Blood Pressure Modulation and Cardiovascular Protection by Melatonin: Potential Mechanisms Behind

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Summary
The production of the pineal hormone melatonin is synchronized with day-night cycle via multisynaptic pathway including suprachiasmatic nucleus linking several physiological functions to diurnal cycle. The recent data indicate that impaired melatonin production is involved in several cardiovascular pathologies including hypertension and ischemic heart disease. However, the mechanisms of melatonin effect on cardiovascular system are still not completely understood. The activation of melatonin receptors on endothelial and vascular smooth muscle cells and antioxidant properties of melatonin could be responsible for the melatonin effects on vascular tone. However, the data from \textit{in vitro} studies are controversial making the explanation of the melatonin effect on blood pressure \textit{in vivo} difficult. \textit{In vivo}, melatonin also attenuates sympathetic tone by direct activation of melatonin receptors, scavenging free radicals or increasing NO availability in the central nervous system. The central and peripheral antiadrenergic action of chronic melatonin treatment might eliminate the mechanisms counter-regulating decreased blood pressure, providing thus additional cardioprotective mechanism. The extraordinary antioxidant activity and antilipidemic effects of melatonin may enhance the modulation of blood pressure by melatonin and probably play the most important role in the amelioration of target organ damage by chronic melatonin treatment. Further investigation of these mechanisms should provide novel knowledge about pathophysiological mechanisms of cardiovascular diseases, additional explanation for their circadian and seasonal variability and potentially generate new impulses for the development of therapeutic arsenal.

Key words
Melatonin • Hypertension • Nitric oxide • Free radicals • Sympathetic nervous system

Introduction
Since the identification of melatonin by Lerner \textit{et al.} (1958), it has been shown, that melatonin is involved in the regulation of many physiological systems, including cardiovascular system (Važan \textit{et al.} 2003, 2004). Melatonin influences blood pressure (Arangino \textit{et al.} 1999), myocardial contractility (Abete \textit{et al.} 1997) and
increases the antioxidant reserve (Girouard et al. 2004). Melatonin receptors were discovered in the heart (Pang et al. 2002) and arteries (Masana et al. 2002). Moreover, decreased melatonin levels were reported in various pathological conditions including hypertension with non-dipper pattern (Jonas et al. 2003), impairment of heart failure (Girotti et al. 2003), ischemic heart disease (Brugger et al. 1995), or in patients after acute myocardial infarction (Dominguez-Rodriguez et al. 2002). Melatonin is often available as dietary supplement without need of medical prescription, what increases the chance of regular melatonin intake by patients suffering from a cardiovascular disease. Therefore, melatonin is coming to the cutting edge of cardiovascular research and its effects on cardiovascular system in clinical situation are being discussed (Šimko and Paulis 2007). However, results obtained on models with different analytical level are partially controversial and the mechanisms behind melatonin influence on cardiovascular system are still not completely understood.

In this review we have summarized and confronted data from studies on isolated cells, animal experiments as well as small clinical trials. Our major aim was to suggest important mechanisms and pathways that might be responsible for the physiological and clinical importance of melatonin in the cardiovascular system. We paid special attention to the regulation of blood pressure, one of the most important determinants of cardiovascular risk. Moreover, we focused on melatonin impact on cardiovascular remodeling and myocardial reperfusion injury. The details about protection against damage to the brain (Reiter et al. 2005) or kidney (Tylicki et al. 2003) by melatonin represent, however, an extensive topic and are behind the scope of this review.

**Background**

**The regulation of melatonin synthesis and melatonin concentrations**

Melatonin, an endocrine product of the pineal gland, is formed predominantly during night-time. Light has an inhibitory effect on pineal melatonin secretion (Wurtman et al. 1964). Melatonin release is synchronized with day-light cycle by a multisynaptic pathway. Light stimulates retina to modulate the activity of suprachiasmatic nucleus (SCN) (Moore 1996), the site of the master biological clock (Dubocovich et al. 1998). GABA-ergic neurons are projected from SCN to paraventricular nucleus (PVN) (Moore 1996) intermittently inhibiting the constant excitatory output for sympathetic intermediolateral nucleus (Kalsbeek et al. 2000). The sympathetic stimulation from intermediolateral nucleus is after interpolation in superior cervical ganglion finally directed to the epiphysis to induce melatonin synthesis (Moore 1996). The activity of rate limiting enzymes in the epiphysis is regulated by norepinephrine binding to pineal β1- and α1-adrenoceptors (Klein et al. 1983, Reiter 1991, Ribelayga et al. 1997). Moreover, other neurohumoral systems, e.g. the local renin-angiotensin system, may modify melatonin secretion as well (Baltatu et al. 2002). The interference of melatonin synthesis and action with other neurohumoral systems plays an important role in the modulation of cardiovascular functions by melatonin. The concentrations of melatonin in the sera of healthy subjects reach 10^{-10} to 10^{-9} mol/l during the night and an order lower value during the day (Kennaway and Voultsios 1998). It should be noted, that physiological blood levels of melatonin do not reach peak concentrations achieved by pharmacological application (10^{-7} to 10^{-5} mol/l after 60-150 min) (Waldhauser et al. 1984, DeMuro et al. 2000).

**Specific mechanisms of melatonin effects**

Many authors suppose that melatonin acts mainly via its membrane receptors (Costa et al. 1995). However, melatonin’s lipophilic nature allows it to act also intracellularly i.e. on its nuclear receptor (Mor et al. 1999).

Since the identification of melatonin binding site (Vaneček et al. 1987), two G-protein-coupled melatonin membrane receptor subtypes have been identified in mammals: MT_1 (formerly Mel 1a or mt_1) and MT_2 (Mel 1b) (Dubocovich et al. 1998). The MT_1 receptor was shown to associate with various second messengers: G_s-coupled decrease in cyclic AMP levels (Capsoni et al. 1994, Reppert et al. 1996, Witt-Enderby and Dubocovich 1996), G_q-coupled phospholipase-C activation resulting in increased cytosolic Ca^{2+} (Brydon et al. 1999) or G-coupled activation of the Kir 3 K-channels (Nelson et al. 1996). MT_2 receptor was demonstrated to couple with G_q-protein mediated phosphatidylinositol-4,5-bisphosphate hydrolysis (Dubocovich 1995). The third receptor type MT_3, which has a lower affinity, is probably not coupled with G protein (Mor et al. 1999).

The highest density of melatonin receptors was shown to be in central nervous system, particularly in the adenohypophysis (Williams and Morgan 1988, Malpaux...
et al. 1995, 2001), SCN (Vaneček et al. 1987, Vaneček and Janský 1989), PVN (Duncan et al. 1989) and area postrema (Williams et al. 1995). In the cardiovascular system melatonin receptors were first revealed in 1990 in rat caudal artery (Viswanathan et al. 1990). MT₁-receptor was identified in chicken (Pang et al. 2002) and human (Ekmeckioglu et al. 2001) coronary arteries as well as in chicken (Pang et al. 1993) and rat (Abete et al. 1997) heart, whereas MT₂-receptor in the human heart, coronary arteries and the aorta (Ekmeckioglu et al. 2003). The precise localization of these receptors is not completely revealed. It was hypothesized that while MT₁-receptor is localized primary on vascular smooth muscle cells, the MT₂-receptor appears on endothelial as well as vascular smooth muscle cells (Masana et al. 2002).

Non-specific mechanisms of melatonin effects

Despite the high density of melatonin receptors in the central nervous system, and on the periphery as well, other mechanisms of melatonin action independent on specific receptors have been reported.

The antioxidant properties of melatonin, especially in pharmacological doses seem to be the most pronounced (Ianas et al. 1991). Melatonin was able to reduce lipid peroxidation more effectively than vitamin C or E (Gitto et al. 2001). The potent antioxidant ability can be explained by the potential to scavenge hydroxyl (Bromme et al. 2000), superoxide (Sewerynek et al. 1991), peroxyl (Pieri et al. 1994) but also NO (Noda et al. 1999) free radical. The reported NO scavenging could have adverse effects on cardiovascular system. Okatani et al. (2001) attributed the vasoconstriction of the human umbilical artery observed after melatonin administration to the potential of melatonin to scavenge NO. However, vasoconstriction was seen only at high melatonin concentrations (Okatani et al. 2001) and in vitro experiments have shown that melatonin scavenges NO only in the presence of oxygen and it possibly interacts with peroxynitrite rather than NO alone (Blanchard et al. 2000). The antioxidant activity of melatonin is enhanced by the induction of antioxidant enzymes (Antolini et al. 1996, Barlow-Walden et al. 1995), the stability of the oxidized form of melatonin (Košťová et al. 2006) and high free radical scavenging activity of melatonin metabolites as well (Tan et al. 2007). The antioxidant properties of melatonin in vivo are demonstrated by the ability of melatonin to reduce ischemia-reperfusion injury in various organs, including the heart (Tan et al. 1998), kidney (Sahna et al. 2003), brain (Cho et al. 1997) and liver (Sewerynek et al. 1996).

Non-specific mechanisms of melatonin action can also reside in direct interaction with calmodulin (Turjanski et al. 2004), inhibition of Ca²⁺ channels (Satake et al. 1986, Shibata et al. 1989) or calcium pump stimulation observed in cardiomyocytes (Chen et al. 1993). In the central nervous system the ability of melatonin to bind and activate GABA-receptors (Wang et al. 2003) along with its ability to reduce oxidative load and to enhance NO signaling may also participate in the central regulation of sympathetic tone.

Melatonin and blood pressure

Since hypertension is one of the most prevalent and pronounced risk factors for various cardiovascular alterations, the effect of melatonin on blood pressure deserves special attention among its influence on cardiovascular system.

Experimental hypertension

In experimental conditions the surgical removal of epiphysis, pinealectomy, which was associated with decreased melatonin production, caused vasoconstriction (Cunnane et al. 1980), unchanged cardiac output (Harlow 1987) and temporary hypertension in adult rats (Zanoboni and Zanoboni-Mucciacci 1967, Zanoboni et al. 1978). Administration of melatonin reversed pinealectomy-induced hypertension (Holmes and Sudgen 1976). The exposure of experimental animals to continuous light (24 hours/day), which prevented the nocturnal rise of melatonin serum levels (Brown et al. 1991), also resulted in suppression of circadian heart rate and blood pressure variability (Briaud et al. 2004). Therefore under the experimental conditions it could be even spoken about “melatonin-deficient” hypertension.

In spontaneously hypertensive rats (SHR) melatonin production was shown to decline with aging more rapidly than in normotensive rats (Kawashima et al. 1987). The pharmacological treatment with melatonin for five days in adult SHR resulted in graduate decrease in blood pressure, heart rate and plasma renin activity (Kawashima et al. 1987). Although in some studies melatonin administration to SHR reverted established hypertension only partially (Pecháňová et al. 2007), its antihypertensive effect was more pronounced than the effect of the antioxidant N-acetylcysteine (Košťová et al. 2006) and was comparable with the effect of spironolactone (Paulis et al. 2006).
In another experiment in melatonin-treated SHR, the reduction of blood pressure and heart rate was associated with increased endothelium-dependent vasodilatation and increased sensitivity to NO-synthase inhibitor (Girouard et al. 2001) suggesting improved NO signaling. This hypothesis is also supported by the observation of increased cytosolic Ca\textsuperscript{2+} levels in endothelial cells (Pogan et al. 2002), which may result in increased NO production via enhancement of NO-synthase activity, increased cyclic GMP levels and decreased intracellular Ca\textsuperscript{2+} in smooth muscle cells with subsequent vasodilatation (Anwar et al. 2001). Interestingly, the antioxidant N-acetylcysteine reduced subsequent vasodilatation (Anwar et al. 2001). Acute administration of melatonin lowered blood pressure, heart rate and catecholamine concentration and β-adrenoceptor expression (both impaired in SHR) in a similar level as melatonin (Girouard et al. 2003). Moreover, the decreased blood pressure and improved baroreflex in SHR correlated with improved antioxidant capacity after long-term melatonin administration (Girouard et al. 2004) suggesting an association of antioxidant melatonin properties with its ability to decrease sympathetic tone.

Acute administration of melatonin lowered blood pressure and reduced norepinephrine blood levels in SHR (K-Laflamme et al. 1998). In vitro, melatonin attenuated constriction of aortic ring in SHR by inhibiting phospholipase C cascade independently on MT-receptor or α\textsubscript{1}-adrenoceptor blockade (K-Laflamme et al. 1998). Since similar inhibitory effect was also achieved with an antioxidant enzyme superoxide dismutase, it might be assumed that the beneficial effect of melatonin was mediated by its ability to prevent excess oxidative load, which was reported to contribute to enhanced vasoconstriction in spontaneous hypertension (Wu et al. 1998).

Melatonin in normotensive and hypertensive humans

The blood pressure lowering effect of melatonin was reported in healthy women receiving contraception (Cagnacci et al. 1997), postmenopausal women on hormonal substitution therapy (Cagnacci et al. 2001) and healthy men (Arangino et al. 1999). The reduction of blood pressure after acute melatonin administration was associated with reduced norepinephrine levels and pulse index (Cagnacci et al. 1998). The unchanged heart rate and decreased pulse index in these experiments indicate that the blood pressure decrease after melatonin is in vivo mediated by attenuation of the peripheral resistance achieved potentially by increased NO formation (Cagnacci et al. 2001).

Impaired circadian rhythm of autonomic tone was observed in several studies on hypertension (Guzzetti et al. 1991, Nakano et al. 2001). This phenomenon was associated with disturbed neurotransmission in suprachiasmatic nucleus as proven on humans post-mortem (Goncharuk et al. 2001), which is the regulatory center for melatonin secretion (Klein and Weller 1972) and autonomic tone (Scheer et al. 1999, 2001). Decreased nocturnal melatonin concentrations were observed in patients with non-dipping blood profile (Zeman et al. 2005). Although in a double-blind randomized cross-over study acute melatonin administration failed to influence blood pressure, chronic 3-week melatonin administration reduced blood pressure and amplified the night time blood pressure decrease (Scheer et al. 2004). The authors explained the inability of melatonin to decrease blood pressure after acute administration by the possible involvement of SCN. While in previous studies melatonin was reported to decrease blood pressure after administration during day-time when the SCN activity is high, in this study melatonin was given before sleep onset, when the SCN activity is low and further inhibition is hardly possible. On the other hand, the long-term regular intake before sleep supported normal rhythm in melatonin concentrations and was therefore effective in restoring circadian variability in blood pressure (Scheer et al. 2004).

The mechanisms of the effect of melatonin on blood pressure

From the mechanistic point of view, blood pressure is the function of cardiac output and peripheral resistance. Studies aimed to investigate the direct influence of melatonin on vascular reactivity were performed in various laboratories. However, the data obtained from these experiments are partly contradictory. Melatonin was reported to have no effect on basal arterial tone (Monroe and Watts 1998), to cause vasoconstriction (Doolen et al. 1998) or to cause vasodilatation (Weekly 1991, 1993).

Also the correlation of these findings with known intracellular pathways mediating the effects of melatonin remains controversial. The constrictive effect of melatonin can be explained by receptor mediated decrease in cyclic AMP levels (Capsoni et al. 1994, Witt- Enderby and Dubocovich 1996) and phosphatidylinositol-4,5-bisphosphate hydrolysis which was reported
by several in vitro studies (Dubocovich 1995) (Fig. 1).

Despite the fact that the vasodilation after melatonin is congruent with decreased blood pressure after melatonin administration, it is difficult to explain it on the basis of melatonin receptor stimulation. The activation of melatonin receptors on vascular smooth muscle cells should therefore diminish vasodilatation or enhance vasoconstriction. MLT, melatonin, MT1, MT2, melatonin receptor MT1, MT2, respectively, Gq, Gi, G-proteins, PLP C, phospholipase C, DAG, diacylglycerol, PK C, protein kinase C, IP3, inositol-1,4,5-trisphosphate, SER, smooth endoplasmatic reticulum, cAMP, cyclic adenosine monophosphate.

Fig. 1. Potential pathways directly mediating melatonin-induced vasoconstriction in vitro. Melatonin receptors associated with Gq and Gi, proteins decrease cyclic AMP levels (Capsoni et al. 1994, Witt-Endbery and Dubocovich 1996) and stimulate phosphatidylinositol-4,5-bisphosphate hydrolysis (Dubocovich 1995). Activation of melatonin receptors on vascular smooth muscle cells should therefore diminish vasodilatation or enhance vasoconstriction. MLT, melatonin, MT1, MT2, melatonin receptor MT1, MT2, respectively, Gq, Gi, G-proteins, PLP C, phospholipase C, DAG, diacylglycerol, PK C, protein kinase C, IP3, inositol-1,4,5-trisphosphate, SER, smooth endoplasmatic reticulum, cAMP, cyclic adenosine monophosphate.

Fig. 2. Possible pathways mediating melatonin-induced vasodilatation. The activation of MT2 receptors on endothelial cells could increase cytosolic Ca2+ in endothelial cells (Pogan et al. 2002). Activated endothelial cells are stimulated to NO production. Antioxidant action of melatonin may further enhance the formation and availability of NO, which stimulates guanylate cyclase in smooth muscle cells leading to vasodilatation. MT, melatonin receptors, NOS, NO-synthase, ROS, reactive oxygen species, scG, soluble guanylate cyclase, cGMP, cyclic guanosine monophosphate.

output (K-Laflamme et al. 1998) and association of decreased heart rate or cardiac output with blood pressure fall after melatonin administration (Kawashima et al. 1987, Arangino et al. 1999, Scheer et al. 2003) support the idea of central action of melatonin.

Although, the mechanisms participating in central effect of melatonin are yet not completely known, several pathways can be suggested:

First, neurons in PVN directly or after intercalation in rostral ventrolateral medulla (RVLM) project to medullar intermediolateral nucleus, which innervates sympathetic ganglia generating thus sympathetic tone and regulating arterial pressure (Coote et al. 1998, Pyner and Coote 2000, Cano et al. 2001, 2004, Stocker et al. 2006). The constant excitatory output of PVN is intermittently inhibited by GABA-ergic innervation from SCN (Kalsbeek et al. 2000), which enables circadian oscillations in sympathetic output synchronized with day-light (Bujs et al. 1999, Scheer et al. 2003). The same sites (SCN, PVN, intermediolateral nucleus) are also responsible for the excitation of sympathetic neurons in the superior cervical ganglion that regulates pineal melatonin synthesis (Moore 1996). It could be hypothesized that the modulation of SCN activity by melatonin (Reppert et al. 1988, Dubocovich et al. 1998) alters sympathetic tone and thus represents a protective mechanism against excessive sympathetic excitation. Moreover, neurons in area postrema were suggested to be epigenetically modified by melatonin (Irmak and Sizlan 2006). These neurons are believed to
set reference point for blood pressure regulation (Irmak and Sizlan 2006) and inhibit the activity of RVLM through caudal ventrolateral medulla (CVLM) (Patel et al. 2001).

Second, GABA-ergic signalization is involved in the inhibition of RVLM by CVLM (Patel et al. 2001). Melatonin was reported to enhance GABA-ergic signalization (Wang et al. 2003), which may contribute to inhibition of these nuclei and subsequent decrease in sympathetic tone.

Third, NO formation was shown to potentiate GABA-ergic inhibitory effects in PVN (Rossi et al. 2004) and RVLM (Patel et al. 2001). The potential of melatonin to increase NO availability may additionally augment inhibition in these areas (Fig. 3).

**The effect of melatonin on cardiovascular remodeling**

Beside the effects of melatonin on blood pressure, an important question remains whether melatonin treatment may beneficially modify the deterioration of organ structure and function associated with hypertension, coronary artery disease or dyslipidemia.

**The effect of melatonin on vascular structure**

Although extensive attention was devoted to the modulation of vascular function by melatonin, the effect of melatonin on vascular morphology was less intensively investigated. Nevertheless, improved NO production and decreased oxidative load after melatonin administration (Anwar et al. 2001) may lead to prevention of endothelial structural alterations. Most promising results were obtained in models with altered metabolic conditions, which produce pronounced endothelial damage. In rats on high-fat diet melatonin administration attenuated atheromatous changes in arteries along with the normalization of blood pressure, body weight, blood glucose, improvement of antioxidant capacity and lipid profile (Hussein et al. 2007). In hypertriglyceridemic rats, melatonin prevented intimal infiltration by foam cells induced by cholesterol in association with modified plasmatic fatty acid composition (Pita et al. 2002). The prevention of endothelial damage may help to explain more effective blood pressure reduction in type 1 diabetic patients than in controls (Cavallo et al. 2004). However, under the conditions of less compromised endothelium melatonin can also improve endothelial function. The prevention of early atheromatous changes and endothelial damage with direct impact on arterial function may help several organs especially the brain to cope with ischemia-reperfusion injury or other pathological conditions.

Deficit of melatonin induced by pinealectomy decreased cross-sectional area, attenuated compliance and increased stiffness of rat cerebral arterioles, whereas low-dose melatonin treatment prevented the development of these alterations (Regrigny et al. 2001). Beside this fact, there is lack of other evidence for modulation of medial structure by melatonin. Yet, there are several attributes of melatonin, which could potentially lead to improvement of vascular remodeling. Numerous melatonin-induced changes such as attenuation of hemodynamic overload, decrease in sympathetic output (Girouard et al. 2003),...
reduction of oxidative load (Tan et al. 2007), increase in bioavailability of NO, which has antiproliferative and antiproteosynthetic effects (Šimko and Šimko 2000) as well as reduction of serum cholesterol levels and lipid profile normalization (Wakatsuki et al. 2001, Sandyk and Awerbuch 1994) encourage future investigations of the modulation of vascular structure by melatonin.

The effect of melatonin on left ventricular hypertrophy

Melatonin prevented cardiac hypertrophy in hyperthyroid rats along with reduced oxidative load and altered expression of metabolically important genes (Ghosh et al. 2007). This study indicates that the effect of melatonin on hemodynamic overload, NO availability, free radicals and lipid profile may modify myocardial remodeling as well. On the other hand, despite the reduction of blood pressure melatonin failed to ameliorate left ventricular hypertrophy in SHR (Šimko et al. 2006), but some promising results were obtained in melatonin-deficient models. Pinealectomy increased heart weight and fibrosis (Mizrak et al. 2004, Sahna et al. 2002) and continuous light increased collagen types I/III ratio (Paulis et al. 2007). Since the increase in heart weight was proportional to the increase in body weight (Sahna et al. 2002, Paulis et al. 2007) and the gain in heart weight did not correlate with blood pressure rise (Sahna et al. 2002), the hemodynamic load was probably not the decisive factor for the development of these alterations. Pinealectomy was also associated with several metabolic alterations including enhanced isoproterenol-induced lipolysis in rats (Borges-Silva et al. 2005), hypercholesterolemia and transient hypertriglyceridemia in type 2 diabetic rats (Nishida et al. 2003) and hypercholesterolemia and hyperlipidemia in rabbits (Damian 1976). Insufficient effect of melatonin on food efficiency and growth factors and insulin levels (Wolden-Hanson et al. 2000) in melatonin-deficient conditions may participate in the development of cardiac remodeling. It can be expected that blood pressure reducing and metabolic impact of melatonin may be especially beneficial against cardiovascular damage associated with metabolic syndrome.

Melatonin and cardiac reperfusion injury

There is evidence for cardioprotective effect of melatonin against ischemia-reperfusion injury. Melatonin reduced the infarct size/risk area (Chen et al. 2003, Sahna et al. 2005) and the incidence of reperfusion arrhythmias (Lagneux et al. 2000, Lee et al. 2002, Sahna et al. 2002). Since ischemia is associated with formation of oxygen free radicals from the residual molecular oxygen (Jennings et al. 2001), the cardioprotective effect is probably associated with melatonin ability to scavenge free radicals (Allegra et al. 2003, Sahna et al. 2005) and to induce the expression of antioxidant enzymes (Reiter 2000). Melatonin was even more efficient in reducing the severity of reperfusion arrhythmias than the antioxidant vitamin C (Tan et al. 1998). There are following possible explanations for the especially high effectiveness of melatonin in preventing reperfusion injury of various organs:

First, beside antioxidant action other mechanisms take part in the protective effect of melatonin. Melatonin was reported to decrease cytosolic calcium in cardiomyocytes (Chen et al. 1993) what could modify the electrical stability of the myocardium and contribute to protective action of melatonin against ischemia-induced arrhythmias (Lagneaux et al. 2000). These changes in cytosolic calcium may result from stimulation of melatonin receptors, which are present in cardiomyocytes (Pang et al. 2002) or from other non-specific melatonin effects like direct interaction with calmodulin (Turjanski et al. 2004), inhibition of Ca$^{2+}$ channels (Satake et al. 1986, Shibata et al. 1989) or calcium pump stimulation (Chen et al. 1993).

Second, the antioxidant action of melatonin is extraordinary high. Melatonin takes a special place among other antioxidants. Melatonin does not undergo redox cycling (Tan et al. 2000), enhances the activity of antioxidant enzymes (Antolin et al. 1996, Barlow-Walden et al. 1995), and its primary, secondary and tertiary metabolites also posses high free radical scavenging activity (Tan et al. 2007). Most importantly, melatonin may penetrate lipid cell membrane (Mor et al. 1999) and act as intracellular antioxidant unleashing its scavenging properties.

Conclusions

Melatonin was shown to be involved in several cardiovascular pathologies and its therapeutic use is being considered (Šimko and Paulis 2007). However, the underlying mechanisms of melatonin protection within the cardiovascular system are not properly understood.

Although melatonin decreases peripheral resistance, results of experiments on isolated arteries are partly controversial and vasodilatation cannot be completely explained only by activation of second
messenger cascades associated with melatonin receptors. Thus, more sophisticated approach should be taken into consideration:

On the periphery, receptor-mediated vasoconstriction on vascular smooth cells might be counterbalanced by receptor-mediated NO release from endothelial cells, which is further enhanced by antioxidant properties of melatonin.

In the central nervous system, enhancement of GABA-ergic signaling, scavenging free radicals and augmentation of NO availability may substantially participate in the reduction of sympathetic output resulting in blood pressure decrease observed in vivo.

Additionally to the reduction of blood pressure, melatonin may be expected to prevent target cardiovascular damage as well. Melatonin protects heart against ischemia-reperfusion injury by its extraordinary antioxidant activity and its antilipidemic effects may attenuate undesirable vascular alterations.

Further investigation of these mechanisms may extend the knowledge on pathogenetic mechanisms of cardiovascular diseases, provide additional explanation for their circadian and seasonal variability and potentially generate new impulses for the development of novel therapeutic approaches.

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