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REVIEW ARTICLE

Melatonin and the cardiovascular system

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Abstract

Melatonin concentrations in serum, as well as urinary levels of its main metabolite, 6-sulphatoxymelatonin, decrease with age. In the course of aging, the frequency of heart diseases, both acute and chronic, systematically increases. The evidence from the last 10 years suggests that melatonin influences the cardiovascular system. The presence of vascular melatoninergic receptors/binding sites has been demonstrated; these receptors are functionally linked with vasoconstrictor or vasodilatory effects of melatonin. Melatonin can contribute in cardioprotection of the rat heart, following myocardial ischemia. 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. There are clinical data reporting some alterations of melatonin in human stroke and coronary heart disease. The suprachiasmatic nucleus and, possibly, the melatoninergic system may also modulate cardiovascular rhythmicity. Hypercholesterolemia and hypertension are the other age-related symptoms. People with high levels of LDL-cholesterol have low levels of melatonin. It has been shown that melatonin suppresses the formation of cholesterol by 38% and reduces LDL accumulation by 42%. A 10-20% reduction of cholesterol concentration in women using the B-oval pill has been observed. It is a very important because, even a 10-15% reduction in blood cholesterol concentration has bee shown to result in a 20 to 30% decrease in the risk of coronary heart disease. People with hypertension have lower melatonin levels than those with normal blood pressure. The administration of the hormone in question declines blood pressure to normal range. It has been observed that melatonin, even in a dose 1 mg, reduced blood pressure and decreased catecholamine level after 90 min in human subjects. Melatonin may reduce blood pressure *via* the following mechanisms: 1) by a direct effect on the hypothalamus; 2) as an antioxidant which lowers blood pressure; 3) by decreasing the level of catecholamines, or 4) by relaxing the smooth muscle in the aorta wall.

It is well known that melatonin concentrations in serum, as well as urinary levels of its main metabolite, 6-sulphatoxymelatonin, decrease in elderly subjects [1]. In the course of aging, the incidence of heart diseases, both acute and chronic, systematically increases. The evidence from the last 10 years suggests that melatonin influences the cardiovascular system. Similarly to other organs and systems, the cardiovascular system exhibits diurnal and seasonal rhythms, including the heart rate, cardiac output, and blood pressure [2]. The suprachiasmatic nucleus and, possibly, the melatoninergic system can modulate the cardiovascular rhythm.

Data obtained in animals indicate that the cardiovascular response to melatonin may be mediated, at least in part, by reducing noradrenergic activity [3, 4]. Also in men, melatonin administration may exert suppressive effects on the sympathetic tone [5]. The facts that seasonal variation in blood pressure of patients on chronic beta-adrenergic receptor blockers was present [2] and that the circadian rhythm of the heart rate was maintained in patients after heart transplantation [6], indicate that seasonal and daily variations in the sympathetic tone may not be the only controlling factors, suggesting an involvement of some other mechanisms. The presence of vascular melatoninergic receptors/binding sites has been demonstrated, these receptors being functionally associated with vasoconstrictor or vasodilatory effects of melatonin. The receptors for melatonin have been detected in walls of cerebral and caudal arteries of rats [7, 8], as well as in walls of cerebral arteries of subhuman primates [9]. Direct actions of melatonin on blood vessels have also been reported [10, 11].

A decrease in nocturnal serum melatonin levels has been shown in patients with clinically non-characterised coronary artery disease. Urinary 6-sulphatoxymelatonin excretion was significantly lower in patients with unstable angina, compared to healthy subjects or patients with stable angina [12]. Brugger et al. [13] showed that serum melatonin concentration at night was more than five times lower in patients with coronary heart disease than in controls. The authors have suggested that melatonin reduces sympathetic activity, which is higher during the day. This effect is important for the body to relax at night. In the morning, an opposite effect can be observed – the concentration of melatonin decreases and, automatically, the sympathetic activity rises.

It has been observed that patients with coronary heart disease have a low melatonin production rate, which correlates with the stage of the disease, e.g., deeper decreases are observed in patients with higher risk of cardiac infarction and/or sudden death. Several studies suggest that some immunological factors can play an important role in the pathogenesis of coronary diseases, for example reactive C protein or cytokines. The increased cytokine levels augment the synthesis of hypothalamic corticotropin-releasing hormone (CRH) and the activity of the pituitary-adrenal axis [14, 15] by an activation of cytokine receptors in the endothelium of cerebral vessels. The data indicate that an increase in circulating CRH reduces melatonin secretion [16] or 6-sulphatoxymelatonin excretion with urine in humans [12].

In addition, the possible use of β-adrenoceptor blockers, which reduces melatonin synthesis, may be an important factor responsible for low melatonin levels in patients with coronary disease. Stoschitzky et al. [17] showed that beta-blockers decreased melatonin release *via* a specific inhibition of $beta_1$-receptors. Nathan et al. [18] demonstrated a dose-dependent relationship between β_1-receptor blockade and the suppression of nocturnal plasma melatonin in humans. On the other hand, Girotti et al. [12] did not observe any significant difference in the levels of 6-sulphatoxymelatonin excretion in patients, either treated or not treated with β-adrenoceptor blockers.

Lower nocturnal melatonin levels might be the cause of sleep disturbances which are well-known side effects of beta-adrenergic antagonists. Several studies indicate that sleep disorders occur more frequently in coronary patients than in non-coronary or normal subjects. Since low melatonin levels can be associated with sleep disturbances, at least in elderly patients, the low melatonin secretion, reported in coronary patients herein, could play a causal role in this respect.

Hypercholesterolemia and hypertension are the other age-related symptoms. People with high levels of low-density lipoprotein (LDL)-cholesterol have low levels of melatonin. It has been shown that melatonin suppresses the formation of cholesterol by 38% and reduces LDL accumulation by 42% in freshly isolated human mononuclear leukocytes [19]. Cohen [20] observed a 10-20% reduction of cholesterol in women using the B-oval pill. It is a very important fact because, for example, Angier [21] suggested that even a 10-15% decrease in blood cholesterol results in a 20 to 30% reduction of the risk of coronary heart disease.

Hoyos et al. [22] showed that chronic melatonin administration decreases serum total cholesterol and LDL-cholesterol, while increasing high-density lipoprotein (HDL)-cholesterol in diet-induced hypercholesterolemia in rats. The results of that study confirm that melatonin participates in the regulation of cholesterol metabolism and in the prevention of oxidative damage to membranes.

Also other authors have shown that melatonin can inhibit the oxidation of LDL [23, 24]. Seegar et al. [25] demonstrated that - although melatonin itself appears to have little anti-atherogenic activity during LDL oxidation - melatonin precursors and breakdown products inhibit LDL oxidation, as compared to vitamin E. In contrast, Abyja et al. [26] reported that melatonin could not prevent LDL lipid peroxidation. Wakatsuki et al. [27] found that melatonin treatment reduced LDL susceptibility to oxidative modification in normolipidemic post-menopausal women. Thus, the oxidised form of LDL-cholesterol (ox-LDL) plays a principal role in the development of atherosclerosis. The findings of Okatani et al. [28] suggest that ox-LDL potentiates the vascular tension in human umbilical artery, probably by suppressing the endothelial synthesis of nitric oxide (NO). In that experiment, melatonin significantly suppressed the vasospastic effect of ox-LDL, possibly because of the fact that

it generally scavenges the hydroxyl radical induced by this fraction of lipid.

The administration of melatonin reduces blood pressure in normal [4], pinealectomized [29], and spontaneously hypertensive rats [30], whereas pinealectomy induces hypertension in rats [31]. Laflamme et al. [32] suggested that melatonin may act as the main antihypertensive agent by stimulating the central inhibitory adrenergic pathways, thereby diminishing the basal tone of the peripheral sympathetic nervous system. The hypotensive action of melatonin appears to be, at least partly, associated with the inhibition of basal sympathoadrenal tone and, finally, it could be mediated by blocking the postsynaptic α_1-adrenergic receptor-induced inositol phosphate formation. On the other hand, a group of authors from Canada [33] concluded that the hypotensive effect of melatonin in rats was not mediated either by melatonin receptors or α-adrenoceptors. Rather, could antioxidative effect of melatonin become important in hypertensive rats, which either demonstrate a lower content of endogenous antioxidants or a greater sensitivity to free radicals of the vascular tissue.

Individuals with hypertension have lower melatonin levels than those with normal blood pressure but the administration of the hormone in question declines blood pressure to normal range. It has been shown that melatonin reduces blood pressure of both normo- [34-36] and hypertensive [37] subjects. Additionally, melatonin influences the resistance of large arteries to blood flow in both men [36] and young women [35].

Cagnacci et al. [35] examined the influence of melatonin administration in a dose of 1 mg on the circulation of young, healthy women. They found that melatonin greatly influences artery blood flow, decreases blood pressure, and blunts noradrenergic activation. Compared to that, Arangino et al. [36] observed that melatonin, in a dose 1 mg, reduced blood pressure and decreased catecholamine level after 90 min in human subjects. Even a decrease of 5 to 10 mm Hg in blood pressure is very important. Rich-Edwards et al. [38] suggested that a similar decrease in diastolic blood pressure in hypertensive subjects is associated with a 20% reduction of cardiovascular mortality. Arangino et al. [36] indicated that endogenous melatonin contributes to the nocturnal decrease in blood pressure and catecholamine levels.

It has been shown that aging and gonadal steroids influence the expression of vascular melatonin receptors in animals [39, 40]. Cagnacci et al. [41] examined the effect of melatonin on the vascular reactivity in postmenopausal women, either on or without hormone replacement therapy (HRT). They have found that the circulatory response to melatonin is preserved in postmenopausal women on HRT but not in untreated postmenopausal women. In their subsequent paper, Cagnacci et al. [42] found that melatonin increased NO levels only in HRT-treated but not in unreplaced postmenopausal women. These results indicate that melatonin may amplify the reported estrogen capacity to increase NOS. Since a normal night-time decline of blood pressure protects women from cardiovascular accidents [43], the authors have suggested that it may be the case that estradiol capability to maintain the circulatory response to melatonin represents one of the mechanisms mediating the reduction of the cardiovascular risk in postmenopausal women. Doolen et al. [44] attempted at determining whether oestrogen modulates the function of vascular melatonin receptors. They have found that estradiol appears to enhance MT2 melatonin receptor function in the thermoregulatory caudal artery of female rat, resulting in an increased vasodilatation in response to melatonin. In that experimental model, MT1 receptors mediated melatonin-induced vasoconstriction, while MT2 receptors mediated melatonin-induced vasodilatation [45].

Weekley [46] found that melatonin relaxed the smooth muscles lining the aorta in rats. The vascular endothelium may contribute to the regulation of vascular smooth muscle tone by producing such vasoconstrictors as endothelin-1 [47] and tromboxane [48], as well as vasodilators, such as prostacyclin [49] and NO [50]. Nitric oxide was originally identified as a principal endothelium-derived vascular relaxation factor. Okatani et al. [51] demonstrated that a pre-treatment with L-N^G-monomethyl arginine, a nitric oxide synthase (NOS) inhibitor, suppressed the potentiating effect of hydrogen peroxide (H_2O_2) on the vascular tension in umbilical artery segments, suggesting that H_2O_2 may exert its vasospastic effect by inhibiting NOS in the endothelium. Melatonin modulates NOS activity and, thereby, influences NO production [52, 53]. The results of the study of Wakatsuki et al. [54] indicate that H_2O_2 may impair NO synthesis in the endothelium of human umbilical arteries. Melatonin significantly suppresses the H_2O_2-induced inhibition effect of NO production, most likely through its ability to scavenge hydroxyl radicals.

The results of many publications suggest an impending decrease in circulating melatonin concentration at different stages of the coronary disease. The antioxidative properties of melatonin have been demonstrated during the last 10 years of studies [55-58]. The results of epidemiological studies have demonstrated a lower incidence of coronary artery disease and mortality rate in persons who consume larger quantities of antioxidants, like vitamin E, beta-carotene, and vitamin C in their diet [59]. The antioxidants, including melatonin, can play a beneficial role in reducing the incidence of coronary events. Tan et al. [60] observed that melatonin protected against arrhythmia induced by ischemia-reperfusion in isolated rat hearts. Melatonin reduced the damage induced by chemical hypoxia and reoxygenation in rat cardiomyocytes [61]. Also Morishima et al. [62] reported that melatonin protected against adriamycin (doxorubicin hydrochloride)-induced cardiomyopathy, the pathogenesis of which may involve free radical and lipid peroxidation. In that study, melatonin has been shown to affect zinc turnover, the element which acts as an antioxidant. Similar results were obtained by Agapito et al. [63] and Xu et al.[64] in an experiment with adriamycin; they found that melatonin was an effective antioxidant against cardiotoxicity of myocardium generated by this antibiotic. Arteaga et al. [65] compared the antioxidative

effect of a few antioxidants. They showed that the antioxidative potency of estradiol *in vitro* was 10-100 times higher than that of α- and γ-tocopherol and melatonin in protection against the oxidation of LDL-cholesterol from postmenopausal women. Benot et al. [66] suggests that the antioxidative mechanism of melatonin plays a very important role in blood pressure decreasing and in the protection against atherosclerosis.

Summarising, melatonin may reduce blood pressure *via* the following mechanisms:
1) by a direct effect on the hypothalamus;
2) as an antioxidant which lowers blood pressure;
3) by decreasing the level of catecholamines, or
4) by relaxing the smooth muscle lining the aorta.

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