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REVIEW ARTICLE

Hypotensive effects of melatonin in rats: Focus on the model, measurement, application, and main mechanisms

Diana Cvikova[1] · Hana Sutovska[1] · Katarina Babarikova[1] · Lubos Molcan[1]

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Abstract

The hypotensive effects of melatonin are based on a negative correlation between melatonin levels and blood pressure in humans. However, there is a positive correlation in nocturnal animals that are often used as experimental models in cardiovascular research, and the hypotensive effects and mechanism of melatonin action are often investigated in rats and mice. In rats, the hypotensive effects of melatonin have been studied in normotensive and spontaneously or experimentally induced hypertensive strains. In experimental animals, blood pressure is often measured indirectly during the light (passive) phase of the day by tail-cuff plethysmography, which has limitations regarding data quality and animal well-being compared to telemetry. Melatonin is administered to rats in drinking water, subcutaneously, intraperitoneally, or microinjected into specific brain areas at different times. Experimental data show that the hypotensive effects of melatonin depend on the experimental animal model, blood pressure measurement technique, and the route, time and duration of melatonin administration. The hypotensive effects of melatonin may be mediated through specific membrane G-coupled receptors located in the heart and arteries. Due to melatonin's lipophilic nature, its potential hypotensive effects can interfere with various regulatory mechanisms, such as nitric oxide and reactive oxygen species production and activation of the autonomic nervous and circadian systems. Based on the research conducted on rats, the cardiovascular effects of melatonin are modulatory, delayed, and indirect.

Keywords Blood pressure · Melatonin · Rats · Tail-cuff plethysmography · Telemetry

Introduction

The pineal gland synthesizes melatonin during the dark phase of the day. Parts of the circadian system, including the suprachiasmatic and paraventricular nuclei of the hypothalamus and several neurotransmitters, such as gamma-aminobutyric acid (GABA), significantly affect melatonin synthesis. The removal of these hypothalamic nuclei suppressed melatonin synthesis and the activity of enzymes responsible for its synthesis in nocturnal rats [1, 2] and diurnal golden hamsters [3]. In contrast, blocking GABAergic neurotransmission in the rat hypothalamic nuclei increased melatonin synthesis during the light phase of the day [4].

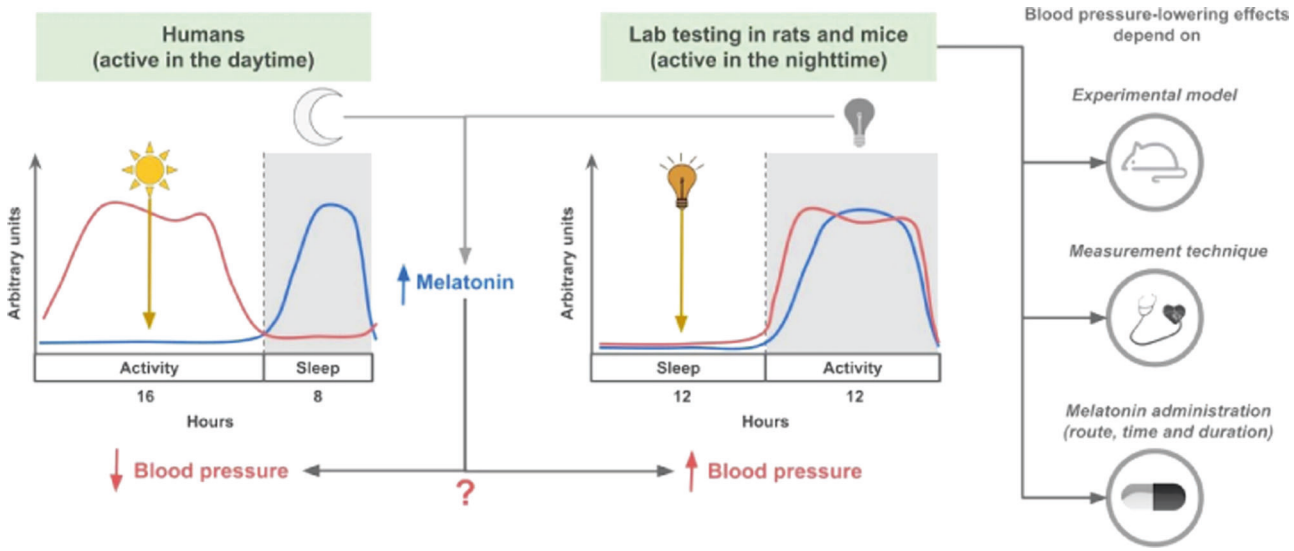
Under normal conditions, elevated melatonin levels negatively correlate with blood pressure in diurnal animals, including humans. Therefore, researchers attributed hypotensive effects to melatonin [5, 6]. In addition, many other effects of melatonin have been discussed, such as its antioxidant properties, immunomodulatory effects and sleep-promoting effects. Melatonin levels decrease with age, while the incidence of insomnia and hypertension increases [7]. Moreover, hypertensive patients often have melatonin deficiency [8]. This fact again supports the hypothesis that melatonin could treat hypertension. Indeed, melatonin has been advised for people with insomnia and hypertension. Clinical trials have proven that, if administered in controlled-release preparations (Circadin), melatonin lowers blood pressure in patients with nocturnal hypertension [8]. Other clinical trials also confirmed the hypotensive effect in patients with metabolic disorders [9]. However, melatonin is not included in the American College of Cardiology/American Heart Association and the European Society of Cardiology/European Society of Hypertension guidelines for the treatment of hypertension [10].

✉ Lubos Molcan
lubos.molcan@uniba.sk

[1] Department of Animal Physiology and Ethology, Faculty of Natural Sciences, Comenius University, Bratislava, Slovakia

Graphical Abstract

Does melatonin have blood pressure-lowering effects, and are nocturnal animals suitable for testing the hypotensive effects of melatonin? The hypotensive effects of melatonin depend on the experimental animal model, blood pressure measurement method, route, time and duration of melatonin administration.



In contrast to humans, there is a positive correlation between melatonin levels and blood pressure in nocturnal animals; plasma melatonin naturally rises during the dark, active phase of the day, when there is also a natural increase in blood pressure [11]. Nevertheless, the hypotensive effects and mechanism of action of melatonin on the heart and blood vessels are often investigated experimentally in nocturnal animals (rats and mice), in which blood pressure is often measured during the light (passive) phase of the day by tail-cuff plethysmography (Fig. 1). Therefore, in this review, we compare the hypotensive effects of melatonin according to the blood pressure measurement model, technique and melatonin application. The second part describes the most frequently discussed hypotensive mechanisms through which melatonin may affect blood pressure, including circadian regulation.

Experimental setup

Earlier experiments showed that removal of the Sprague–Dawley rat pineal gland transiently (over 60 days) increased blood pressure to more than 150 mmHg [12–14]. Therefore, it was hypothesized that the pineal gland has an inhibitory effect on sympathetic activity and the activity of the renin-angiotensin-aldosterone system [13]. The hypothesis of the hypotensive effect of melatonin was also supported by the fact that administration of melatonin (drinking water, 1 mg/ml, a daily dose of approximately 100 mg/kg) prevented a blood pressure increase in pinealectomized rats [12]. Studies on the hypotensive effect of melatonin using various techniques and animal models thus began.

Animal models

The most common animal models in which the hypotensive effects of melatonin are studied in vivo are rats and, to a lesser extent, mice and sheep (Table 1). In rats, the effects of melatonin on blood pressure are often studied in spontaneously hypertensive rats (SHRs), normotensive Wistar rats, or Wistar rats with induced hypertension. In SHRs, a significant decrease in blood pressure was often observed after melatonin application compared to untreated SHRs [15]. In normotensive Wistar rats, the hypotensive effect of melatonin was more [16, 17] or less [18] pronounced. However, some studies did not observe the hypotensive effects of melatonin in normotensive rats [15, 19, 20]. In contrast, after melatonin administration (a single dose, 10 mg/kg, i.p., 30-min blood pressure measurement), blood pressure in adult rats increased significantly compared to that in the control subgroup [21].

Another standard experimental model is the mouse. Melatonin production varies between mouse strains; while some strains (i.e., CBA) have robust melatonin rhythm, others (i.e., C57B1) show almost no rhythm [22]. Melatonin has been reported to contribute to better cardiovascular outcomes in mice, mostly due to its antioxidant properties [23]. Under certain experimental conditions, hypotensive, vasoprotective, and cardioprotective effects of melatonin have been shown [24–26]. In a mouse model of gestational

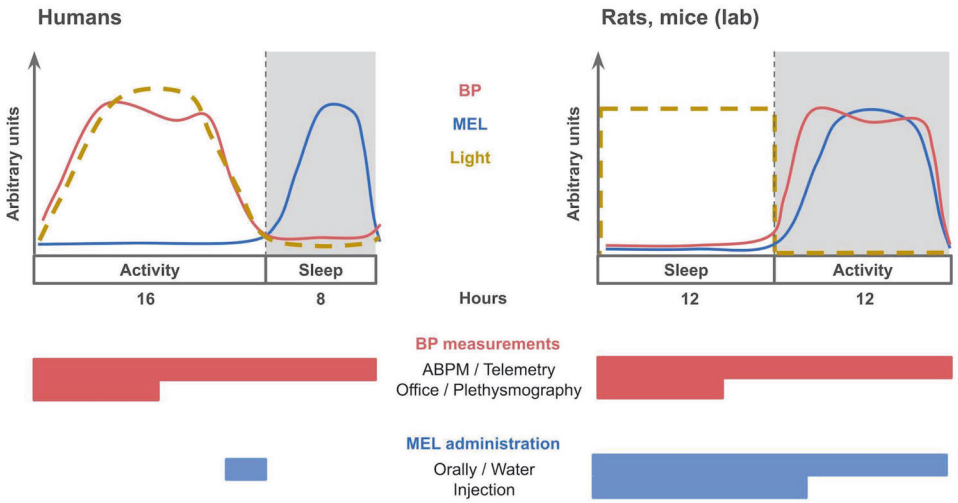


Fig. 1 Positive and negative correlation of melatonin (MEL) levels and blood pressure (BP) in humans and laboratory animals such as rats or mice. ABPM ambulatory BP monitoring

hypertension, melatonin suppressed systolic blood pressure in pregnant mice [27]. Among other rodents, the vasoprotective effects of melatonin have also been studied in hamsters [28], but research has focused more on the behavioral effects of melatonin [29]. Finally, pregnant ewes were also given melatonin to study the prenatal development of the cardiovascular system [30, 31]. Since the effects of melatonin on blood pressure and the cardiovascular system are mostly studied in rats, we decided to focus on this animal model.

Tail-cuff vs. telemetry

The hypotensive effects of melatonin in rats are often measured by noninvasive tail-cuff plethysmography (Table 1). Tail-cuff plethysmography is an indirect method of measuring blood pressure commonly used by researchers, but this method has limitations compared to telemetry [32]. During plethysmography measurements, the animals are handled and immobilized, which elicits a stress response and thus increases blood pressure [33]. The tail artery has a relatively low blood flow in rats under resting conditions. Therefore, to amplify the measured signal, it is necessary to warm the animal; thus, the tail artery dilates. However, heatstroke is another stressor that affects blood pressure [34].

The effects of melatonin on blood pressure have been studied to a lesser extent using telemetry recording (Table 1), which allows stress-free long-term recording of blood pressure in freely moving rats [32]. Telemetric measurements showed that blood pressure and heart rate had a marked circadian (approximately 24-h) pattern with a clear increase during the active (dark) phase of the day in normotensive Wistar [35] and Sprague–Dawley rats [36] as well as in hypertensive Ren-2 transgenic rats (mREN2)27 (TGRs; applies only for heart rate) [36] and SHRs [37] but also in mice [38]. Light suppresses melatonin synthesis at night, with even very dim light (1–2 lx) reducing plasma melatonin concentrations at night, accompanied by a decrease rather than an increase in blood pressure during the dark phase of the day in rats [35, 39]. Similar data were observed in telemetrically measured rats exposed to a constant light intensity of 100–200 lx [40]. In contrast, when blood pressure was measured by tail-cuff plethysmography, constant light (250–300 lx; or undefined) increased blood pressure in rats [41, 42]. Earlier work has also shown that SHRs respond to pharmacological agents with more pronounced blood pressure and heart rate changes when measured by plethysmography compared to telemetry. It has been suggested that there is a relationship between stress intensity during physiological measurement and measured blood pressure [37].

Administration

Melatonin is often administered to experimental rats directly in drinking water, with the concentration being adjusted according to the animal's daily intake (Table 1) [25, 43]. However, the application of melatonin in drinking water has its limitations: (1) nonspecific dosing and availability of water with melatonin during the entire 24-hour period, although it is assumed that rats and mice have reduced motor activity and water intake during the light (passive) phase of the day [44]; and (2) the cumulative daily dose of melatonin in drinking water often reaches a remarkably high concentration, such as 50–100 mg/kg [15, 16, 45, 46]. The literature reports that repeated exceedance (more than 1 mg, orally) of the physiological dose of melatonin may alter the sensitivity of melatonin receptors [47].

Melatonin has also been administered subcutaneously (5 mg/kg/day) [48], intraperitoneally (1 mg/kg, final concentration 1 mg/ml) [36] or microinjected into hypothalamic areas of the brain [49]. Compared to melatonin intake in drinking water, injection is limited by the time of

Table 1 Effects of melatonin on blood pressure (BP) depend on the animal model, melatonin application and blood pressure recording method

Animal (sex)	Melatonin	Effect on BP	BP measurement	Mechanism of BP change	Note	Reference
Wistar (male)	60, 600, 60000 ng/kg/h; i.p.	=	High-speed chart recording of the pulse pressure signal			[108]
Wistar (male)	1 mg/kg	↓	Tail-cuff piezometric machine	ANG II and $GABA_A$ receptor	Stress-induced hypertension	[109]
Wistar (male)	2.5 mg/kg, 5 mg/kg; i.p.; L and D period	=	Radiotelemetry	Sleep-wake cycle		[19]
Wistar (male)	10 mg/kg/day; drinking water (all day), 4 weeks	↓	Tail-cuff plethysmography	Morphological changes in the heart; reduced Ang II	L-NAME	[53]
Wistar (male)	10 mg/kg/day; drinking water (all day); 6 weeks	↓	Tail-cuff plethysmography	Melatonin deficiency in continuous light causes neurohumoral imbalances		[79]
Wistar (male)	10 mg/kg/day; drinking water (all day); 5 weeks	=	Carotid artery punctuation, at the end of the experiment, under terminal anaesthesia in the morning	NO-independent mechanisms, reduction of oxidative load and enhancement of endothelium-derived hyperpolarising factor in particular		[20]
Wistar (male)	10 mg/kg/day; i.p.; 5 days/ week; 6 weeks	= / ↓	Left femoral artery punctuation, under anaesthesia	Oxidative stress		[110]
Wistar (male)	10 mg/kg/day; drinking water (all day); 6 weeks	=	Tail-cuff plethysmography	Collagen in the LV and stimulated the NO pathway		[18]
Wistar (male)	10 mg/kg; i.p.; from 10 a.m. to 3 p.m.	↑	Tail-cuff plethysmography	Age-dependent changes		[21]
Wistar (male)	10 mg/kg/day; drinking water	↓	Tail-cuff plethysmography	Oxidative stress	Doxorubicin	[111]
Wistar (male)	10 mg/kg/day; drinking water	↓	Tail-cuff plethysmography	Fibrosis	Constant light	[112]
Wistar (male)	10 mg/kg, i.p.	↓	Tail-cuff method; at the end of the experiment, carotid artery punctuation	Oxidative stress		[113]
Wistar (male)	10 mg/kg/day; drinking water; 4 weeks	↓	Tail-cuff plethysmography		L-NAME	[54]
Wistar (male)	10 mg/kg/day; drinking water; 5 weeks	↓	Tail-cuff plethysmography	Reduced fibrosis, oxidative stress	L-NAME	[55]
Wistar (male)	10 mg/kg/day; i.p.	↓		Reduction of oxidative stress, inhibition of infiltration of inflammatory cells, and the enhancement of antioxidant molecules	Renal clip	[114]
Wistar (male)	20 mg/kg; drinking water	↓	Tail-cuff plethysmography	Oxidative stress		[115]
Wistar (male)	30 mg/kg/day; oral gavage	↓	Femoral artery punctuation at the end of the experiment	Renal sympathetic activity and oxidative stress, ROS	Renal clip	[81]
WKY (male)	105 ± 34 pg/mL; i.v.; 30 min at 9 a.m.	↓/area postrema lession =	Femoral artery punctuation	Baroreflex sensitivity, area postrema	Area postrema lesion	[86]

Table 1 (continued)

Animal (sex)	Melatonin	Effect on BP	BP measurement	Mechanism of BP change	Note	Reference
SHR (male)/ WKY (male)	0.1%; drinking water (all); 8 weeks	SHR ↓ /WKY =	Tail-cuff plethysmography	NO pathway		[46]
SHR (male)/ Wistar (male)	10 mg/kg/day; drinking water (all day); 67 days	=	Tail-cuff plethysmography	NO pathway		[43]
SHR (male)/ WKY (male)	10 mg/kg/day; orally treated; 3 weeks	SHR ↓ /WKY =	Tail-cuff plethysmography	NO pathway		[15]
SHR (male)/ WKY (male)	10 or 20 mg/kg, i.v.	↓(both strains, after 20 mg/kg)	Femoral artery catheter	Stimulation of central inhibitory adrenergic pathways; diminished arterial basal tone, and α_1-adrenergic stimulation of vascular activity		[89]
SHR (male)/ WKY (male)	30 mg/kg; drinking water	SHR ↓ /WKY =	Femoral artery catheter; at the end of the experiment at 11 a.m.	Normalise the plasma noradrenaline concentration and the relative density of β-adrenoceptor subtypes		[56]
SHR (male)/ WKY (male)	30 mg/kg; drinking water	SHR ↓ /WKY =	Abdominal artery catheter, at the end of the experiment	Baroreflex, antioxidative effects		[78]
SHR (male)/ WKY (male)	30 mg/kg; drinking water	SHR ↓ /WKY =	Femoral artery catheter, at the end of the experiment	NOS		[116]
SHR (male)	0.01%; drinking water	↓	Tail-cuff plethysmography	Increased DDAH activity, decreased ADMA, and oxidative stress in kidney	L-NAME	[117]
SHR (male)	10 mg/kg/day; i.p.; 5 weeks (daily at 6 p.m.)	↓	Tail-cuff plethysmography			[50]
SHR (male)	10 mg/kg/day; drinking water	↓	Tail-cuff plethysmography	Oxidative stress	Constant light	[118]
SHR (male)	10 mg/kg/day; drinking water (all day); 6 weeks	↓	Carotid artery puncture	Increased NO and increased cGMP level in vascular smooth muscle cells		[17]
SHR (male)	10 mg/kg/day; drinking water; 6 weeks	≦	Tail-cuff plethysmography	Oxidative stress		[45]
SHR (male)	10 mg/100 ml; drinking water (all day); 6 weeks	↓	Tail-cuff plethysmography	Antioxidant activity		[16]
SHR (male)	10 mg/kg/day; drinking water; 5 weeks	↓	Tail-cuff plethysmography	Fibrosis, antioxidative effects		[57]
SHR (male)	10 mg/kg/day; drinking water; from GD 1 to 21	↓	Tail-cuff plethysmography	Oxidative stress		[119]
SHR (male)	20 mg/kg; osmotic minipump	↓	Arterial catheter	Renin		[82]
SD (male)	0.01%; drinking water, pregnancy and lactation	↓	Tail-cuff method	RAAS, NO, kidney	Caloric restriction-prenatal programming hypertension; prenatal treatment	[120]

Table 1 (continued)

Animal (sex)	Melatonin	Effect on BP	BP measurement	Mechanism of BP change	Note	Reference
SD (male)	0.01%; drinking water, pregnancy and lactation	↓	Tail-cuff method	Increase NO production, epigenetic regulation of genes related to blood pressure control, and inhibition of SEH protein	Maternal fructose intake-induced programmed hypertension in the offspring	[121]
SD (male)	0.01%; drinking water; 3 weeks during the lactation period	↓	Tail-cuff method	RAAS	Neonatal dexamethasone exposure induced programmed hypertension	[122]
SD (male)	0.01, 0.1 and 1 mmol/L; RVLM injection	↓	Pressure sensor connected to a biometric recording system	Sympathetic activation, RAAS	Stress-induced hypertension	[123]
SD (male)	0.01%, drinking water; during entire pregnancy and lactation	↓	Tail-cuff method	RAAS	Dexamethasone	[124]
SD (male)	1 mmol/L; AHA injection	↓	Arterial catheter	Decreased glutamate release and increased GABA and taurine release in the RVLM	Stress-induced hypertension	[83]
SD	10 mg/kg/day; i.p., from GD 8 to 19	↓	Tail-cuff method	Oxidative stress	Model of L-NAME-induced gestational hypertension	[125]
SD (male)	10 mg/kg/day; i.p.; 21 days (administered each day 30 min before hypoxic exposure)	=	Tail-cuff plethysmography	Vascular inflammation and antioxidant defence		[75]
SD (male, female)	10 mg/kg/day; drinking water	↓	Tail-cuff method		Adenine-induced chronic kidney disease	[126]
SD (male)	0.01%; drinking water; entire pregnancy and lactation (6 weeks)	↓	Tail-cuff method	Oxidative stress, epigenetic modifications, and RAAS	Maternal high fructose combined with post-weaning high-salt diet-induced hypertension	[127]
SD (male)	20 mg/kg/day; oral gavage	↓	Tail-cuff plethysmography	Oxidative stress	Fructose diet	[128]
SD (male)	30–60 mg/kg; i.v.	↓	Catheter in the femoral artery	Serotonin		[129]
TGR (male) / SD (male)	1 mg/kg melatonin antagonist and agonist; i.p.; the time of lights off	= (in both strains)	Telemetry			[36]
TGR (male)	40 µg/ml; drinking water; during the dark phase beginning	=	Tail-cuff plethysmography			[91]
Zucker diabetic fatty rats (male)	10 mg/kg/day; drinking water	↓	Tail-cuff method			[130]
Dahl salt-sensitive rats (male)	30 mg/kg/day; drinking water	=	Tail-cuff method	Oxidative stress	High-salt diet-induced hypertension	[131]
Albino rats (male)	30, 60 and 120 mg/kg	↓		Oxidative stress	L-NAME	[74]

Table 1 (continued)

Animal (sex)	Melatonin	Effect on BP	BP measurement	Mechanism of BP change	Note	Reference
Mice (male)	10 µM	↓	Carotid artery catheter	Endothelial dysfunction	Melatonin was added to culture media with embryos 48 h before transfer to pseudopregnant females	[132]
Obese *ob/ob* mice (male)	100 mg/kg; drinking water (all day); 8 weeks	↓	Tail-cuff plethysmography	Oxidative stress and inflammation	Obesity-induced cardiovascular diseases; leptin-deficient mice	[25]
C57/BL6 mice (male)	100 mg/kg; drinking water	↓	Carotid artery catheter	Vascular dysfunction, NOS	High-fat diet-fed insulin-resistant mice	[133]
BALB/c mice (male)	0.01–100 ng (1 µl/min), i.c.v., 6 h after lights on	= and ↓	Femoral artery catheter	Central melatonin receptor signalling	Light-induced hypertension	[26]
C57BL/c mice (female)	5 mg/kg/day, 10 mg/kg/day or 15 mg/kg/day; oral gavage	↓	Tail-cuff plethysmography	BK_{Ca} channels in uterine arteries involved	Gestational hypertension induced by electrical stimulation	[27]
Welsh Mountain sheep	0.05/0.5 µg/kg/min; i.v.; GD 129	↓	Foetal arterial catheter	Catecholamines	Prenatal hypoxia, full-term 145 days	[31]
Sheep	10 mg/day; per os; at 18:00; during the last third of gestation until delivery; from GD 100 to 150	↓	Carotid artery catheter	NO-dependent and independent mechanisms	Prenatal chronic hypoxia, full-term 148–155 days	[30]
Wistar (male)	Pinealectomy or 4 mg/kg; i.v.	=/=	Carotid artery catheter		Myocardial ischemia-reperfusion	[134]
Wistar (male)	Pinealectomy	↑	Tail-cuff method	RAAS, the sympathetic nervous system		[135]
SD (male)	Pinealectomy or 60 mg/kg; i.p.	↑ pinealectomy/ ↓ melatonin administration	Tail-cuff method			[12]
SD (male)	Pinealectomy	↑	Carotid artery catheter	The sympathetic nervous system, RAAS	Hypertension for 60 days	[13]
SD (male)	Pinealectomy	↑	Tail-cuff method	RAAS		[136]
SD (male)	Pinealectomy	↑	Microphonic manometer (tail)	RAAS	Spironolactone	[137]
SD (male)	Pinealectomy	↑	The photoelectric method from the hind leg			[138]
SD (male)	Pinealectomy	↑	Cannulated	The sympathetic nervous system, RAAS		[139]

ADMA asymmetric dimethylarginine, *AHA* the anterior hypothalamic area, *Ang II* angiotensin II, BK_{Ca} large-conductance Ca^{2+}-activated K^{+}, *cGMP* cyclic guanosine monophosphate, *DDAH* dimethylarginine dimethylaminohydrolase, *GABA* gamma-aminobutyric acid, *GD* gestation day, *i.c.v.* intracerebroventricular, *i.p.* intraperitoneal, *i.v.* intravenous, *L-NAME* N(gamma)-nitro-L-arginine methyl ester, LV left ventricle, *NO* nitric oxide, NOS nitric oxide synthase, *RAAS* the renin-angiotensin-aldosterone system, *ROS* reactive oxygen species, *RVLM* the rostral ventrolateral medulla, *SD* Sprague Dawley rats, *SEH* soluble epoxide hydrolase, *SHR* spontaneously hypertensive rats, *WKY* Wistar Kyoto rats

administration, which must be considered in the context of circadian blood pressure variability. Melatonin is injected either in the light (passive; 10:00 to 15:00) phase of the day when endogenous melatonin levels are low [21] or at the beginning of the dark (active) phase of the day [36]. Administration of the melatonin receptor agonist piromelatine (5–50 mg/kg) at the beginning (18:00) of the dark phase of the day caused a decrease in blood pressure (tail-cuff plethysmography) at both 9:00 and 21:00 in SHRs but not normotensive Wistar rats depending on the dose and week of application [50]. Single-dose intraperitoneal administration of melatonin (1 or 10 mg/kg, tail-cuff plethysmography) during the light (10:00–15:00) phase of the day had the opposite effect, and blood pressure increased in 3-, 15- and 22-month-old Wistar rats compared to control animals [21]. Thus, both the time of application and blood pressure measurement should be considered. However, melatonin injection also has disadvantages, such as phase advance of wheel-running activity in mice [51] and synchronization of rat circadian rhythms in constant dark. Synchronization of circadian rhythms was observed, especially with repeated application of melatonin at the beginning of the subjective active phase of the day in rats [52]. In humans, the administration of melatonin (1.5 mg) has been shown to alter locomotor activity and dependent cardiovascular parameters [51].

In addition to the route and time of administration, the duration of melatonin application is also important (Table 1). Significant effects on blood pressure were observed after long-term application of melatonin in drinking water at concentrations of 10 mg/kg/day and 10 mg/100 ml from 3 to 8 weeks compared to age-matched untreated rats [15, 46]. In Wistar rats, after 2–4 weeks of melatonin treatment (melatonin in drinking water), a decrease in blood pressure of approximately 20 mmHg was observed [53, 54]. A longer treatment period has a similar hypotensive outcome;[55] thus, for Wistar rats, the first 3 weeks were likely to be more critical in terms of experiment length. In SHRs, a shorter period of melatonin treatment (melatonin in drinking water) led to a decrease in blood pressure averaging 20 mmHg [15, 56, 57]. In contrast, prolonged melatonin administration led to a more pronounced drop in blood pressure, reaching approximately 25–40 mmHg [16, 45, 46, 57]. However, it should be noted that the rats in these experiments were not of the same age, did not have the same etiology of hypertension, and blood pressure measurements were not taken at the same time of day.

Hypotensive mechanisms of melatonin

Melatonin receptors

The hypotensive effects of melatonin may be mediated through specific membrane G-coupled MT_1 and MT_2 receptors inhibiting adenylyl cyclase activity (IUPHAR/BPS Guide to Pharmacology) [58]. Melatonin also affects ion channels, for example, large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels, through both the [G_q – phospholipase C – Ca^{2+}] and [G_i – cyclic adenosine monophosphate – protein kinase A] pathways [59]. Earlier work on the caudal artery suggested vasoconstriction via MT_1 and vasorelaxation via MT_2 receptors [60]. However, the contraction of the caudal vessel also depends on the concentration of melatonin; at concentrations below 10^{-7} M, the contraction potency is more robust than at higher concentrations (10^{-7}–10^{-5} M) [61]. Because melatonin receptors in the caudal arteries are thought to mediate the thermoregulatory response [60], the opposite vasoactive effect of melatonin MT_1 and MT_2 receptors may not be present in other vessels of the cardiovascular system.

Melatonin receptors have also been localized in the endothelium and tunica adventitia of the rat aorta [62, 63], where melatonin is thought to protect the vessel from inflammation and oxidative damage [63]. Melatonin MT_1 receptors have been found in resistance vessels in the endothelial and smooth muscle layers and the surrounding perivascular adipose tissue and were shown to attenuate vascular vasocontractility after melatonin administration in vitro [24, 64]. Zhao et al. found MT_2 receptors in rat mesenteric vessels and pointed to the association of BK_{Ca} channel activation with vessel relaxation [65]. Similarly, in rat cerebral vessels, melatonin-mediated vasorelaxation by activating BK_{Ca} channels in myocytes probably affects the MT_1/MT_2 receptor – phospholipase C – protein kinase C pathway indirectly [66]. In addition to blood vessels, melatonin receptors have also been detected in the hearts of mice and rats [67–69]. In the mouse myocardium, under pathological conditions, MT_2 but not MT_1 receptor levels increased [69]. With increasing age in rats, the expression of both types of receptors in the heart decreased, with a more pronounced decrease in MT_1 receptors [68]. Thus, different parts of the cardiovascular system have a different distribution of melatonin receptors. Moreover, melatonin receptors also occur in the form of heteromers and may thus determine the effect of melatonin [70].

Due to its lipophilic nature, melatonin readily crosses the cell membrane independently of the presence of membrane receptors. Therefore, the potential hypotensive effects of melatonin can also be attributed to its interference with a relatively wide range of regulatory mechanisms (Fig. 2).

Endothelial-dependent vasodilatation

The endothelium is an inner single-cell layer of blood vessels. Based on various chemical and mechanical stimuli, it synthesizes vasoactive substances that cause vasoconstriction or vasodilation, thereby regulating blood flow, resistance, and pressure. The major players with which

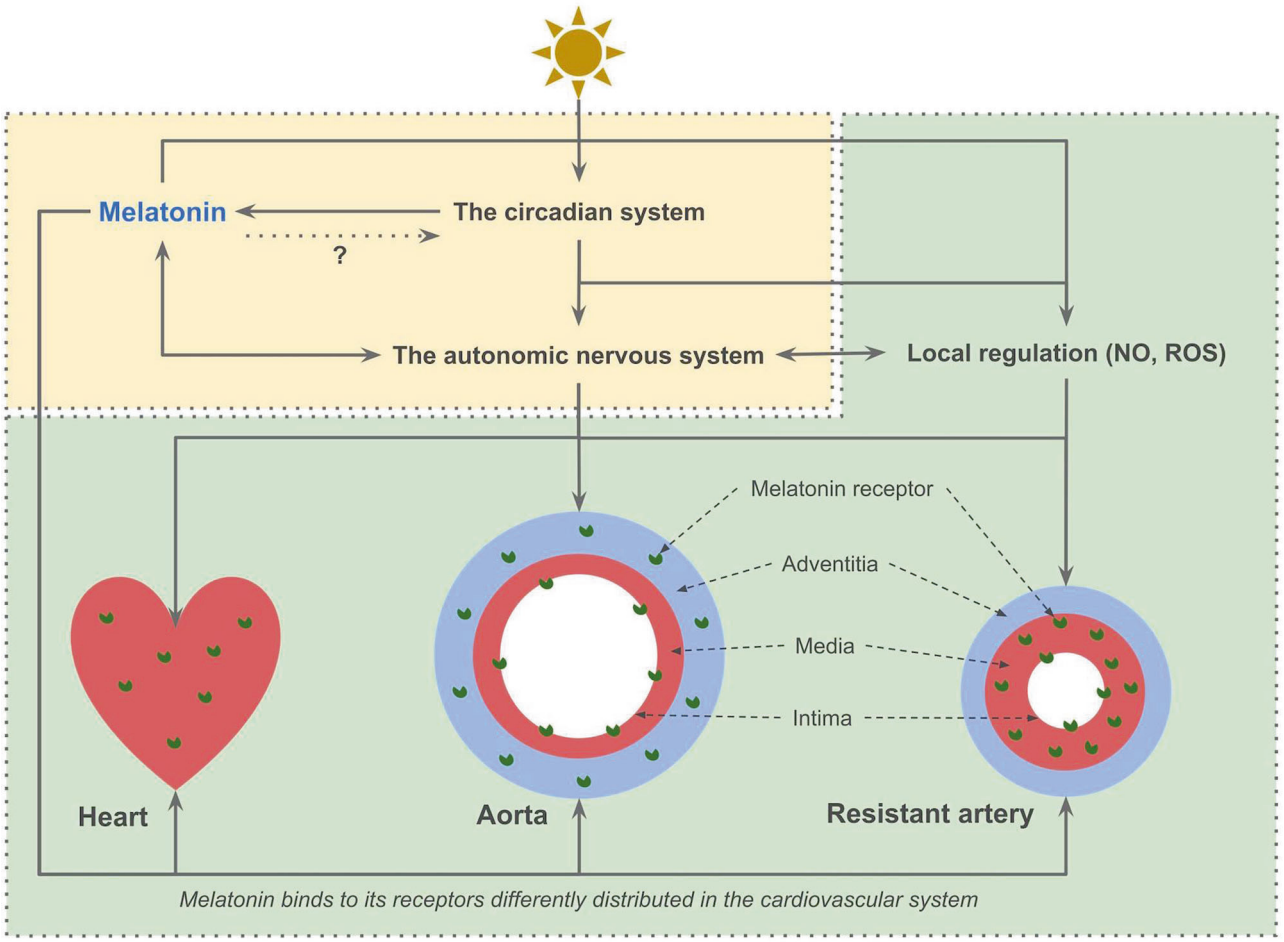


Fig. 2 Melatonin binds to its MT_1 and MT_2 receptors, which are differentially distributed in the cardiovascular system and interfere with a relatively wide range of regulatory mechanisms. NO nitric oxide, ROS reactive oxygen species

melatonin can interact and thus affect blood pressure include nitric oxide (NO), prostaglandin I2, endothelium-derived hyperpolarizing factor, and endothelin-1 [71]. Other endothelium-derived factors concerning melatonin are less studied and usually correlate with NO changes [72]. Therefore, one of the most studied vasodilatory mechanisms that melatonin interferes with is NO [20, 73]. Administration of melatonin to normotensive Wistar rats with L-NAME (N (gamma)-nitro-L-arginine methyl ester; NO synthase inhibitor)-induced hypertension caused a less pronounced decrease in blood pressure compared to that of SHRs, with increased endothelial NO synthase activity in the left ventricle of the heart and kidneys but also a decrease in total collagen in the left ventricle of the heart. Thus, the hypotensive effects of melatonin may be associated with the NO system [17, 18, 20]. Melatonin is also thought to increase NO bioavailability. However, high doses of melatonin in L-NAME-induced hypertension reduced NO bioavailability [74]. In rats exposed to intermittent hypoxia, melatonin increased endothelial NO synthase protein expression in the aorta to the same level as in control normoxic rats [75]. Melatonin thus reduced peripheral vasoconstriction induced by hypoxia, and this effect was NO dependent [31]. In sheep exposed to prenatal hypoxia, the effects of melatonin on hemodynamic parameters were associated with both NO-dependent and NO-independent pathways, with no changes associated with the oxidative stress marker 3-nitrotyrosine or vascular morphological changes [30].

Antioxidant properties

Melatonin also reduces oxidative stress by 1) increasing the activity of other antioxidant enzymes and 2) acting directly as a scavenger of radicals. Mitochondria, the major source of reactive oxygen species (ROS), generate energy by the oxidation of substrates in the process of mitochondrial respiration. If mitochondria are damaged and dysfunctional, electron leakage from the electron transport chain increases. The subsequent formation of ROS causes oxidative stress,

damaging not only the mitochondria but also surrounding tissues, including the heart and blood vessels (for more detail, see review) [76]. Melatonin has been proven to protect mitochondria from damage by several mechanisms that improve mitochondrial function and maintain mitochondrial integrity (for more detail, see review) [77]. Other sources of ROS in the cardiovascular system are xanthine oxidase, NADPH oxidase and NO synthase. The formation of ROS activates the cell's antioxidant defense, which includes an increase in the activity of several antioxidant enzymes [76]. Administration of melatonin to SHRs increased glutathione peroxidase activity in plasma and erythrocytes without changing superoxide dismutase activity. No changes in antioxidant enzyme activity were observed in Wistar rats [78]. The effects of melatonin on antioxidant enzyme activity and expression also depend on the etiology of hypertension. In all cases, melatonin ultimately reduced oxidative stress in hypertensive animal models with L-NAME-induced hypertension [74], SHRs [16], and rats exposed to hypoxia prenatally [31] or in adulthood [75] and altered the structural properties of blood vessels [79] and the heart [18, 53, 80]. In hypertensive rats, a decrease in oxidative stress and ROS in the brain promoted the involvement of melatonin in central blood pressure regulation [78] in areas involved in the autonomic and reflex regulation of cardiovascular activity [81].

The autonomic nervous system

The combined decrease in blood pressure and heart rate after melatonin administration also indicates a central inhibitory effect of melatonin on the sympathetic nervous system [82]. Microinjection of melatonin into the anterior hypothalamic area reduced the amount of glutamate and increased GABA release in the rostral ventrolateral medulla, the area that regulates peripheral sympathetic activity [83]. It is thought that the effects of melatonin on blood pressure may also be mediated through sympathetic and baroreflex regulation, as melatonin receptors have been found in paraventricular nuclei [84] and the area postrema [85, 86].

SHRs, which have increased sympathetic nervous system activity, increased plasma catecholamine concentration and β-adrenergic receptor density, especially in the developing heart, are a suitable model for studying the relationship between melatonin and the autonomic nervous system [87, 88]. Following phenylephrine administration, blood pressure increased in SHRs treated and not treated with melatonin, with the heart rate decreasing significantly only in melatonin-treated rats. The same decrease in blood pressure was observed in melatonin-treated and nontreated SHRs in response to sodium nitroprusside. Heart rate increased more in melatonin-treated rats than in melatonin nontreated rats. The effect of melatonin on the baroreflex response was not observed in normotensive rats [78]. In another experiment, melatonin improved the dose-dependent chronotropic response of the heart to isoproterenol in SHRs, while melatonin had no effect on normotensive Wistar rats. In addition, in SHRs, melatonin normalized the β_1/β_2 adrenergic receptor ratio by decreasing β_2-adrenergic receptor density and increasing β_1-adrenergic receptor density compared to nontreated SHRs [56]. Melatonin also decreased plasma catecholamines in SHRs [31, 56, 78] without affecting the reflex release of norepinephrine and adrenaline after the induction of hypotension [78]. The action of melatonin on catecholamines is primarily mediated through inhibition of the effect on the sympathetic fibers innervating the adrenals, as a result of which plasma levels of adrenaline (-60%) and noradrenaline (-30%) are significantly reduced in SHRs after melatonin injection [89].

Prenatal hypoxia also increases sympathetic activity and blood pressure in adult rats [39, 90]. Prenatal administration of melatonin has been shown to prevent the increase in plasma catecholamines in a dose-dependent manner [31], thereby reducing adrenergic activation, increasing cholinergic stimulation [31, 81], and improving baroreflex activity [81] in adult rats exposed to prenatal hypoxia. Experiments have shown that melatonin, in addition to its effects on the regulatory mechanisms of blood pressure in adulthood, also has a significant effect on programming in the prenatal period.

The renin-angiotensin-aldosterone system

Melatonin administration reduced plasma renin levels in SHRs [82, 89]. However, when melatonin was administered to TGRs, a model of hypertension with increased renin-angiotensin-aldosterone system activity, no decrease in blood pressure was observed [91]. In L-NAME-induced hypertension, a decrease in the plasma concentration of the renin-angiotensin-aldosterone system components was observed, and melatonin administration did not alter this, although a partial decrease but not normalization in blood pressure was observed [20, 53]. In contrast, treating L-NAME-induced hypertension with an angiotensin-converting enzyme inhibitor (captopril) reduced blood pressure significantly in Wistar rats compared to only L-NAME-treated Wistar rats [73]. Experiments have shown that melatonin effects on blood pressure depend on the etiology of hypertension, and these effects can probably be mediated without affecting the renin-angiotensin-aldosterone system directly [53, 91].

The circadian system

In humans, several studies point to the beneficial effect of melatonin in restoring the nondipping blood pressure profile associated with decreased melatonin levels [5, 92, 93].

Melatonin is thought to act on the suprachiasmatic nuclei through its receptors [94] and reaches the suprachiasmatic nuclei via the cerebrospinal fluid [95, 96]. The application of melatonin to rat brain sections caused a phase advance of the electrical activity of the suprachiasmatic nuclei [97]. However, no direct effect on the expression of clock genes in the suprachiasmatic nuclei was observed [98]. Similarly, in vivo pinealectomy did not alter the function of the suprachiasmatic nuclei in Djungarian hamsters [99] or rats [100]. This is consistent with observations in melatonin-proficient C3H mice and melatonin-deficient C57BL/6 mice, whose circadian rhythms do not differ fundamentally but respond differently to the light pulse during the subjective night (for more detail, see review) [101].

The removal of the suprachiasmatic nuclei suppresses not only the circadian profile of cardiovascular parameters in normotensive and hypertensive rats [36] but also the circadian rhythm of melatonin synthesis, with its maximum levels during the dark phase of the day reaching one-fifth of that in animals with intact suprachiasmatic nuclei [2, 4]. Additionally, the disruption of suprachiasmatic nuclei activity by phase shifts [102], dimmed night light [35] and constant light [103] caused a significant decrease in melatonin. Administration of melatonin to normotensive Wistar rats at the beginning of the subjective night partially restored the heart rate but not the blood pressure rhythm [103]. Similar effects were observed after phase administration of melatonin (i.p., onset of light and dark phase of the day, 2.5 or 5 mg/kg) according to telemetry measurements in normotensive Wistar rats [19]. No change in blood pressure was observed in either the light or dark phase of the day. Heart rate decreased after melatonin administration, only in the dark phase of the day and after administration of 2.5 mg/kg, not 5 mg/kg [19]. On the other hand, administration of a melatonin agonist to rats with suprachiasmatic nucleus lesions did not restore the lost circadian profile of cardiovascular parameters. Conversely, the melatonin antagonist did not suppress the circadian variability of cardiovascular parameters in Sprague–Dawley rats or TGRs [36]. In addition, in TGRs with an inverse blood pressure profile to heart rate and locomotor activity, no difference in melatonin levels was observed [104], and melatonin administration did not improve the circadian blood pressure profile [91]. Other publications have shown that animals with intact suprachiasmatic nuclei exposed to constant dark became entrained to melatonin injections, but in rats with suprachiasmatic nucleus lesions, the application of melatonin did not affect blood pressure circadian variability [26, 97, 105, 106]. Therefore, the central effect of melatonin appears to be dependent on functional suprachiasmatic nuclei and circadian system arrangements in mammals, but feedback is significantly less involved in the central circadian pacemaker regulation compared to that in fish, reptiles, and birds [107].

Conclusion

The hypotensive effects of melatonin are often tested experimentally in nocturnal animals (rats and mice), which show positive correlations between melatonin plasma concentrations and blood pressure. In rats, the hypotensive effects of melatonin depend on the strain, the technology and timing of blood pressure recording, and the route, time and duration of melatonin administration. The most appropriate combination for testing the hypotensive effects of melatonin seems to be to measure blood pressure telemetrically and to administer melatonin during the dark phase of the day, ideally in water, thus minimizing animal handling and unwanted synchronization. Although melatonin receptors in the heart and blood vessels have been detected, it is not entirely clear whether and to what extent they mediate hypotensive effects. Therefore, several studies have associated the hypothetical properties of melatonin with its antioxidant properties or interaction with other cardiovascular system regulatory mechanisms. Based on research conducted on rats, the cardiovascular effects of melatonin are modulatory, delayed, and indirect.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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