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REVIEW ARTICLE

# Impact of melatonin on central blood pressure regulation

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**Abstract**

The dysbalance between the sympathetic and parasympathetic vegetative system and increased free radical burden in the central nervous system (CNS) are the important pathophysiological disorders and therapeutic targets in hypertension. Besides the effects on cardiovascular system, the pineal hormone, melatonin (N-acetyl-5-methoxytryptamine) may exert part of its antihypertensive action just through its interaction with the CNS. Melatonin may be protective in CNS on several different levels: it reduces production of reactive oxygen species, improves endothelial dysfunction, reduces inflammation and shifts the balance between the sympathetic and parasympathetic system in favor of the parasympathetic system. Increased level of serum melatonin observed in some types of hypertension may represent a counterregulatory adaptive mechanism against the sympathetic overstimulation. All these effects of melatonin may include increased production of nitric oxide in their mechanisms of protection. In different experimental models of hypertension upregulation of nitric oxide synthase (NOS) activity and NOS isoform expression in different parts of brain after melatonin treatment have been documented. Thus, it is supposed that the correction of absolute or relative melatonin deficiency by exogenous melatonin administration in conditions of increased blood pressure, may help to attenuate the excessive catecholamine outflow providing a rational background for therapeutic application of melatonin in hypertension treatment.

## Introduction

Primary hypertension is a complex hemodynamic and structural disorder and is likely to be the consequence of an interaction between environmental and genetic factors. Long term high blood pressure is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease (Hrenak *et al* 2015; Pechanova & Simko 2009). Besides peripheral alteration also central nervous system disorders may contribute to the development of hypertension. Thus the term neurogenic hypertension was suggested, involving the dysbalance between sympathetic and parasympathetic components on the base of disturbed interplay on the level of central and peripheral autonomic nervous system (Paton & Waki 2009; Waki 2011). Recently, it has been suggested that the inflammation in the brainstem may underlie this neurogenic hemodynamic disorder (Waki 2011). Pro-inflammatory molecules, e.g. junctional adhesion molecules, are overexpressed in the endothelium of the microvasculature in the nucleus tractus solitarii, the principal structure controlling arterial blood pressure with a subsequent leukocyte adherence to inflamed endothelium and inflammatory cytokines release, while this type of inflammatory

response seems to be quite specific for the hypertensive brainstem (Waki 2008). If the endothelium inflammation in the variable parts of the central nervous system is involved in the pathogenesis of hypertension in a more general term, then the substances with potential anti-inflammatory, antioxidant and endothelium protecting action in the CNS, such as melatonin, might become an important player in the therapeutic targeting.

Melatonin is a hormone secreted by the pineal gland in the brain and acting as a messenger of the suprachiasmatic nucleus and synchronisig the daily rhytms of variable physiological functions (Pevet & Challet 2011; Reiter *et al* 2013; Zeman *et al* 2013). It helps regulate other hormones in the body and plays an important role in the regulation of several parameters of the cardiovascular system including blood pressure (Dominguez-Rodriguez *et al* 2012). Thus, it is considered to be a putative antihypertensive agent (Paulis *et al* 2009, 2010; Simko *et al* 2013). However, the mechanisms and pathways involved in its blood pressure lowering action are complex and not entirely clear. Both effects mediated by specific melatonin receptors and direct unspecific actions, particularly those involving the antioxidant nature of melatonin, are of significant biological value.

## Melatonin and oxidative burden in CNS

Melatonin and its metabolites (Tan *et al* 2012; Galano *et al* 2013) have extraordinary antioxidant potential and reduce the level of free radical burden on the level of both oxygen- and nitrogen species (Galano *et al* 2013; Agil *et al* 2013; Pechanova *et al* 2007), and their lipophilic action enables them to cross the cell membrane and extend the protective action to all subcellular structures (Venegas *et al* 2013; Simko *et al* 2013; Simko & Paulis 2013). Acting as a direct scavenger, melatonin is able to neutralize different free radicals, such as singlet oxygen, superoxide anion radical, hydroperoxide, hydroxyl radical, lipid peroxide radical and highly toxic peroxynitrite anion (Rosen *et al* 2006; Reiter *et al* 2010). Indirect antioxidant actions of melatonin reside in the improvement of mitochondrial efficiency (Acuna-Castroviejo *et al* 2001), stimulation of gene expressions and activation of superoxide dismutase (SOD), catalase, and glutathione peroxidase (Tomas-Zapico *et al* 2005). Furthermore, the ability of melatonin to potentiate the antioxidant action of substances with an antioxidant potential, like glutathione, vitamin E and vitamin C, may also contribute to the regulation of vascular functions and blood pressure regulation (Reiter *et al* 2000). Since the attenuation of the free radical burden in the CNS was shown to attenuate hypertension (Kojsova *et al* 2006; Rehakova *et al* 2016) the antioxidant nature of melatonin may act beneficially particularly in the brain – the tissue especially susceptible to the increased oxidative load.

Angiotensin II represents a key factor enhancing ROS production in the central nervous system predominantly by the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Besides cardiovascular system, also the CNS suffers seriously from the long-term impact of the increased reactive oxygen or nitrous species. The brain is remarkably susceptible to the oxidative stress because its antioxidant defense is rather poor (Pechanova 2010). In the brain, only the low catalase activity and moderate levels of the antioxidant enzymes like superoxide dismutase and glutathione peroxidase were detected. The high levels of iron and ascorbic acid in the brain participate significantly on the catalysis of lipid peroxidation. Additionally, neurotransmitters may be autoxidized generating thus ROS (Lau *et al* 2005). Thus, antioxidant, scavenging and anti-inflammatory effects of melatonin in CNS may additionally contribute to blood pressure reduction. Melatonin is able to increase the activity and/or mRNA of glutathione peroxidase, copper-zinc superoxide dismutase, manganese superoxide dismutase and reduced glutathione in different brain regions, observed during both acute and chronic treatment with melatonin (Tomas-Zapico *et al* 2005; Kotler *et al* 1998). Furthermore, melatonin, similarly like different polyphenolic compounds, directly affects the assembly of NADPH oxidase in microglia, potentially through the inhibition of NADPH oxidase phosphorylation via a PI3K/Akt-dependent signaling pathway, blockade of p47(phox) and p67(phox) subunits translocation to the membrane, and down-regulation of p47(phox) binding to gp91(phox) (Zhou *et al* 2008; Kovacsova *et al* 2010; Pechanova *et al* 200).

Importantly, angiotensin II itself increases melatonin synthesis in the pineal gland (Carrera *et al* 2006), which may be considered as the self-defending mechanisms restraining the deleterious effects of chronic angiotensin II activation including hypertension and pathologic remodeling development.

## Melatonin and nitric oxide in CNS

Among the intracellular melatonin targets, $Ca^{2+}$-calmodulin complex, which increases endothelial and neuronal NOS activity, plays a major role. Nano molar concentrations of melatonin interact with the $Ca^{2+}$-calmodulin complex, modifying thus its effects in many physiological and pathophysiological conditions (Benitez-King & Anton-Tay 1993). The $Ca^{2+}$-calmodulin interactions with melatonin in vascular bed result in the modification of intracellular $Ca^{2+}$ concentrations. While in smooth muscle cells, the melatonin effect on $Ca^{2+}$-calmodulin complex may decrease the level of $Ca^{2+}$ and lead to relaxation; in endothelial cells the reduced $Ca^{2+}$ level may inhibit endothelial NOS triggering thus vasoconstriction (Pandi-Perumal *et al* 2008). Suggestively, the biological effect of melatonin-$Ca^{2+}$-calmodulin interplay depends on the type of target cell.

The relation of melatonin regarding its effect on nitric oxide level is rather complex in the brain tissue.


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This indolamine and its derivates inhibit nNOS and iNOS, while the effect on eNOS is less clear. Melatonin inhibits iNOS through NF-κB-dependent signaling pathway (Mauriz *et al* 2013; Parohova *et al* 2009; Reiter *et al* 2000; Barta *et al* 2012), and eNOS via modification of $Ca^{2+}$-calmodulin complex (Pozo *et al* 1997). Neuronal NOS is activated by calcium similarly to eNOS and analogic mechanism in melatonin – nNOS interaction in the brain may be supposed. The study of (Koh 2008), however, documented that melatonin prevented decrease of eNOS expression during ischemic brain injury. Thus, it is plausible that scavenging and antioxidant effect of melatonin may stabilize eNOS and potentially also nNOS isoform. Interestingly, in rats with metabolic syndrome melatonin did not affect NOS activity and eNOS protein expression in the heart left ventricle and aorta, while it increased these parameters in the brain cortex and cerebellum (Klimentova *et al* 2016; Matuskova *et al* 2013).

Truth is that central nitric oxide can reduce blood pressure via attenuation of sympathetic activity in hypertensive rats (Zhou *et al* 2014; Ramchandra *et al* 2014). The question arise which NOS isoform may contribute mostly to this blood pressure reduction. Although Guo *et al* (2009) suggested predominant role of nNOS in this process, other studies preferred increased eNOS expression in both sympathetic activity and blood pressure reduction (Kimura *et al* 2007;Sakai *et al* 2005; Kishi *et al* 2001). In accordance with the last studies, in rats with metabolic syndrome, melatonin treatment increased brain eNOS, while had no effect on nNOS protein expression. Thus, in rats with metabolic syndrome melatonin may up regulate rather brain eNOS with decreasing effect on blood pressure.

It seems that final melatonin effect on different NOS isoforms may vary according to the pathophysiological conditions, dose or strain tested (Tain *et al* 2014). In any case, melatonin-nitric oxide pathway interplay on the level of CNS may affect BP regulation differentially.

## Receptor-dependent effects of melatonin in CNS

Specific melatonin receptors were described in the cellular membrane systems, cytosol and even nucleus. Both MT1 and MT2 melatonin receptors are membrane-bound G protein-coupled receptors (GPCR). MT1 are primarily linked with Gαi, and Gαq subunits, while MT2 is mainly connected with Gαi (Paulis *et al* 2012; Slominski *et al* 2012). The cytosolic MT3 melatonin receptor is actually the quinone reductase 2A having a low-affinity binding site (Nosjean *et al* 2000). The melatonin receptor subtype distribution in peripheral arteries can significantly influence the biological effect of melatonin in terms of vasorelaxation or vasoconstriction (Benova *et al* 2009). However, MT receptors may be involved in BP regulation also through the central regulatory mechanisms, since the highest density of melatonin receptors has been shown to be in central nervous system, particularly in the adenohypophysis (Malpaux *et al* 2001), SCN (Vaněcek & Janský 1989), PVN (Duncan *et al* 1989) and area postrema (Williams *et al* 1995).

Recently it has been shown that administration of a melatonergic MT1/MT2 agonist – agomelatine significantly attenuated two-kidney-one-clip (2K1C)-hypertension induced impairments in memory, endothelial function, nitrosative stress, mitochondrial dysfunction, inflammation and brain damage. Therefore, modulators of MT1/MT2 receptors may be considered as potential agents for the management of renovascular hypertension (Singh *et al* 2015).

Moreover, it has been shown that in stress-induced hypertensive rats, melatonin levels in the anterior hypothalamic area were reduced. A microinjection of melatonin into this site reduced blood pressure along with increased GABA-ergic activity and reduced glutamate-ergic activity in the rostral ventrolateral medulla. This effect was prevented by MT1/MT2 blockade (Schepelmann *et al* 2011). Interestingly, in the study of Klimentova *et al* (2016) melatonin along with increased brain NOS activity and decreased blood pressure elevated MT1 protein expression as well. It was hypothesized, that activation of MT receptors on endothelial cells would trigger NO production and contribute to blood pressure reduction (Barta *et al* 2012). It seems, however, that MT receptors may regulate blood pressure also through the central mechanisms, since the highest density of melatonin receptors has been shown just in the central nervous system (Masana *et al* 2002; Tunstall *et al* 2011).

## Melatonin and sympathetic activity

The physiology of melatonin is closely bound with the sympathetic nervous system. On one hand the control of melatonin release is controlled by sympathetic afferentation to the pineal gland, mediating the inhibitory effect of light on pineal melatonin secretion (Wurtman *et al* 1964). This pathway starts in the retina influencing the master biological clock in the suprachiasmatic nucleus (SCN) (Moore 1996; Dubocovich *et al* 1998). The SCN then inhibits the paraventricular nucleus (PVN) by GABA-ergic innervation (Moore 1996) leading to interruption of the constant stimulation of the sympathetic intermediolateral nucleus by the PVN (Kalsbeek *et al* 2000). This sympathetic pathway including interpolation in the superior cervical ganglion induces the production of melatonin (Moore 1996) by stimulation of pineal β1- and α1-adrenoceptors (Reiter 1991; Cecon *et al* 2010). On the other hand, melatonin modulates the tone of the autonomic nervous system. Pinealectomized rats showed higher catecholamine levels upon interleukin-1-beta stimulation, an effect which was abolished by intraventricular infusion of melatonin (Wang *et al* 1999). In SHR, acute admin-

istration of melatonin reduced blood pressure along with norepinephrine levels (K-Laflamme *et al* 1998). Acute administration of melatonin to normotensive rats reduced blood pressure, heart rate along with the reduction of serotonin levels in corpus striatum and hypothalamus (Chuang *et al* 1993). Moreover, in these experiments, the effect of melatonin on blood pressure and heart rate was abolished by spinal transection or bilateral vagotomy, suggesting the involvement of sympathetic inhibition or parasympathetic stimulation by melatonin (Chuang *et al* 1993). Chronic administration of melatonin, similarly to the antioxidant N-acetylcysteine, decreased the blood pressure and heart rate, improved the chronotropic response to isoproterenol, in association with an inhibition of sympathetic activity and the restoration of cardiac beta-adrenoceptor function (Girouard *et al* 2003) and improvement of baroreflex (Girouard *et al* 2003). In young healthy men, melatonin reduced pulsatile index and systolic blood pressure along with norepinephrine levels (Arangino *et al* 1999) and reduced blood pressure and pulse wave velocity in association with the attenuation of sympathetic tone (Yildiz *et al* 2006). These sympathicolytic effects of melatonin may be involved in the blood pressure reducing effect of melatonin seen in SHR (Pechanova *et al* 2007), L-NAME rats (Paulis *et al* 2010a,b), healthy volunteers (Yildiz *et al* 2006) or patients with essential hypertension (Simko & Paulis 2007; Tengattini *et al* 2008; Simko & Pechanova 2009) and also participate on the improvement of insomnia and depression (Cardinali *et al* 2012).

## Conclusion

All, the partly contradictory effects of melatonin on vascular reactivity (Paulis *et al* 2009), the association of melatonin administration with sympatholytic effects (Girouard *et al* 2003) and the dependence of melatonin-induced blood pressure decrease on intact spinal cord (Chuang *et al* 1993) suggest a prominent role of the central effects of melatonin on blood pressure regulation. The precise site of this action, however, still needs to be determined. Previously, several possible sites for the modulation of central nervous system output by melatonin were suggested: (i) the activity of the SCN might be modulated by melatonin activity (Reppert *et al* 1988; Dubocovich *et al* 1998), reducing thus the sympathetic tone and providing a protective mechanism against excessive sympathetic excitation, (ii) in neurons projecting from the SCN to the PVN (Klein *et al* 1983), or in neurons projecting from the CVLM to the RVLM, (Patel *et al* 2001), the GABA-ergic signaling might be potentiated by melatonin (Wang *et al* 2003) either directly or via enhancement of the NO bioavailability (Rossi *et al* 2004) and (iii) in the area postrema, which inhibits the activity of RVLM through caudal ventrolateral medulla (CVLM) (Patel *et al* 2001), melatonin is supposed to modify the epigenetic effect (Irmak *et al* 2006). In addition, in all of these brain targets, melatonin prominent antioxidative nature may participate on the attenuation of the sympathetic tone. It could be suggested that while the action of melatonin on the SCN might interfere with the nocturnal blood pressure level, the effect of melatonin on RVLM – most likely associated with augmented GABA-ergic signaling may inhibit the sympathetic tone and induced the overall blood pressure reduction independently on the light-dark daily periods.

In conclusion, it is supposed that the correction of absolute or relative melatonin deficiency by exogenous melatonin administration in conditions of increased blood pressure may help to attenuate the excessive catecholamine outflow providing a rational background for therapeutic application of melatonin in hypertension treatment.

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***Conflicts of Interest.*** *The authors declare no conflict of interest.*

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