immune system, mammary glands, retinal pituitary gland, adipose tissue, SCN, blood vessels, testicles, gastrointestinal tract, kidney, and skin.

2. Melatonin and CVDs relationship

Nowadays, deaths due to CVD are among the most important causes of death, approximately one-third of all deaths. Considering the pathophysiology of cardiovascular diseases, preventive measures and effective substances will reduce the formation and development of these disorders [7].

Melatonin is gaining more and more important in the pathophysiology of CVD. Because low secretion of melatonin has been reported to be associated with various CVDs, including myocardial infarction (MI), coronary heart disease, congestive heart failure, and nocturnal hypertension [8, 9]. Furthermore, working in illuminated environments also causes glucose intolerance, insulin resistance, metabolic circadian irregularity and sleep disturbance with aging, and lack of melatonin secretion [10].

Melatonin receptors have been identified within the cardiovascular system, including various vascular tissues. Hypertension and peripheral vasoconstriction have been reported in animals undergoing pinealectomy [8, 11].

3. Antioxidant and free radical scavenger activity of melatonin

Melatonin is a powerful antioxidant substance and also has protective effects on the mitochondria [12–15]. A study showed beneficial effects on plasma MDA, GSH, PCO, and NO levels after the administration of 5 mg of melatonin (twice a day) for 12 weeks in diabetic patients [15]. Melatonin performs its antioxidant and free radical scavenging activity through two main mechanisms. In the first mechanism, melatonin binds to the MT3 receptor and acts as an antioxidant by suppressing the electron transfer reactions of quinones [16]. In the second pathway, they scavenge free radicals [17]. Depending on the dose of endogenous or exogenous melatonin, it acts by receptor-dependent or receptor-independent mechanisms [18].

Additionally, the aforementioned two mechanisms, melatonin indirectly increases antioxidant enzymes such as glutathione peroxidase, glutathione reductase superoxide dismutase, and glucose-6-phosphate dehydrogenase and suppresses molecular damage under conditions of severe oxidative stress [19]. Antioxidant enzymes realize this stimulation via MT1 and MT2 receptors. Due to its high lipophilicity, melatonin can easily pass through cell membranes and reach intracellular compartments including the nucleus and mitochondria. Melatonin reduces cell death while maintaining normal mitochondrial function [20].

Melatonin and metabolites of melatonin [cyclic 3-hydroxymelatonin and N1-acetyl-N2-formyl-5-methoxyquinuramine] are free radical scavengers [18]. Therefore, melatonin and its metabolites support the main molecule in terms of the antioxidant effect. In addition, the total antioxidant capacity of melatonin is higher than that of other known antioxidants such as vitamin E and vitamin C under in vivo and in vitro conditions [4]. Recent studies have reported that melatonin decreases mammalian Mst1 phosphorylation and increases Sirt3 expression and modulates the autophagic cell death process. Autophagy is a lysosomal cell death process that removes damaged organelles and misfolded proteins to maintain cellular homeostasis [21]. Disruption in autophagy causes cardiac hypertrophy [22], heart failure [Thomas et al. 2013], and ischemia/reperfusion [I/R] damage [23]. Melatonin administration alleviated the left ventricular remodeling. Melatonin also reduces cardiac dysfunction in diabetic animals [24] and has shown a significant protective effect on ischemia/reperfusion [I/R] injury and hypertension [23, 25].

4. Melatonin and immune system

The immunological role of melatonin was first reported by Maestroni et al. in 1987 [26]. In the study, it was observed that immune functions were suppressed in conditions where melatonin formation was inhibited by continuous exposure to light or the administration of β-adrenergic receptor blockers at night. This effect of melatonin is not evident under normal conditions. However, the effect becomes evident in cases where the immune system is suppressed, such as aging, viral diseases,

corticosteroid use, or acute stress [27–29]. In another study, they reported that suppression of immune functions as a result of soft tissue trauma and hemorrhagic shock in mice was reversed with melatonin, and that chronic melatonin treatment increased natural killer cell activity in humans [30]. The effects of melatonin against immunosuppression or enhancing immune functions are related to its binding to specific receptors on T-helper lymphocytes. The binding of melatonin to these receptors increases the secretion of gamma-interferon, IL-2, or opioid peptides. In addition, the administration of melatonin in tumor-formed mice protected blood cells from the toxic effects of chemotherapeutic drugs [29]. Also, some studies reported the melatonin anti-inflammatory effect in periodontitis [31–36]. However, melatonin also shows an immunodepressant effect in relation to the dose. At high pharmacological doses (> 100 mg/kg BW), melatonin suppresses antibody formation [29]. The inhibitory effect of melatonin on the immune response and its antioxidant effect suggest that melatonin may be beneficial in organ transplantation. In addition, the lack of toxicity supports that this agent is an agent that can be used safely in transplantation [27].

5. Mechanisms for a relation cardiovascular disease

Melatonin stimulates the phospholipase C pathway by activating MT1 and MT2 receptors via the G inhibitor protein. This results in an increase in Ca++ concentration and leads to phosphorylation of protein kinase C (PKC). PKC activates the protein/activation transcription factor cAMP-responsive element-binding protein and activating transcription factor (CREB-ATF). This pathway immediately regulates early gene transcription and thus gene transcription regulation and antioxidant enzyme levels. The production of reactive oxygen species (ROS) stimulates the expression of genes involved in inflammatory processes in the cell. Thus, the transcription of nuclear factor kappa (NF-kB) increases the expression of these inflammatory genes. Inactive NF-kB resides in the cytoplasm due to an inhibitory subunit [I-kB]. I-κB is phosphorylated, and NF-κB is translocated into the nucleus via stimulation of the cells by oxidative stress. PKC may also activate NF-κB, and it binds to the κB response element in its target genes' enhancer and promoter regions. Some of these are located in the promoter regions of the major antioxidant enzymes. Thus, an early cellular response to oxidative stress activates the antioxidant systems [37–39]. The role of melatonin on the protein kinase C (PKC) and activating transcription factor (CREB-ATF) pathway is described in **Figure 2**.

Recent studies have reported the effects of melatonin [receptor-dependent and non-receptor-mediated] on the cardiovascular system. Melatonin causes vasoconstriction in cerebral arteries and vasodilation in peripheral vascular beds. Myocardial infarction (MI) risk, coronary heart patients with sudden death risk, high LDL-cholesterol levels, and also in hypertensive patients, melatonin levels were found to be low [40–42]. The vasodilator effect of melatonin also plays an important role in inducing sleep through thermoregulation. The effects of free radicals play an important role in oxidant damage, especially in the cardiovascular system, caused by high blood pressure [43]. In addition, a decrease was observed in echocardiographic measurements, biochemical parameters in the myocardium, and measured tissue damage parameters in experimental hypertension with melatonin administration [44] (**Figure 2**). It is known that inflammation plays an important role in coronary heart diseases including atherosclerosis. Active compounds released by immune cells that

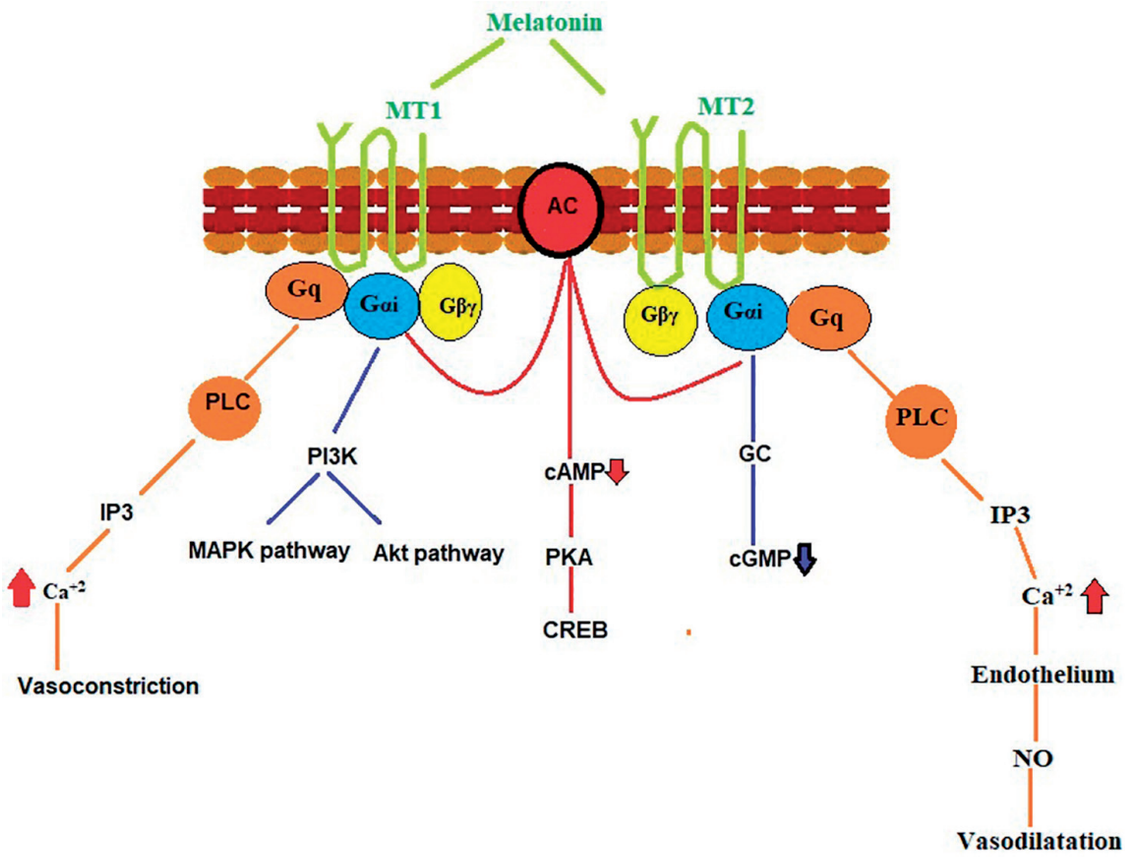

Figure 2.
MT 1 and MT 2 melatonin receptor signaling. PKA, protein kinase a; cAMP response element-binding protein; MT, melatonin receptor; Akt, threonine protein kinase B [PKB; also known as Akt]; cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CREB, IP3, inositol trisphosphate; MAPK, mitogen-activated protein kinase.

become dominant in the early stages of atherosclerosis cause the progression of both atherosclerotic lesions and inflammation. An increased incidence of MI and sudden death in coronary heart muscles have been associated with decreased melatonin levels in these patients. In animals with hyperlipidemia fed with high cholesterol, melatonin administration was found to be protective of the aorta by increasing antioxidant enzyme activities in these animals [45].

5.1 The relationship between melatonin and blood pressure

It has been reported in previous studies that blood pressure and catecholamine levels are related to circadian rhythm. Blood serum melatonin levels of patients with hypertension were found to be low [46]. In addition, melatonin administration has been found to decrease blood pressure in hypertensive and normotensive patients [47, 48]. Yıldız and Akdemir investigated the endogenous role of melatonin on arterial elasticity and blood pressure for arterial expandability as assessed by aortic pulse wave velocity [49]. Melatonin reduces vascular pressure through its receptor on the arterial wall or by modulation of autonomic activity [50]. It has been reported that the vasodilator effect of melatonin can be achieved by inhibiting the methylation of endothelial nitric oxide synthase [51]. In some studies, melatonin has been reported to cause vasoconstriction by inducing norepinephrine signaling as a result of melatonin binding to MT1 receptors on smooth muscle cells [52]. Doolen

et al. demonstrated a vasodilator effect on rat caudal arteries by administering 4-phenyl-2-acetamidotetralin, a selective MT2 agonist [53]. According to our current knowledge, MT1 receptor activation causes vasoconstriction, while MT2 receptor activation causes vasodilation [53]. Differential responses of the vascular bed to melatonin uptake are associated with different distribution of melatonin receptors.

5.2 The relationship between melatonin and lipid profile

Melatonin positively affects the lipid profile regarding CVD [54]. The intestinal system and liver play a significant active role in the metabolism and production of lipoproteins. Lipids are digested in the intestine system and then transported from the intestine to the liver as chylomicrons. In the liver, it is biochemically transformed, and free fatty acids are converted to triglycerides (TGs) and phospholipids. They are transported into the blood system by lipoproteins. LDL is the form of lipoprotein that carries cholesterol into cells, and it also tends to be oxidized by free oxygen radicals, damaging cells and promoting inflammation [55]. Some studies have focused on the damage caused by highly reactive oxygen species (ROS), which leads to atherosclerotic progression. An experimental study reported that melatonin supplementation with an atherogenic diet increased atherosclerotic lesions in the proximal aorta in hypercholesterolemic mice, in contrast to the majority of other studies, by increasing the susceptibility of atherogenic lipoproteins to γ-radiolysis and Cu2+ oxidation [55]. In another study, the administration of melatonin for 14 months in individuals with fatty liver disease (not alcoholic) showed that LDL and triglyceride levels decreased compared to the health group [56]. Melatonin administration reduced blood pressure as well as LDL-cholesterol levels [54]. Melatonin protects macromolecules from oxidation damage with its direct effect and free radical scavenging effect by stimulating antioxidant enzymes. The positive effects of melatonin on the lipid profile may be related to its anti-inflammatory and antioxidative effects. In addition, melatonin decreases lipid levels by increasing the conversion of endogenous cholesterol to bile acids and suppresses cholesterol synthesis and accumulation.

6. Recommendations for future research

Although the inflammation hypothesis provides a plausible and compelling explanation for CVDs, including their association with atherosclerosis, more research is needed to define the mechanisms linking the two diseases and how best to manage them to reduce the risk of inflammation and ROS production. Specific questions that the consensus panel believes should be addressed in future research include as follows:

1. Is inflammation an independent risk factor for CVD?

2. If inflammation is an independent risk factor for atherosclerosis and CVD, what is the mechanism of the association, and at what stage[s] of atherogenesis is it important?

3. Regardless of whether inhibition of ROS production is an independent risk factor for atherosclerosis and CVD, should risk factors for CVD in these situations be treated more aggressively than current guidelines recommend for the general population?

Conflict of interest

The authors declare no conflict of interest.

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