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Melatonin and clock genes expression in the cardiovascular system

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1. ABSTRACT

Generation of circadian oscillations is based on rhythmic expression of clock genes and subsequent post-transcriptional and post-translational modifications. In addition to the central circadian oscillator - the suprachiasmatic nucleus (SCN), peripheral oscillators have been demonstrated in many tissues, including the heart and blood vessels. Melatonin mediates cyclic lighting conditions to rhythmic endocrine signal and is able to synchronize neuronal firing in the SCN via membrane receptors. Clock gene expression is melatonin sensitive in the *pars tuberalis*, genes *cry1* and *tim1* respond to single injection while *neurod1* and *npas4* are influenced via long lasting mechanisms. In the rat heart, melatonin phase advanced expression of *per2* and *bmal1* independently from its effects on the SCN. Melatonin is an important endogenous signal able to synchronize circadian oscillations in the cardiovascular system. It may be effective especially *in situ*ations when the circadian control is weakened or organism must adapt to rapid changes in rhythmic environmental conditions.

2. INTRODUCTION

The physiological functions of the cardiovascular system exhibit distinct day/night rhythms which are determined by rhythmic changes of autonomous nervous system activity, hormone secretion, renal functions, plasma electrolyte concentrations and so on. In addition to the rhythmic oscillations in the system function, the onset of several cardiovascular diseases exhibit daily variations. Such temporal variations have been documented for myocardial infarction, stroke, angina pectoris, ventricular arrhythmias and sudden cardiac death (1, 2). Moreover, the results of clinical trials (Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events - MAPEC study) suggest that time dependent treatment of cardiovascular diseases (chronotherapy) results in better outcomes and lower cardiovascular risk (3). As such there is a growing interest in understanding the circadian rhythmicity control mechanisms in the cardiovascular system as new knowledge may improve the diagnostics and treatment of cardiovascular diseases.

3. CIRCADIAN OSCILLATIONS AND CLOCK GENES

Circadian rhythms are generated at the molecular level by clock genes and controlled by the circadian system. Since melatonin can influence the cardiovascular system and is involved in circadian system regulation, studies in this field are expected to bring new data with therapeutic importance. The circadian system consists of circadian oscillators that are present in all studied cells of the human body (4). The functional basis of circadian oscillations represents a rhythmic expression of clock genes and processes involving subsequent post-transcriptional and post-translational modifications (5). The basic principle of circadian rhythm generation at the molecular level is a negative feed-back loop, formed when the protein product of a gene turns off its own production by inhibition of corresponding mRNA transcription. Transcriptional factors BMAL1 and CLOCK proteins heterodimerize and bind a DNA element called the E-box and in this way initiate expression of clock genes *cry* and *per*, as well as other genes with the functional E-box. When concentrations of PER and CRY proteins in the cytoplasm achieve a critical level, PER and CRY create a complex which is translocated back into the nucleus and terminates BMAL1:CLOCK initiated transcription (5, 6, 7).

There are also additional loops generated by transcriptional factors with the capacity to regulate clock gene expression. Possibly the most important additional loop is created by the nuclear receptors reverse erythroblastosis virus-alpha (REV-ERBalpha) and retinoic acid receptor-related orphan receptor-alpha (RORalpha). *Rev-erbalpha* expression can be induced by heterodimer BMAL1:CLOCK via E-box (8) and REV-ERBalpha and RORalpha via the REV-ERBalpha/RORalpha response element (RORE) influence *bmal1* expression (9, 10). REV-ERBalpha competes with the stimulatory factor ROR for binding on the RORE element in the promoter region of *bmal1* and inhibits BMAL1 expression (11). A similar mechanism of regulation, mediated by the REV-ERBalpha/RORA, was found by *in vitro* studies for *npas2* transcription (12). REV-ERBalpha regulates expression of *clock* mRNA in HepG2 cells via the REV-ERB response element (RevRE) (13).

The circadian system consists of both central and peripheral parts. The central oscillator (master clock) is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The SCN displays a robust rhythmicity in neuronal electric activity as well as clock gene expression (14). Moreover, the presence of self sustaining oscillators has been found also in peripheral tissues, and even in cell cultures (15) and in single cells (16, 17). The molecular mechanism of the central and peripheral oscillator functioning are generally the same, although the importance of the molecular clock components, and the interactions among them, may vary in a tissue-specific manner (7). Peripheral oscillators are situated in all tissues studied till now and they are synchronized by the central oscillator in the brain under normal conditions (18). Several pathways are involved in the synchronization of circadian oscillators inside the body to external conditions, such as the light:dark (LD) cycle, food availability, social cues, temperature and so on (4). The dominant input for the central oscillator is the LD cycle, conveyed from the retina to the SCN by the retinohypothalamic tract (19), and the signal is then widespread throughout the body via multiple pathways, including rhythmic melatonin secretion from the pineal gland.

4. MELATONIN AND THE CIRCADIAN SYSTEM

Plasma melatonin rhythm is the most pronounced hormonal rhythm driven by the circadian system. This circadian signal modulates many physiological processes including the cardiovascular system (20, 21). Moreover, the melatonin rhythm can provide feedback to the circadian system via interference with central and/or peripheral oscillators (22, 23). Therefore, the main aim of the present review is to summarize recent knowledge about melatonin influence on clock gene expression and explain the role of melatonin in the regulation of daily rhythms in the cardiovascular system. We will also outline pathological situations in which the melatonin rhythm can be disrupted.

Melatonin can influence target cells in several ways. Melatonin is a highly lipophilic compound that can pass through biological membranes, scavenge free radicals (24), interact with orphan nuclear receptors (25) and modulate gene transcription (26, 27). Many of the physiological effects of melatonin are mediated via its specific membrane receptors (22). Both subtypes of melatonin receptors MT_1 and MT_2 (originally Mel 1a and Mel 1b, respectively) were cloned in mammals and belong to a family of G protein-coupled receptors. The first cloned mammalian melatonin receptor MT_1 is a Gi protein-coupled receptor that inhibits forskolin-stimulated cyclic AMP formation via both pertussis toxin sensitive and insensitive G proteins. MT_2 is a Gi protein-coupled receptor capable of inhibiting cAMP and cGMP production and stimulating PKC activity (28).The highest level of MT_1 and MT_2 expression has been detected in the *pars tuberalis* of the anterior pituitary but both subtypes of melatonin receptors are also distributed in many other tissues of the human body (suprachiasmatic nuclei of the hypothalamus, heart, arteries, liver etc.) (23, 28, 29).

4.1. Melatonin and the clock genes in the central oscillator

The effects of melatonin on the central circadian oscillator have been investigated by monitoring SCN neuron firing under *in vitro* conditions. Melatonin acutely inhibits neuronal firing in the mammalian SCN predominantly via MT_1 receptors. The phase dependent effect of melatonin, which influences the circadian rhythm of neuronal SCN firing and other measured outputs, is mediated via MT_1 and MT_2 receptors (28, 30, 31).

The effect of melatonin on clock gene expression in the SCN has been studied as well. However, in spite of the significant acute effect of melatonin on SCN neuronal firing, melatonin does not seem to influence clock gene expression immediately after administration. Under

Table 1. Effect of melatonin on clock gene experssion

Structure	Clock genes	Melatonin	Pinealectomy	Species	Ref.
SCN	*per1*	minor effect	n/a	rat	32
		no effect	n/a	sheep	91
	per1, per2	reverse effect of PINX	phase angle difference	rat	34
	per2	no effect	n/a	rat	35
		no effect	n/a	sheep	91
		n/a	no effect	rat	92
	per3	minor effect	n/a	rat	32
	Bmal1	minor effect	n/a	rat	32
		phase advance	n/a	rat	33
		no effect	n/a	rat	35
		no effect	n/a	sheep	91
	cry1	no effect	n/a	sheep	91
	rev-erb alpha	phase advance	n/a	rat	33
Parst tuberalis	*per1*	up-regulated in PINX	down-regulated	C3H/HeN mice	43
		down-regulated	n/a	sheep	91
		lowered amplitude	n/a	rat	45
		lowered amplitude	n/a	siberian hamster	93
	per2	down-regulated	n/a	sheep	91
	Bmal1	down-regulated	n/a	sheep	91
	cry1	up-regulated	n/a	sheep	91
		up-regulated	n/a	rat	45
		up-regulated	n/a	melatonin proficient mice	42
		induction	n/a	siberian hamster	93
		induction	n/a	rat	45
	rev-erb alpha	down-regulated	n/a	sheep	91
		phase advanced	n/a	siberian hamster	93
	tim	down-regulated	n/a	melatonin proficient mice	42
Cardiomyocytes	*per1*	phase delayed	n/a	mice	94
Heart	*per2*	n/a	minor effect	rat	92
		phase advance	n/a	rat	35
	Bmal1	phase advance	n/a	rat	35

SCN: suprachiasmatic nucleus, PINX: pinealectomy, Ref: number of reference, n/a: not applicable

constant darkness (to avoid masking effects of a L:D cycle) melatonin injection did not change the expression pattern of *per1, per2, per3, Bmal1, Cry1,* or *Avp* (arginine vasopressin) mRNAs in the SCN immediately. Rather, melatonin injection was effective on the second day after the treatment as indicated by changed expression of *per1, per3, Bmal1* and *Avp*. This finding indicates that melatonin in the SCN acts via post-translational rather than via transcriptional mechanisms (32).

Melatonin can also modulate the effects of nuclear orphan receptors on the clock genes expression. A single injection of melatonin administered to rats kept in constant darkness caused a phase-advance in *rev-erbalpha* and *Bmal1* mRNA expression in the SCN during the first subjective night after the melatonin administration (33). However, in pinealectomized rats lowered melatonin levels in their circulation did not influence clock gene expression in the SCN eight days after the surgery. The influence of pinealectomy on clock gene expression was detected three months after the treatment when a significant phase angle difference between *per1* and *per2* peaks appeared. This effect was prevented by daily melatonin administration in the drinking water (34). Finally, when melatonin was administered to control and genetically hypertensive rats during the dark phase in drinking water during 6 weeks the daily pattern of *per2* mRNA expression in the SCN was not changed (35).

All of the above mentioned data suggests that the molecular circadian loop in the SCN is sensitive to melatonin administration but that melatonin effects are detectable after longer time, and most probably under conditions of initial or chronic desynchronization. These data are well supported by results obtained in humans showing that melatonin is effective especially when the circadian system is somehow weakened (36, 37, 38). This assumption is in accordance with studies using *clock*/+ mutant mice capable of melatonin synthesis. *clock*/+ mice are characteristic by a lengthening of their circadian period of locomotor activity. SCN explants from Period2Luciferase *clock*/+ reporter mice are more responsive to melatonin compared to wild type animals and the *clock*/+ mutant phenotype is suppressed by melatonin or melatonin agonist ramelteon (39).

4.2. The effect of melatonin on the peripheral oscillators

The effects of melatonin on clock gene expression are much more pronounced in the *pars tuberalis* of the anterior pituitary compared to the SCN. The physiological role of the *pars tuberalis* consists in the control of reproduction of photoperiodic animals. Melatonin, via abundantly expressed MT_1 receptors, influences specific cells in the pars tuberalis, affects clock gene expression (Table 1), and by inducing prolactin stimulating factor(s) promotes prolactin secretion (40, 41).

There is a possible functional relationship between the melatonin control of photoperiodism and clock gene expression in the pars tuberalis. This can be concluded on the basis of studies employing MT_1-deficient and clock protein PERIOD1-deficient mice. Moreover, melatonin can influence thyrotropin beta-chain expression directly and also via a PER1 mediated pathway (42).

Studies performed with the use of MT_1 and MT_2 mutant mice confirm the crucial role of melatonin in clock gene expression in the pars tuberalis of mammals. While

MT_2 mutant mice do not show significant changes in rhythmic expression of *per1*, *cry1*, *clock* and *bmal1* mRNA in the pars tuberalis compared to controls, in MT_1 mutant animals the expression of *per1*, *cry1*, *clock* and *Bmal1* mRNA was substantially decreased (43). Similarly, the protein products of clock genes *per1*, *cry1*, *clock* and *Bmal1* were significantly reduced in MT_1 mutant mice while expression of clock genes *per1*, *per2*, *cry1*, *cry2*, *Bmal1* was still rhythmic in the SCN of MT_1 as well as MT_2 mutant animals. This finding suggests a crucial role of melatonin input for pars tuberalis clock gene expression (44).

A single injection of melatonin at the end of the subjective day to rats kept in constant darkness causes a decrease in the amplitude of rhythmic *per1* expression and an acute increase in *cry1* expression in the pars tuberalis. Furthermore, melatonin administered in the middle of the subjective day caused an increase in *cry1* expression as well (45). The melatonin dependent regulation of *per1* expression seems to be based on the sensitization of the adenosine A2b receptor (46). In accordance with previous results, pinealectomy abolished rhythmic expression of *per1*, *rev-erb alpha* and *ror beta* mRNA in rat pars tuberalis and melatonin administration in drinking water partially restored their rhythmicity (34).

A microarray study targeted at MT_1-dependent gene expression in the mouse pars tuberalis identified 27 melatonin responsive (positively or negatively) genes. Among them *cry1*, *tim1*, *neurod1* and *npas4* significantly differed between wild type and MT_1 -/- genotypes. The expression of *cry1* and *tim1* was responsive to melatonin injection while *neurod1* and *npas4* were more likely to be influenced via longer term melatonin dependent mechanism (47).

There are daily rhythms in clock gene expression in the rat fetus adrenal gland *in vivo*. This rhythm is changed under *in vitro* conditions and can be restored by melatonin (48). Clock gene expression in the SCN and the adrenal gland of the fetus is sensitive to melatonin administration in pinealectomized Capuchin monkeys (*Cebus apella*) (49). Under *in vitro* conditions *per2* and *bmal1* expression in capuchin monkey adrenal explants in culture was sensitive to melatonin in a phase dependent manner (50).

4.2.1. Cardiovascular system

Changed circadian phenotype, as a result of clock gene deletion, usually influences several parameters of behaviour and physiology. Since the cardiovascular system exhibits a strong circadian variability, it is not surprising that a clock gene malfunction influences the cardiovascular system and vice versa. Several hypertensive rat strains displaying major changes in their circadian blood pressure (BP) profile have been identified (51). A pronounced increase in the amplitude, mesor and a significant phase delay of acrophase towards the pasive phase has been shown in stroke-prone spontaneously hypertensive rats (52) and modifications of the normal daily pattern of BP have also been seen in spontaneously hypertensive rats (53).

Our recent study (35) demonstrated the effects of melatonin on clock gene expression in the heart of control and genetically hypertensive TGR(mRen2)27 rats. Melatonin administered in drinking water during the dark phase for 6 weeks affected expression of *per2* and *bmal1* in the left ventricle of control as well as TGR rats. Expression of *per2* was increased during the light phase and decreased during the dark phase of LD cycle in both control and TGR rats after the melatonin treatment. Expression of *bmal1* was decreased during the light phase and increased during the dark phase after the melatonin treatment. The effect of melatonin on *bmal1* expression was observed only in control, not in hypertensive rats. The unifying functional explanation of all the observed changes in the clock gene expression was a phase advance in *per2* and *bmal1* expression in the heart after melatonin treatment. Therefore, the present results indicate that melatonin administration in drinking water can influence peripheral oscillators in the heart independent from the SCN, although neuronally mediated melatonin effects cannot be excluded.

The interactions between the loop of interacting clock proteins, ensuring the generation of circadian rhythms, and rhythmic melatonin production are very complex. It is apparent that the melatonin input is not essential for the generation of circadian oscillations in peripheral structures. Therefore, it is not surprising that pinealectomy does not result in arrhythmicity of clock gene expression in rats and it induces only minor, tissue specific, changes of *per2* rhythmicity (54). However, because of the rhythmic nature of melatonin biosynthesis and clock gene expression, the stability of phase angles between these two rhythmic events can be changed (55). In particular, the dynamics of phase shifts to disturbance stimuli can be affected by melatonin. In our experiments, the re-adjustment of the circadian *per2* and *bmal1* rhythm to phase delay shifts of lighting regimen, mimicking the rotation shift work program, was not acheived within two days. Rhythmic expression of both clock genes was completely out of phase with the ambient LD cycle, while the melatonin rhythm was phase delayed only in 2-3 hours (56). Therefore, it is possible that the melatonin rhythm can facilitate the entrainment of peripheral oscillators after shifts of environmental cues. Melatonin can influence circadian rhythms in the cardiovascular system by multiple pathways: 1) either through the central oscillator in the SCN; 2) the sympathetic output to the heart and vessels; 3) via interactions with other hormonal systems involved in the control of cardiovascular system.

Although, the influence of melatonin on the physiology of the cardiovascular system has been studied extensively so far there is limited information about melatonin and clock gene expression in the vasculature. However, the significance of intrinsic tissue clocks for vessel function is suggested by transplantation studies using *per2* and *per3* double knockout or *Bmal1* knockout mice. Aortic grafts from knockout mice transplanted into

the littermate wild type controls developed robust artherosclerosis disease (57).

5. DISTURBANCES OF CIRCADIAN RHYTHMS IN THE CARDIOVASCULAR SYSTEM

Regular synchronized circadian rhythms signal well functioning biological systems and aberrations of these biological rhythms are frequently observed as the early signs of diseases. Many parameters of the cardiovascular system exhibit pronounced circadian rhythmicity with their acrophases occurring in different parts of the 24-hr cycle (58). Heart rate and BP values are usually closely related and they both frequently parallel the locomotor activity rhythm reflecting a LD and rest/activity cycle. High values occur during the active phase of the 24hr cycle (during the day in humans and during the night in nocturnal laboratory rodents).

5.1. Non-dipping blood pressure profile

Probably the best studied disturbance of circadian rhythms is the inverse BP daily rhythm seen in hypertensive patients. Patients with a non-dipping BP profile (non-dippers) have greater organ damage (59) and therefore the non-dipping BP profile is considered as an independent risk factor of cardiovascular diseases (60). In non-dippers the normal circadian pattern in heart rate (HR) is preserved and is parallel with locomotor activity, while BP either does not exhibit rhythmicity or is rhythmic but the acrophase of the rhythm occurs during the passive phase of the 24hr period.

A high prevalence of non-dipping is associated with kidney diseases, especially chronic kidney disease (61). Such patients exhibit a sympathetic activation (62) or increased arterial stiffness connected with microproteinuria (63). The increased sympathetic activation in these patients leads to reduced baroreceptor (64) and sodium sensitivity since it can directly modulate renal sodium excretion (65). An involvement of the central nervous system in the inverted BP rhythm development can be assumed because in *Bmal1*-knockout mice the BP rhythms are disturbed (66) while endothelial cell specific deletion of *Bmal1* does not result in the BP rhythm disturbance (67).

Another pathological situation connected with a high prevalence of the non-dipping BP pattern is obstructive sleep apnea syndrome (OSAS) (68). OSAS results in disorganized physical activity, sodium sensitivity and sympathetic activity that cause the non-dipping profile in these patients (61). Plasma melatonin concentrations were repeatedly measured in patients with obstructive sleep apnoea syndrome with rather inconsistent results. Among 33 male patients with OSAS (69) there were patients exhibiting normal night-time melatonin concentrations and patients with prolonged melatonin secretion who had higher indices of apnea and lower quality of sleep. Another study (70) which included also a control group, found a disturbed nocturnal melatonin peak in OSAS patients and in some patients the peak was even absent. However, as the blood was collected during nights when patients underwent diagnostic polysomnography or continuous positive airway pressure titrations, it is not clear if the sampling procedure could have interfered with the night-time melatonin peak. In a third study dealing with the melatonin pattern in OSAS patients, no differences in the nighttime increase in plasma melatonin concentrations and the area under the curve were found between patients and age-matched controls (71) indicating that this problem require further study. When a melatonin receptor agonist ramelteon was given in a randomised, double-blind, placebo-controlled pilot clinical trial it improved objective sleep onset latency in older patients with sleep apnea (72). Obviously, more studies are warranted in order to examine the role of the circadian system and melatonin in this disease.

5.2. Mechanisms underlying non-dipping BP rhythmicity

In spite of its clinical significance, the pathophysiological mechanisms underlying the non-dipping BP profile are not known and animal studies are needed. Transgenic hypertensive rats (TGR (mRen2)27) harboring an additional mouse renin gene in their genome (73) seem to be a useful animal model to study the physiological mechanisms determining the non-dipping BP profile (74, 75). In parallel with the situation in non-dipping hypertensive patients, these rats exhibit an inverted BP profile (Figure 1, reproduced with permission from ref. 76), with higher values found during the rest phase (L) than during the active phase (D) (74, 75, 76). Detailed studies of the neuroendocrine (for a review see 75) and the circadian system (77, 78, 79) indicate that the disturbed rhythmic functions of the renin–angiotensin–aldosterone system and the sympathetic system are involved.

5.2.1. Renin-angiotensin-aldosterone system and sympathetic system

Hypertensive TGR rats exhibit much higher (10x) amplitude of the aldosterone rhythm than controls (Figure 2, part A reproduced with permission from ref. 79) and the maximum concentrations of aldosterone were found at the end of passive phase (79). High aldosterone concentrations in TGR rats at the end of daytime may cause desensitization of mineralcorticoid receptors and may lead to a shift in BP control in distinct brain centers. Aldosterone has been found to regulate the expression of clock genes *Per1, Per2* and *Bmal1* in H9c2 cardiomyoblasts (80) while the aldosterone antagonist spironolacton attenuated this effect. The authors suggest that *Per1* rhythm induction is a direct action of aldosterone while *Per2* rhythm generation is a secondary phenomenon. Aldosterone acts via mineralcorticoid receptors and their presence has been confirmed not only in the kidney, heart and vasculature, but also in the brain areas involved in the control of the cardiovascular system (for a review 81). In addition to aldosterone, angiotensin II is also known as an entraining agent able to synchronize circadian rhythms in endothelial cells of large vessels (82), at least under *in vitro* conditions.

Experimental studies with rodent models support the role of catecholamines in the circadian control of cardiovascular parameters and BP. Mice with the deleted clock gene Bmal1 have a hypotensive phenotype (66) and

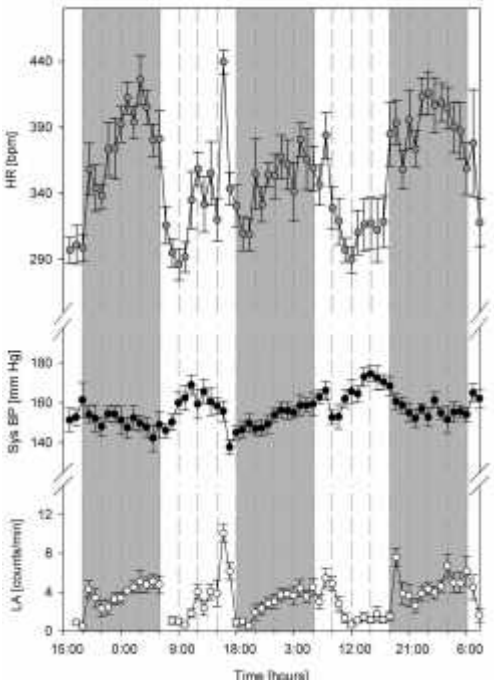

Figure 1. Daily rhythms of heart rate (HR), systolic blood pressure (Sys BP) and locomotor activity (LA) in mature male TGR rats. Each value represents the mean ± SEM (n = 10). The gray fields in the graph represent a dark phase of 24 h cycle (LD 12:12). Reproduced with permission from 76.

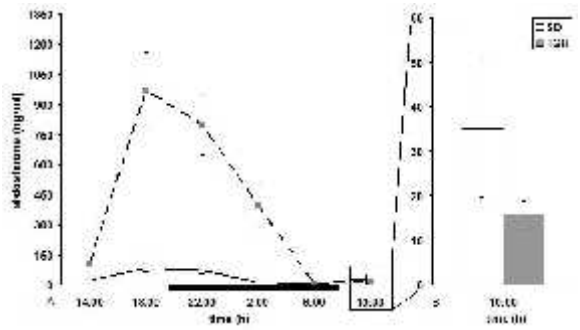

Figure 2. Plasma aldosterone levels during 24h cycle (A) and in the morning (B) in Sprague Dawley control (SD, white color) and hypertensive TGR (gray color) rats synchronized to L:D cycle 12:12. Black bars on the bottom of the graph A represent the darktime. Full line represents control and dashed line demonstrates TGR rats. Data are expressed as mean ± SEM (n = 6). Reproduced with permission and modified from 79.

substantially reduced circulating concentrations of norepinephrine and epinephrine (83). The *per1* promoter contains several enhancers, such as the cAMP response element in its upstream region and the expression of *per1* can be induced by treatment with adrenoceptor agonists (84). Clock mutant mice also exhibit a loss of circadian variation of arterial BP (85) together with the reduced endothelial-dependent vascular relaxation. Double knockout Cry1/Cry2 mice also exhibit a loss of circadian variation of arterial BP and this circadian disruption is accompanied by the increased baroreflex sensitivity and reduced norepinephrine-mediated vasoconstriction. The disruption of different clock genes is accompanied by the loss of circadian BP variation, illustrating the role of clock genes in regular circadian rhythms in the cardiovascular system. However, the deletion of different genes results in different phenotypes, and it is not clear if all the same pathways are involved in circadian BP disruption.

5.2.2. Circadian system, clock genes and melatonin

The non-dipping BP profile cannot be explained by the lost rhythms of clock gene expression in the central circadian oscillator (77, 78) of TGR(mREN-2)27 rats. In fact expression of *bmal1* and *clock* was even up regulated in the SCN of TGR rats as compared to controls, while daily rhythms in *per2* and *dbp* (albumin D-element-binding protein) were similar in both groups (77). Rhythmic expression of *per2* and *dbp* displayed significant changes in acrophase and expression of the *clock* gene showed significantly lowered amplitude in the heart of TGR rats in comparison with control animals. The rhythmic pattern of *Bmal1* and *clock* gene was significantly attenuated also in the kidneys of TGR rats as compared to controls (77).

The circadian oscillations in clock gene expression in selected brain structures were affected more than in the heart and kidney by the additional renin gene in TGR rats (77, 78). The most robust differences between TGR and control rats in clock gene expression were found in the circumventricular organ, the area postrema that is situated in the caudal brainstem and plays a crucial role in the mediation of the angiotensin II signal to the central nervous system (86). The area postrema projects into several structures involved in BP control and it is indirectly connected also with the SCN (87). Expression of *per2* gene was substantially phase delayed in the area postrema of TGR while *bmal1* expression was phase advanced in comparison with controls (78). The antiphase pattern in the expression of both genes was substantially disturbed in this structure with possible negative effects on rhythmic BP control.

Significant differences in circadian clock gene expression were found also in other brain areas implicated in control of the cardiovascular system (77, 78). Up regulation of clock gene expression was observed in the rostral ventrolateral medulla and down regulation in the nucleus of the solitary tract that are involved in the baroreflex control of BP (77). Hypothalamic dorsomedial nucleus, anteroventral third ventricle and *nucleus ambiguus* (78) that are related to cardiovascular control and autonomous nerve system activity also displayed modified clock gene expression. Results suggest that the inversion of BP rhythms occurs downstream of the central circadian oscillator and is related to brain structures implicated in osmotic and water balance as well as in autonomous nervous control. Melatonin receptors are present in the area postrema (88) and therefore melatonin can act via this structure and influence BP control.

Disruption of rhythmic melatonin production has been suggested in hypertensive patients with the non-

dipping BP profile (89) who exhibited a lack of rhythmic excretion of 6-sulphatoxymelatonin, which represents the main metabolite of melatonin found in urine. In our study (90) we recorded a significant melatonin rhythm in both dippers and non-dippers but the night/day difference in plasma melatonin concentrations was blunted in non-dippers. Interestingly, the day/night difference was more pronounced when diastolic BP was used as the selection criterion as compared to systolic BP. This may be important since systolic BP is more affected by locomotor activity than diastolic BP.

6. SUMMARY AND PERSPECTIVE

Entrained circadian oscillations in the heart, vessels and coordinating brain centers are necessary for the optimal functioning of the cardiovascular system. Clock genes represent the molecular basis of circadian rhythm generation and mutations in these genes affect the cardiovascular system indicating an important role of circadian oscillations in cardiovascular function. Hormone melatonin exerts beneficial effects on cardiovascular system functioning. Possible synchronizing effects of MEL on clock genes expression suggest the multiple action of the hormone on different organs and corresponding peripheral clocks. This synchronizing effect of melatonin is probably organ specific and may reflect the density of melatonin receptors as suggested by the data from the *pars tuberalis*. Therefore more data is needed on melatonin receptor localization and density in different tissues, especially in vessels and structures controlling volume and vascular resistance. Moreover, the possibility that MEL can bind b-RORs broadens the transcriptional control of melatonin over a wide extent of physiological processes in the cardiovascular system. The cardiovascular system is modulated by multiple control mechanisms and circadian oscillations and melatonin are important part of this network. Circadian desynchronization can have negative effects on the cardiovascular system functioning.

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Abbreviations: AVP: arginine vasopressin; BP: blood pressure; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; DBP: albumin D-element-binding protein; HR: heart rate; LD: light:dark cycle; MT_1: melatonin type 1 receptors; MT_2: melatonin type 2 receptors; MAPEC: Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events; OSAS: obstructive sleep apnea syndrome; REV-ERBalpha: nuclear receptors reverse erythroblastosis virus-alpha; RORE: REV-ERBalpha/RORalpha response element; RevRE: REV-ERB response element; RORalpha: retinoic acid receptor-related orphan receptor-alpha; SCN: suprachiasmatic nucleus

Key Words: Circadian rhythms, Heart, Vessels, *per2*, *bmal1*, Angiotensin, Aldosterone, Sympaticus, Non-dipping, Blood pressure, Review

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