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REVIEW ARTICLE

Melatonin and circadian biology in human cardiovascular disease

Abstract: Diurnal rhythms influence cardiovascular physiology, i.e. heart rate and blood pressure, and they appear to also modulate the incidence of serious adverse cardiac events. Diurnal variations occur also at the molecular level including changes in gene expression in the heart and blood vessels. Moreover, the risk/benefit ratio of some therapeutic strategies and the concentration of circulating cardiovascular system biomarkers may also vary across the 24-hr light/dark cycle. Synchrony between external and internal diurnal rhythms and harmony among molecular rhythms within the cell are essential for normal organ biology. Diurnal variations in the responsiveness of the cardiovascular system to environmental stimuli are mediated by a complex interplay between extracellular (i.e. neurohumoral factors) and intracellular (i.e. specific genes that are differentially light/dark regulated) mechanisms. Neurohormones, which are particularly relevant to the cardiovascular system, such as melatonin, exhibit a diurnal variation and may play a role in the synchronization of molecular circadian clocks in the peripheral tissue and the suprachiasmatic nucleus. Moreover, mounting evidence reveals that the blood melatonin rhythm has a crucial role in several cardiovascular functions, including daily variations in blood pressure. Melatonin has antioxidant, anti-inflammatory, chronobiotic and, possibly, epigenetic regulatory functions. This article reviews current knowledge related to the biological role of melatonin and its circadian rhythm in cardiovascular disease.

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Introduction

Heart rate, blood pressure, endothelial function and fibrinolytic activity, among other cardiovascular variables, exhibit diurnal variations consistent with a circadian rhythm [1]. Moreover, serious cardiovascular events also appear to exhibit circadian patterns. Indeed, the incidence of acute myocardial infarction, myocardial ischemia, cardiac arrest, ventricular tachycardia and sudden death in patients with heart failure all vary according to the time of day [2]. It has been suggested that social and commercial pressures, such as shift work, which opposes the 'physiological' temporal circadian order, may be factors underlying chronic illnesses, such as cardiovascular disease [3, 4].

In many disease states (e.g. diabetes mellitus, hypertension), neurohumoral circadian rhythms are 'chronically' impaired and result in dyssynchrony of cellular cross talk in different tissues [5]. The cardiovascular system actually exhibits significant daily variation regarding physiological, pathophysiological and molecular processes. Diurnal variations also affect gene and protein expression. An increasing number of experimental and clinical studies have shown that the coordination of these rhythmic processes plays a fundamental role in organ function [6].

The existence of a circadian clock mechanism has recently been documented in cardiomyocytes. This information helps to explain the circadian rhythms in cardiac physiology (e.g. heart rate, cardiac output) and pathophysiology (e.g. arrhythmias) [6, 7].

The internal 'oscillator', or control station regulating the body's circadian clock, is the suprachiasmatic nucleus, a small group of cells (comprising approximately 70,000 neurons) located in the hypothalamus above the optic chiasm [8]. The suprachiasmatic nucleus processes external signals, such as ambient light information as well as inputs from the brain to regulate a variety of cyclic functions including body temperature, sleep/wake cycles and the secretion of hormones such as melatonin [9]. This review describes the current understanding of the role of melatonin in modulation of circadian rhythms with particular focus on cardiovascular disease.

Circadian rhythm and cardiovascular function

The existence of a daily rhythm affecting heart rate, blood pressure, platelet and endothelial function, among other components of the cardiovascular system, has been known

for several decades. Epidemiological studies reported a morning peak regarding the incidents of cardiovascular events, such as ischemic strokes, myocardial infarction, sudden cardiac death and ventricular arrhythmias [10–12].

Circadian clocks exist in cardiomyocytes, vascular smooth muscle cells and endothelial cells. Circadian clocks within individual cells of the cardiovascular system have the potential to influence cardiovascular function by allowing anticipation of the onset of neurohumoral stimuli (e.g. increased sympathetic nervous stimulation before awakening), thereby ensuring an appropriately rapid response. [6]. In the in vivo setting, a complex interplay occurs between environmental influences and intrinsic mechanisms (i.e. central and peripheral circadian clocks), which contributes to changes in cardiovascular function over the course of a given 24-hr period (Fig. 1). For example, day-to-night differences in physical and mental activity appear to be the major determinates of blood pressure circadian rhythms [10, 13]. Diabetes mellitus, a major risk factor for the development of heart disease in humans, is associated with a phase shift in the cardiac circadian clock [14, 15]. Shift workers have an increased incidence of cardiovascular disease [16–18], which might be related to alterations in cardiovascular intracellular circadian clock function.

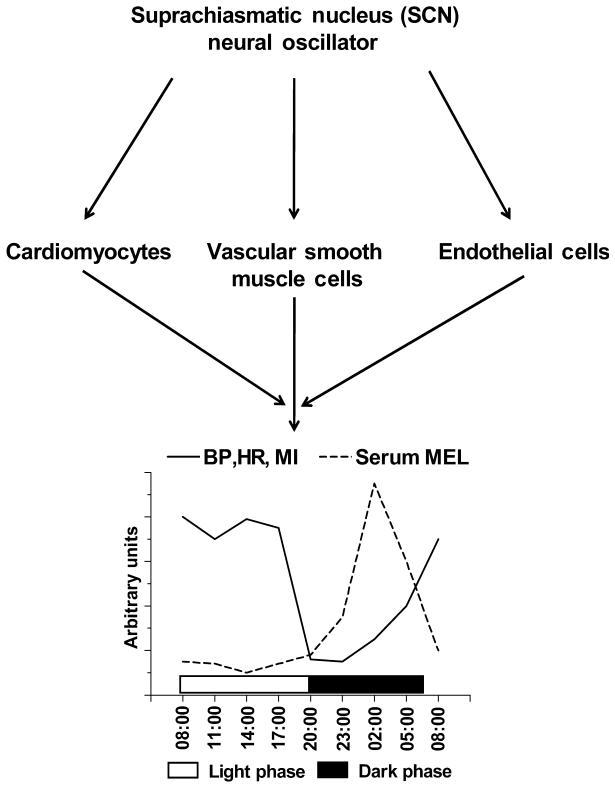

Fig. 1. The suprachiasmatic nucleus synchronizes peripheral oscillators including those within the cardiomyocytes, vascular smooth muscle cells and endothelial cells through a combination of autonomic, behavioral, endocrine and genetics cues. Thus, the network of peripheral circadian oscillators in vascular tissues likely influences clock-dependent cardiovascular phenomenon, including blood pressure (BP), heart rate (HR) and myocardial infarction (MI).

There is a temporal incidence in adverse cardiovascular events, including transient myocardial ischemia [19], myocardial infarction [20], sudden cardiac death [21] and stroke [22, 23]. These events typically occur more often in the early morning hours, just after awakening. There are also second more subtle peaks of these events in the late afternoon.

There are published reports supporting the view that the timing of onset of adverse cardiovascular events is linked directly to the intrinsic clock mechanism, as opposed to the 'stress' caused by awakening. Using creatine kinase MB (CK-MB) as a marker of myocardial damage, the peak incidence of acute myocardial infarction around 06:00 hr and its coincidence with a reported chest pain is documented [24]. In another retrospective study of sudden cardiac death on the Hawaiian island of Kauai [25], the prevalence of sudden cardiac death peaked between 06:00 and 12:00 hr for native Kauaians and between 12:00 and 16:00 hr for recent Japanese visitors to the island, corresponding to the early morning in Japan. Krantz et al. [26] studied 63 patients with stable coronary artery disease using a well-validated structured events diary and electrocardiographic monitoring; the results of this study further supported the idea that an intrinsic diurnal mechanism influenced the timing of onset of adverse cardiovascular events, possibly more than increased physical or mental activity. Hu et al. [27] used a mathematical analysis of heart beat dynamics to support the hypothesis that intrinsic diurnal influences on cardiac control, as opposed to extrinsic behavior, may be involved in the diurnal pattern of adverse cardiac events in vulnerable individuals. In addition to the morning peaks in CK-MB and reported pain, Muller et al. [24] also observed a secondary peak in the evening. Manfredini et al. [28], in a review on ischemic stroke, noted a secondary peak in the evening in the occurrence of myocardial infarction in patients with sleep apnea [29].

Others factors involved in the development of cardiovascular disease are likewise temporally modulated. Endothelial function, vascular tone, lipid metabolism, platelet and leukocyte reactivity, and fibrinolysis all vary with the time of day [30]. Scheer et al. [31] demonstrated a circadian rhythm in the platelet function, while Brezinski et al. [32] found that platelet aggregability is higher during the morning hours.

Core molecular oscillators have been identified in both the heart [33] and vascular tissue [34] encompassing both the vascular smooth muscle and endothelial compartments. Recent evidence has documented a role of molecular oscillators in regulating cardiovascular physiology [35, 36]. The endothelium secretes low levels of tissue plasminogen activator (tPA) along with platelet inhibitors, prostacyclin and nitric oxide [37, 38], which are also responsible for regulating vascular tone [39] and blood pressure [40]. An early morning surge in blood pressure is accompanied by a decline in endothelial function, as assessed by flow-mediated vasodilation [41–43]; both phenomena coincide with the clinically observed morning peak incidence in thrombotic events [44]. The tendency of platelets to aggregate, which can promote thrombogenesis, has suggested a diurnal pattern of this process in humans. However, aggregometry studies are conflicting and poten-

tially affected by artifact [30]. Other mediators of the hemostatic system display diurnal variations, including coagulation factors (II, VII, X and tissue factor pathology inhibitor) [45–47]. The morning onset of myocardial infarction may partly result from circadian variation of fibrinolytic activity. Fibrinogen, the circulating precursor of fibrin (a clot-stabilizing protein), displays a circadian variation in humans [48].

Taken together, these data suggest that suprachiasmatic nucleus-driven diurnal variations in autonomic stimulation, coupled to the cardiomyocyte circadian clock-driven daily fluctuations in responsiveness of the heart to autonomic stimulation, act as major determinants of cyclic cardiovascular functions [6]. Whether environmental modulation of the synchronization of peripheral and central clocks contributes to the development of cardiovascular disease has not been established but is suspected. Loss of synchronization occurs when there are changes in feeding or sleep patterns, and during exposure to light at abnormal times, i.e. at night [49, 50]. Such dyssynchronization is seen in patients with hypertension, diabetes mellitus, obesity and shift workers, in whom there is an elevated risk of cardiovascular disease [51, 52].

Specific links between the melatonin and cardiovascular disease

The circadian pacemaker within the suprachiasmatic nucleus triggers the pineal gland to produce a melatonin increase at night [53]. The production of melatonin by the pineal gland in vertebrates exhibits an unambiguous circadian rhythm with its peak near the middle of the scotophase and basal levels during the photophase. The daily and seasonal melatonin rhythms are involved in 'time of day' and 'time of year' signaling, and it is for this reason that they are considered to serve as a bio-clock and bio-calendar [54].

The amount of melatonin produced by the pineal gland of mammals changes with the age of the animal. The production of melatonin wanes with the aging process [55, 56]. In humans, melatonin production not only diminishes with age [57] but is also significantly lower in many age-related diseases, including cardiovascular disease [58–61]. Mounting evidence reveals that the rhythmicity of melatonin has a crucial role in a variety of cardiovascular pathophysiological processes including anti-inflammatory, antioxidant, antihypertensive and possibly antilipidemic functions (Fig. 2).

Evidence gathered in the last 15 yr indicates that melatonin influences multiple factors of the cardiovascular function [62]. Patients with coronary artery disease have low melatonin production rates, and blood melatonin concentrations correlate with the severity of the disease, i.e. greater reductions in melatonin production are observed in patients with a higher risk of myocardial infarction and/or sudden death [9, 62]. In addition, the use of β-adrenoceptor blockers, which reduce melatonin synthesis in the pineal gland, may also be responsible for low melatonin levels in patients with coronary disease. Stoschitzky et al. [63] showed that beta-blockers decrease pineal melatonin synthesis via a specific inhibition of

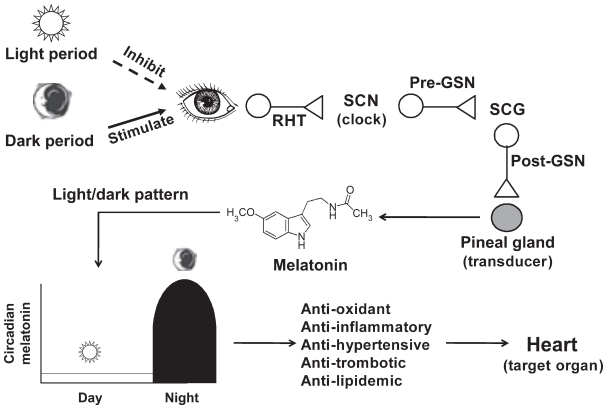

Fig. 2. Photic regulation of human physiological melatonin biosynthesis. RHT, Retinohypothalamic tract; SCN, Suprachiasmatic nucleus; pre-GSN, preganglionic sympathetic neuron; SCG, superior cervical ganglia; post-GSN, postganglionic sympathetic neuron.

β_1-receptors. Nathan et al. [64] demonstrated a dose-dependent relationship between β_1-receptor blockade and the suppression of nocturnal plasma melatonin in humans. Unexpectedly, however, Girotti et al. [65] did not observe a significant difference in the urinary levels of 6-sulfatoxymelatonin (the chief hepatic metabolite of melatonin) excretion in patients treated with β-adrenoceptor blocker compared to levels in nontreated individuals. Lower nocturnal melatonin concentrations may be the cause of sleep disturbances which are well-known side effects of β-adrenergic antagonists [9]. Several studies indicate that sleep disorders occur more frequently in patients with coronary than in noncoronary or normal subjects. As low melatonin levels can be associated with sleep disturbances [66, 67], at least in elderly patients, the low melatonin secretion, reported in patients with coronary, could play a causal role in the sleep disorders they experience [9].

Hypercholesterolemia and hypertension are also common consequences of aging. Oxidized low-density lipoprotein is a critical factor in the initiation and progression of atherosclerosis and it contributes to endothelial dysfunction and plaque destabilization through multiple mechanisms [68]. People with high levels of low-density lipoprotein cholesterol typically have low levels of melatonin. It has been shown that melatonin suppresses the formation of cholesterol by 38% and reduces low-density lipoprotein accumulation by 42% in freshly isolated human mononuclear leukocytes [69]. Several *in vitro* studies have documented the antioxidant actions of melatonin on low-density lipoprotein oxidation. According to Kelly and Loo [70], melatonin inhibits oxidative low-density lipoprotein modification. Furthermore, Seegar et al. [71] demonstrated that although melatonin itself appears to have little anti-atherogenic activity, melatonin's precursors and breakdown products inhibit low-density lipoprotein oxidation, comparable to vitamin E. Melatonin has been also shown to depress plasma levels of total cholesterol and very low-density lipoprotein cholesterol as well as the low-density lipoprotein cholesterol subfraction in hypercholesterolemic

rats [72]. Melatonin may exert these effects by increasing endogenous cholesterol clearance. In contrast, Abuja et al. [73] claimed that melatonin did not prevent the oxidative modification of low-density lipoprotein. Because of its lipophilic nature, however, melatonin readily enters the lipid phase of the low-density lipoprotein particles and prevents lipid peroxidation [74]. Dominguez-Rodriguez et al. [75] showed an association between nocturnal elevated serum levels of oxidized low-density lipoprotein and reduced circulating melatonin levels in patients with acute myocardial infarction, while Tamura et al. [76] found that melatonin treatment of peri- and postmenopausal women cause a significant elevation of high-density lipoprotein cholesterol without influencing total cholesterol levels. These findings generally support the notion that melatonin may lower total cholesterol and stimulate high-density lipoprotein levels while reducing the oxidation of low-density lipoprotein, changes that would generally be protective against cardiovascular disease [77].

The administration of melatonin reduces blood pressure in normal [78], pinealectomized [79] and spontaneously hypertensive rats [80], whereas pinealectomy leads to hypertension in rats [81]. Individuals with hypertension have lower melatonin levels than those with normal blood pressure, and the administration of melatonin reduces blood pressure. It has been shown that melatonin reduces blood pressure in both normo- and hypertensive subjects [82–85]. Melatonin has been shown to reduce the resistance of the large arteries to blood flow in adult men [84] and young women [83]. The administration of melatonin reportedly reduces blood pressure as a consequence of various mechanisms including a direct hypothalamic effect, a reduction of catecholamine levels, relaxation of the smooth muscle wall and, most importantly, as a result of its antioxidant properties [9, 86, 87]. Additionally, it is known that nitric oxide plays a key role in the maintenance of vascular tone, which in turn influences blood pressure. A relative nitric oxide deficiency has been documented in different forms of hypertension [62]. Pechanova et al. [88] demonstrated that melatonin reduces blood pressure significantly and that this treatment enhanced nitric oxide synthase activity, reduced oxidative stress and decreased NF-$\kappa\beta$. Finally, melatonin was also shown to reduce some of the pathophysiological consequences of renovascular hypertension because of its ability to function as an antioxidant [89].

Several studies suggest that some immunological factors play an important role in the initiation of inflammatory processes that predispose to coronary artery disease. Moreover, interactions exist between the endocrine and the immune system [90]. In this context, melatonin plays an essential role as a modulator of a large number of inflammatory molecules [91, 92]. We have demonstrated that light/dark variations in the production of endogenous inflammatory markers in patients with coronary artery disease might be related, at least in part, to day/night fluctuations in melatonin circulating levels [93–96].

Melatonin and its metabolites have been widely tested for their ability to attenuate the tissue damage resulting from transient occlusion of the blood supply to organs [97–99]. Salie et al. [100] reported that melatonin, *via* inhibition of reactive oxygen species generation and intracellular Ca^{2+} accumulation, protects rat ventricular myocytes against ischemia/reperfusion-induced morphologic damage. Using a Langendorff rat heart preparation, Tan et al. [101] found that when melatonin, infused throughout the period of coronary artery occlusion and after reopening of the vessel, highly significantly reduced both premature ventricular contractions and the ventricular fibrillation. Investigations have also confirmed the beneficial effects of pharmacological doses of melatonin on abnormal function and cardiac tissue damage resulting from ischemia/reperfusion injury [102–104]. A significant portion of melatonin's antioxidant actions may derive from its stimulatory effect on antioxidative enzymes including superoxide dismutase, glutathione peroxidase, glutathione reductase and glucose-6 phosphate dehydrogenase as well as its ability to inhibit the pro-oxidative inducible nitric oxide synthase [105, 106]. Additionally, a number of early studies suggested that the reported protective effects of melatonin are mediated via melatonin's receptor-independent actions as a radical scavenger [104, 107]. Recent investigations in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention confirmed a relationship between melatonin concentrations and ischemia-modified albumin, a marker of myocardial ischemia. Our data thus suggest that melatonin acts as a potent antioxidant agent, reducing myocardial damage induced by ischemia/reperfusion [108] (Fig. 3).

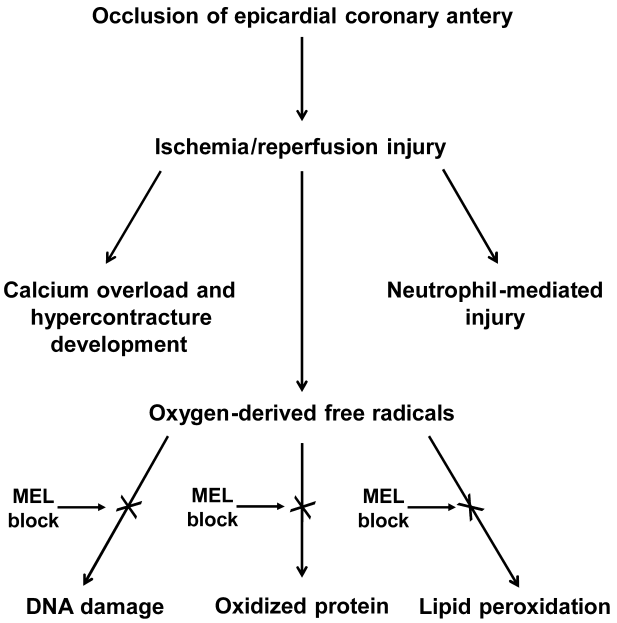

Fig. 3. As illustrated in this simplified figure, the events that lead to molecular damage and cell death during ischemia/reperfusion injury are complex. Considering the numerous intracellular actions of melatonin as a direct free radical scavenger, as an indirect antioxidant because of its ability to stimulate antioxidative enzymes and its effect on mitochondrial electron transport, this indole has a role in reducing molecular damage and cell death in patients with ST-segment elevation myocardial infarction.

Melatonin and cardiovascular disease: genetic background

That disturbances of circadian rhythmicity are associated with the risk of cardiovascular events is established [109], but addressing these issues is challenging as the major circadian hormone, i.e. melatonin, is modulated by several variables including genetic and especially environmental factors. A number of recent investigations have demonstrated how alterations in the circadian melatonin rhythm may be involved in adverse cardiovascular outcomes and possibly also influence common manifestations of metabolic disorders [110]. Up to 10% of the transcriptome might be under the control of the circadian clock [111]. Understanding the specific contribution that melatonin in this context may be assisted by the fact that costs of DNA analysis have been reduced recently [112, 113].

The marked variability of melatonin production by the pineal gland may be because of mutations in genes encoding for critical enzymes involved in melatonin biosynthesis [e.g. arylalkylamine N-acetyltransferase (AANAT) and tryptophan hydroxylase 1 (TPH1)]. In the case of the AANAT gene, eleven coding single-nucleotide polymorphisms (SNPs) have been described, with six of them having a similar function and five representing missense mutations with one amino acid substituted for another [114]. Hohjoh et al. [115] demonstrated a relationship between the SNP rs28936679 in the AANAT gene and the delayed sleep-phase syndrome. Also, the SNP rs10488682 located in the promoter region of TPH1 is related with the synthesis of melatonin [116]. An impaired maturation of the photoneuroendocrine system caused by a genetic absence or mutation of these enzymes may cause a lethal imbalance in the chemical interactions among serotonin, progesterone, catecholamines and intracellular calcium. This stresses the fact that a misfiring circadian release of melatonin can lead to cardiovascular disease because of abnormal levels of other hormones (e.g. abnormally high levels of aldosterone influence blood pressure through water retention) [117]. Melatonin levels were reported to be significantly reduced in victims of the sudden infant death syndrome compared to age-matched controls with nonsudden infant death syndrome victims [118]. It is hypothesized that a delayed ontogenesis of melatonin is a challenge facing newborns who are at risk for sudden infant death syndrome because of gene mutations or immature cardiac responses [119]. Melatonin deficiency may potentially increase electrical instability of the heart during the sleep period. These observations suggest that genetic screening in neonates at risk for cardiac disorders might be important in the design-protective strategies.

Two G protein-coupled membrane receptors for melatonin have been cloned and are identified as MTNR1A (MT1) and MTNR1B (MT2) [120]. In mammals, these melatonin receptors are expressed in the majority of the central and peripheral tissues including the cardiovascular system [121, 122]. These receptors share a high degree of sequence homology with the G protein-coupled receptor 50 (GPR50), which plays a pivotal role in mediating the intracellular effects of numerous neurotransmitters and hormones, including melatonin [123]. There are nine coding SNPs in the MTNR1A gene (5 missenses, 3 synonymous and 1 insertion) and another nine coding SNPs in the MTNR1B gene (7 missenses and 2 synonymous). These SNPs may be associated with less-effective melatonin receptors and specific patterns of expression, emphasizing the possibility of novel cardiovascular syndrome pathways and potential preventative therapies.

Two-stage approaches, genome-wide association followed by selective SNP genotyping, have been adopted as an efficient strategy for personalizing medicine by identifying high cardiovascular risk individuals. A major limitation is the modest number of melatonin-related markers included in ongoing independent analyses, especially when a large proportion of disease associations may well be population specific, or are likely to be because of chance. Finding genetic variants of the melatonin pathway linked to obesity and prediabetes traits are patently associated with cardiovascular disorders, including hypertension and atherosclerosis, as results from the effects of SNPs within the MTNR1B locus [124]. Recent studies on individuals carrying the minor G allele of SNP rs10830963 in the MTNR1B gene revealed that this melatonin receptor subtype is associated with higher glucose levels and increased diabetes risk [125–127]. Among a number of physiological variations, the SNP rs1562444 located in the 3′-untranslated region of *MTNR1B* could be associated with the rheumatoid arthritis by altering its appropriate expression or RNA folding [128]. In addition, three genome-wide association studies identified two SNPs in the MTNR1B (rs1387153, rs10830963) predicting susceptibility to type 2 diabetes. [129].

These may be good examples on how different genotypes affecting the production of melatonin or the function of its receptors could be useful to elicit cardiovascular disease risk given the modest effects of common variants that contribute to these complex traits.

The aim of ongoing studies is to identify gene polymorphisms that confer susceptibility to inflammation, variations in blood pressure or even those affecting the therapeutic efficacy of specific cardiovascular drugs [130, 131]. Recently, two SNPs (rs10455872 and rs3798220) have been identified at the locus encoding Lp(a) lipoprotein, which are strongly associated with both an increased level of Lp(a) lipoprotein and an elevated risk of coronary disease [132]. There are also results, however, indicating that SNPs in the melatonin-related receptor gene (GPR50) might be associated with circulating triglyceride and high-density lipoprotein levels [133], and additional findings suggest that melatonin may inhibit the activity of lipoprotein lipase [134].

Finally, it is worth stressing that we have been assessing the relationship between C-reactive protein polymorphisms, i.e. 1059G > C, rs1800947 and MTNR1A (G166E, rs28383653) to ascertain whether these two SNPs are associated with an increased risk for acute myocardial infarction. We have performed a case–control study in 300 consecutive patients with acute myocardial infarction and 250 healthy controls (unpublished data). For validation of this association, we are presently examining larger subject panels for an extended set of markers, including several

genetic variants of the melatonin pathway. The information of the new SNPs could be linked to advance cardiovascular risk factors or at least to propose new ways to treat circadian clock–related cardiovascular events. Moreover, the relevance of the identified polymorphisms to protein structure or function will be required to provide some insights into the pathomechanism that might underpin various cardiovascular syndromes.

Conclusions

Synchrony between external and internal circadian rhythms and harmony among molecular fluctuations within cells are essential for normal organ biology. Circadian clocks exist within multiple components of the cardiovascular system. These clocks have the potential of affecting multiple cellular processes and, therefore, hold promise of modulating various aspects of cardiovascular function over the course the 24-hr cycle. Many aspects of cardiovascular physiology are subject to diurnal variations, and serious adverse cardiovascular events appear to be conditioned by the time of day. The suprachiasmatic nucleus is responsible for the control of circadian rhythms in peripheral tissues, acting via neural and humoral signals such as melatonin.

Numerous cardiac conditions are a consequence of free radical damage and processes involving an inflammatory response [62, 74, 92, 135]. The beneficial effects of melatonin administration against these conditions are because of its direct free radical scavenger activity and its indirect antioxidant properties. Likewise, the results from many investigations documented a role of melatonin against inflammatory molecules in patients with acute coronary syndrome indicating that this indoleamine has significant beneficial immunomodulatory effects. Therefore, melatonin rhythmicity appears to have crucial roles in various cardiovascular functions as an antioxidant, an anti-inflammatory agent chronobiotic and possibly as an epigenetic regulator [136].

References

1. Muller JE, Tofler GH. Circadian variation and cardiovascular disease. N Engl J Med 1991; **325**:1038–1039.
2. Willich SN, Goldberg RJ, Maclure M et al. Increased onset of sudden cardiac death in the first three hours after awakening. Am J Cardiol 1992; **70**:65–68.
3. Rajaratnam SM, Arendt J. Health in a 24-h society. Lancet 2001; **358**:999–1005.
4. Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003; **53**:103–108.
5. Young ME, Bray MS. Potential role for peripheral circadian clock dyssynchrony in the pathogenesis of cardiovascular dysfunction. Sleep Med 2007; **8**:656–667.
6. Young ME. The circadian clock within the heart: potential influence on myocardial gene expression, metabolism, and function. Am J Physiol Heart Circ Physiol 2006; **290**:H1–H16.
7. Durgan DJ, Hotze MA, Tomlin TM et al. The intrinsic circadian clock within the cardiomyocyte. Am J Physiol Heart Circ Physiol 2005; **289**:H1530–H1541.
8. Damiola F, Le Minh N, Preitner N et al. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. Genes Dev 2000; **14**:2950–2961.
9. Sewerynek E. Metabolism and the cardiovascular system. Neuro Endocrinol Lett 2002; **23**:79–83.
10. Muller JE. Circadian variation in cardiovascular events. Am J Hypertens 1999; **12**:35S–42S.
11. Marsh EE, Biller J, Adams HP et al. Circadian variation in onset of acute ischemic stroke. Arch Neurol 1990; **47**:1178–1180.
12. Gupta A, Shetty H. Circadian variations in stroke-a prospective-hospital-based study. Int J Clin Pract 2005; **59**:1272–1275.
13. Degaute JP, Van Cauter E, Van De Borne P, Linkowski P. Twenty-four-hour blood pressure and heart rate profiles in humans. A twin study. Hypertension 1994; **23**:244–253.
14. Oishi K, Kasamatsu M, Ishida N. Gene- and tissue-specific alterations of circadian clock gene expression in streptozotocin-induced diabetic mice under restricted feeding. Biochem Biophys Res Commun 2004; **317**:330–334.
15. Young ME, Wilson CR, Razeghi P, Guthrie PH, Taegtmeyer H. Alterations of the circadian clock in the heart by streptozotocin-induced diabetes. J Mol Cell Cardiol 2002; **34**:223–231.
16. Harma MI, Ilmarinen JE. Towards the 24-hour society-New approaches for aging shift workers?. Scand J Work Environ Health 1999; **25**:610–615.
17. Knutsson A, Akerstedt T, Jonsson BG, Orth-Gomer K. Increased risk of ischaemic heart disease in shift workers. Lancet 1986; **12**:89–92.
18. Koller M. Health risks related to shift work. An example of time-contingent effects of long-term stress. Int Arch Occup Environ Health 1983; **53**:59–75.
19. Hausmann D, Lichtlen PR, Nikutta P, Wenzlaff P et al. Circadian variation of myocardial ischemia in patients with stable coronary artery disease. Chronobiol Int 1991; **8**:385–398.
20. Ridker PM, Manson JE, Buring JE et al. Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. Circulation 1990; **82**:897–902.
21. Muller JE, Tofler GH, Willich SN, Stone PH. Circadian variation of cardiovascular disease and sympathetic activity. J Cardiovasc Pharmacol 1987; **10**(Suppl 2):S104–S109.
22. Manfredini R, Gallerani M, Portaluppi F, Salmi R et al. Chronobiological patterns of onset of acute cerebrovascular diseases. Thromb Res 1997; **88**:451–463.
23. Gallerani M, Manfredini R, Ricci L et al. Chronobiological aspects of acute cerebrovascular diseases. Acta Neurol Scand 1993; **87**:482–487.
24. Muller JE, Stone PH, Turi ZG et al. Circadian variation in the frequency on onset of acute myocardial infarction. N Engl J Med 1985; **313**:1315–1322.
25. Couch RD. Travel, time zones, and sudden cardiac death. Emporiatric pathology. Am J Forensic Med Pathol 1990; **11**:106–111.
26. Krantz DS, Kop WJ, Gabbay FH et al. Circadian variation of ambulatory myocardial ischemia. Triggering by daily activities and evidence for an endogenous circadian component. Circulation 1996; **93**:1364–1371.
27. Hu K, Ivanov P, Hilton MF et al. Endogenous circadian rhythm in an index of cardiac vulnerability independent of changes in behavior. Proc Natl Acad Sci USA 2004; **101**:18223–18227.

28. Manfredini R, Boari B, Smolensky MH et al. Circadian variation in stroke onset: identical temporal pattern in ischemic and hemorrhagic events. Chronobiol Int 2005; **22**:417–453.
29. Kuniyoshi FH, Garcia-Touchard A, Gami AS et al. Day-night variation of acute myocardial infarction in obstructive sep apnea. J Am Coll Cardiol 2008; **52**:343–346.
30. Reilly D, Westgate EJ, Fitzgerald GA. Peripheral circadian clocks in the vasculature. Arterioscler Thromb Vasc Biol 2007; **27**:1697–1705.
31. Scheer FA, Evoniuk H, Kelly E et al. Effect of circadian system and behavioral stressors on platelet activity and reactivity: implications for the morning peak in cardiovascular incidents. Sleep 2009; **32**:A7.
32. Brezinski DA, Tofler GH, Muller JE et al. Association with assumption of the upright posture. Circulation 1988; **78**:35–40.
33. Young ME, Razeghi P, Taegtmeyer H. Clock genes in the heart: characterization and attenuation with hypertrophy. Circ Res 2001; **88**:1142–1150.
34. Rudic RD, Mcnamara P, Reilly D et al. Bioinformatic analysis of circadian gene oscillation in mouse aorta. Circulation 2005; **112**:2716–2724.
35. Curtis AM, Cheng Y, Kapoor S et al. Circadian variation of blood pressure and the vascular response to asynchronous stress. Proc Natl Acad Sci USA 2007; **104**:3450–3455.
36. Viswambharan H, Carvas JM, Antic V et al. Mutation of the circadian clock gene Per2 alters vascular endothelial function. Circulation 2007; **115**:2188–2195.
37. Weksler BB, Marcus AJ, Jaffe EA. Synthesis of prostaglandin I2 (prostacyclin) by cultured human and bovine endothelial cells. Proc Natl Acad Sci USA 1997; **74**:3922–3926.
38. Vanhoutte PM. Say NO to ET. J Auton Nerv Syst 2000; **81**:271–277.
39. Luscher TF, Richard V, Tschudi M et al. Endothelial control of vascular tone in large and small coronary arteries. J Am Coll Cardiol 1990; **15**:519–527.
40. Rees DD, Palmer RM, Moncada S. Role of endothelium-derived nitric oxide in the regulation of blood pressure. Proc Natl Acad Sci USA 1989; **86**:3375–3378.
41. Elherik K, Khan F, Mclaren M et al. Circadian variation in vascular tone and endothelial cell function in normal males. Clin Sci (Lond) 2002; **102**:547–552.
42. Otto ME, Svatikova A, Barretto RB et al. Early morning attenuation of endothelial function in healthy humans. Circulation 2004; **109**:2507–2510.
43. Bridges AB, Mclaren M, Saniabadi A et al. Circadian variation of endothelial cell function, red blood cell deformability and dehydro-thromboxane B2 in healthy volunteers. Blood Coagul Fibrinolysis 1991; **2**:447–452.
44. Muller JE. Circadian variation and triggering of acute coronary events. Am Heart J 1999; **137**:S1–S8.
45. Pinotti M, Bertolucci C, Portaluppi F et al. Daily and circadian rhythms of tissue factor pathway inhibitor and factor VII activity. Arterioscler Thromb Vasc Biol 2005; **25**:646–649.
46. Kanabrocki EL, George M, Hermida RC et al. Day-night variations in blood levels of nitric oxide, T-TFPI, and E-selectin. Clin Appl Thromb Hemost 2001; **7**:339–345.
47. Soulban G, Labrecque G. Circadian rhythms of blood clotting time an coagulation factors II, VII, IX and X in rats. Life Sci 1989; **45**:2485–2489.
48. Brenner WF, Sothern RB, Kanabrocki EL et al. Relation between circadian patterns in levels of circulating lipoprotein(a), fibrinogen, platelets, and related lipid variables in men. Am Heart J 2000; **139**:164–173.
49. Erren TC, Reiter RJ. Defining chronodisruption. J Pineal Res 2009; **46**:245–247.
50. Cabezas-Cerrato J, Hermida RC, Cabezas-Agricola JM, Ayala DE. Cardiac autonomic neuropathy, estimated cardiovascular risk, and circadian blood pressure pattern in diabetes mellitus. Chronobiol Int 2009; **26**:942–957.
51. Dominguez-Rodriguez A, Abreu-Gonzalez P, Kaski JC. Disruption of normal circadian rhythms and cardiovascular events. Heart Metab 2009; **44**:11–15.
52. Dominguez-Rodriguez A, Samimi-Fard S, Abreu-Gonzalez P, Kaski JC. Melatonina y atherosclerosis coronaria. Clin Invest Arterioscl 2009; **21**:247–256.
53. Reiter RJ. Pineal melatonin: cell biology of its synthesis and its physiological interactions. Endocr Rev 1991; **12**:151–180.
54. Reiter RJ. The melatonin rhythm: both a clock and a calendar. Experientia 1993; **49**:654–664.
55. Reiter RJ, Richardson BA, Johnson LY. Pineal melatonin rhythm: reduction in aging Syrian hamsters. Science 1980; **210**:1372–1373.
56. Reiter RJ, Craft CM, Johnson JEJR et al. Age-associated reduction in nocturnal pineal melatonin levels in female rats. Endocrinology 1981; **109**:1295–1297.
57. Sack RL, Lewy AJ, Erb DL et al. Human melatonin production decreases with age. J Pineal Res 1986; **3**:379–388.
58. Sakotnik A, Liebmann PM, Stoschitzky K et al. Decreased melatonin synthesis in patients with coronary artery disease. Eur Heart J 1999; **20**:1314–1317.
59. Altun A, Yaprak M, Aktoz M et al. Impaired nocturnal synthesis of melatonin in patients with cardiac syndrome X. Neurosci Lett 2002; **327**:143–145.
60. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia MJ et al. Decreased nocturnal melatonin levels during acute myocardial infarction. J Pineal Res 2002; **33**:248–252.
61. Yaprak M, Altun A, Vardar A et al. Decreased nocturnal synthesis of melatonin in patients with coronary artery disease. Int J Cardiol 2003; **89**:103–107.
62. Tengattini S, Reiter RJ, Tan DX et al. Cardiovascular diseases: protective effects of melatonin. J Pineal Res 2008; **44**:16–25.
63. Stoschitzky K, Sakotnik A, Lercher P et al. Influence of beta-blockers on melatonin release. Eur J Clin Pharmacol 1999; **55**:111–115.
64. Nathan PJ, Maguire KP, Burrows GD, Norman TR. The effect of atenolol, a β1-adrenergic antagonist, on nocturnal plasma melatonin secretion: evidence for a dose-response relationship in humans. J Pineal Res 1997; **23**:131–135.
65. Girotti L, Lago M, Ianavsky O et al. Low urinary 6-sulphatoxymelatonin levels in patients with coronary artery disease. J Pineal Res 2000; **29**:138–142.
66. Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. Pharmacol Rep 2009; **61**:383–410.
67. Hoebert M, Van Der Heijden KB, Van Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. J Pineal Res 2009; **47**:1–7.
68. Landmesser U, Harrison DG. Oxidant stress as marker for cardiovascular events: Ox marks the spot. Circulation 2001; **104**:2638–2640.

69. Muller-Wieland D, Behnke B, Koopmann K, Krone W. Melatonin inhibits LDL receptor activity and cholesterol synthesis in freshly isolated human mononuclear leukocytes. Biochem Biophys Res Commun 1994; **203**:416–421.
70. Kelly MR, Loo G. Melatonin inhibits oxidative modification of human low-density lipoprotein. J Pineal Res 1997; **22**:203–209.
71. Seegar H, Mueck AO, Lippert TH. Effect of melatonin and metabolites on cooper-mediated oxidation of low density lipoprotein. Br J Clin Pharmacol 1997; **44**:283–284.
72. Hoyos M, Guerrero JM, Perez-Cano R et al. Serum cholesterol and lipid peroxidation are decreased by melatonin in diet-induced hypercholesterolemic rats. J Pineal Res 2000; **28**:150–155.
73. Abuja PM, Liebman P, Hayn M et al. Antioxidant role of melatonin in lipid peroxidation of human LDL. FEBS Lett 1997; **413**:289–293.
74. Wakatsuki A, Okatani Y, Ikenoue N et al. Melatonin protects against oxidized low-density lipoprotein-induced inhibition of nitric oxide production in human umbilical artery. J Pineal Res 2001; **31**:281–288.
75. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez M et al. Elevated levels of oxidized low-density lipoprotein and impaired nocturnal synthesis of melatonin in patients with myocardial infarction. Atherosclerosis 2005; **180**:101–105.
76. Tamura H, Nakamura Y, Narimatsu A et al. Melatonin treatment in peri- and postmenopausal women elevates serum high-density lipoprotein cholesterol levels without influencing total cholesterol levels. J Pineal Res 2008; **45**:101–105.
77. Reiter RJ. Melatonin: lowering the high price of free radicals. News Physiol Sci 2000; **15**:246–250.
78. Chuang JI, Chen SS, Lin MT. Melatonin decreases brain serotonin release, arterial pressure and heart rate in rats. Pharmacology 1993; **47**:91–97.
79. Holmes SW, Sugden D. The effect of melatonin on pinealectomy-induced hypertension in the rat. Br J Pharmacol 1976; **56**:360–361.
80. Kawashima K, Miwa Y, Fujimoto K et al. Antihypertensive action of melatonin in the spontaneously hypertensive rat. Clin Exp Hypertens A 1987; **9**:1121–1131.
81. Karppanen H, Airaksinen MM, Sarkimaki I. Effects in rats of pinealectomy and oxypertine on spontaneous locomotor activity and blood pressure during various light schedules. Ann Med Exp Biol Fenn 1973; **51**:93–103.
82. Cagnacci A, Sodani R, Yen SSC. Melatonin enhances cortisol levels in aged women: reversible by estrogens. J Pineal Res 1997; **22**:81–85.
83. Cagnacci A, Arangino S, Angiolucci M et al. Influence of melatonin administration on the circulation of women. Am J Physiol 1998; **274**:R335–R338.
84. Arangino S, Cagnacci A, Angiolucci M et al. Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men. Am J Cardiol 1999; **83**:1417–1419.
85. Birau N, Peterssen U, Meyer C, Gottschalk J. Hypotensive effect of melatonin in essential hypertension. IRCS Med Sci 1981; **9**:906–911.
86. Reiter RJ, Tan DX, Korkmaz A. The circadian melatonin rhythm and its modulation: possible impact on hypertension. J Hypertens 2009; **6**:S17–S20.
87. Reiter RJ, Tan DX. Melatonin and cardiac pathophysiology. Heart Metab 2009; **44**:31–34.
88. Pechanova O, Zicha J, Paulis L et al. The effect of N-acetylcysteine and melatonin in adult spontaneously hypertensive rats with established hypertension. Eur J Pharmacol 2007; **561**:129–136.
89. Erşahin M, Sehirli O, Toklu HZ et al. Melatonin improves cardiovascular function and ameliorates renal, cardiac and cerebral damage in rats with renovascular hypertension. J Pineal Res 2009; **47**:97–106.
90. Dominguez-Rodriguez A, Abreu-Gonzalez P, Kaski JC. Inflammatory systemic biomarkers in setting acute coronary syndromes- effects of the diurnal variation. Curr Drug Targets 2009; **10**:1001–1008.
91. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. Endocrine 2005; **27**:189–200.
92. Veneroso C, Tuñón MJ, González-Gallego J, Collado PS. Melatonin reduces cardiac inflammatory injury induced by acute exercise. J Pineal Res 2009; **47**:184–191.
93. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia M et al. Light/dark patterns of interleukin-6 in relation to the pineal hormone melatonin in patients with acute myocardial infarction. Cytokine 2004; **26**:89–93.
94. Dominguez-Rodriguez A, Garcia-Gonzalez M, Abreu-Gonzalez P et al. Relation of nocturnal melatonin levels to C-reactive protein concentration in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2006; **97**:10–12.
95. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez MJ, Reiter RJ. Relation of nocturnal melatonin levels to serum matrix metalloproteinase-9 concentrations in patients with myocardial infarction. Thromb Res 2007; **120**:361–366.
96. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez MJ et al. Light/dark patterns of soluble vascular cell adhesion molecule-1 in relation to melatonin in patients with ST-segment elevation myocardial infarction. J Pineal Res 2008; **44**:65–69.
97. Reiter RJ, Tan DX, Leon J et al. When melatonin gets on your nerves: its beneficial actions in experimental models of stroke. Exp Biol Med 2005; **230**:104–117.
98. Cervantes M, Moralí G, Letechipía-Vallejo G. Melatonin and ischemia-reperfusion injury of the brain. J Pineal Res 2008; **45**:1–7.
99. Chen Z, Chua CC, Gao J et al. Prevention of ischemia/reperfusion-induced cardiac apoptosis and injury by melatonin is independent of glutathione peroxidase 1. J Pineal Res 2009; **46**:235–241.
100. Salie R, Harper I, Cillie C et al. Melatonin protects against ischaemic-reperfusion myocardial damage. J Mol Cell Cardiol 2001; **33**:343–357.
101. Tan DX, Manchester LC, Reiter RJ et al. Ischemia/reperfusion-induced arrhythmias in the isolated rat heart: prevention by melatonin. J Pineal Res 1998; **25**:184–191.
102. Szarszoi O, Asemu G, Vanecek J et al. Effects of melatonin on ischemia and reperfusion injury of the rat Herat. Cardiovasc Drugs Ther 2001; **15**:251–257.
103. Sahna E, Olmez E, Acet A. Effects of physiological and pharmacological concentrations of melatonin on ischemia-reperfusion arrhythmias in rats: can be the incidence of sudden cardiac death be reduced? J Pineal Res 2002; **32**:194–198.

104. Lee YM, Chen HR, Hsiao G et al. Protective effects of melatonin on myocardial ischemia/reperfusion injury *in vivo*. J Pineal Res 2002; **33**:72–80.
105. Rodriguez C, Mayo JC, Sainz RM et al. Regulation of antioxidant enzymes: a significant role for melatonin. J Pineal Res 2004; **36**:1–9.
106. Sahna E, Parlakpinar H, Turkoz Y, Acet A. Protective effects of melatonin on myocardial ischemia/reperfusion induced infarct size and oxidative damage. Physiol Res 2005; **54**:491–495.
107. Chen Z, Chua CC, Gao J et al. Protective effect of melatonin on myocardial infarction. Am J Physiol 2003; **284**:H1618–H1624.
108. Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia-Gonzalez MJ et al. Association of ischemia-modified albumin and melatonin in patients with ST-elevation myocardial infarction. Atherosclerosis 2007; **199**:73–78.
109. Martino TA, Sole MJ. Molecular time: an often overlooked dimension to cardiovascular disease. Circ Res 2009; **105**:1047–1061.
110. Rüger M, Scheer FA. Effects of circadian disruption on the cardiometabolic system. Rev Endocr Metab Disord 2009, doi:10.1007/s11154-009-9122-8.
111. Panda S, Antoch MP, Miller BH et al. Coordinated transcription of key pathways in the mouse by the circadian clock. Cell 2002; **109**:307–320.
112. Tucker T, Marra M, Friedman JM. Massively parallel sequencing: the next big thing in genetic medicine. Am J Hum Genet 2009; **85**:142–154.
113. Ragoussis J. Genotyping technologies for genetic research. Annu Rev Genomics Hum Genet 2009; **10**:117–133.
114. Blomeke B, Golka K, Griefahn B, Roemer HC. Arylalkylamine-N-acetyltransferase (AANAT) genotype as a personal trait in melatonin synthesis. J Toxicol Environ Health 2008; **71**:874–876.
115. Hohjoh H, Takasu M, Shishikura K et al. Significant association of the arylalkylamine N-acetyltransferase (AANAT) gene with delayed sleep phase syndrome. Neurogenetics 2003; **4**:151–153.
116. Wang H, Wu Z, Zhuang Q et al. Association study of tryptophan hydroxylase 1 and arylalkylamine N-acetyltransferase polymorphisms with adolescent idiopathic scoliosis in Han Chinese. Spine 2008; **33**:2199–2203.
117. Doi M, Takahashi Y, Komatsu R et al. Salt-sensitive hypertension in circadian clock-deficient Cry-null mice involves dysregulated adrenal Hsd3b6. Nat Med 2009, doi:10.1038/nm.2061.
118. Sturner WQ, Lynch HJ, Deng MH et al. Melatonin concentrations in the sudden infant death syndrome. Forensic Sci Int 1990; **45**:171–180.
119. Weissbluth L, Weissbluth M. Sudden infant death syndrome: a genetically determined impaired maturation of the photoneuroendocrine system. A unifying hypothesis. J Theor Biol 1994; **167**:13–25.
120. Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine 2005; **27**:101–110.
121. Ekmekcioglu C, Haslmayer P, Philipp C et al. 24h variation in the expression of the mt1 melatonin receptor subtype in coronary arteries derived from patients with coronary heart disease. Chronobiol Int 2001; **18**:973–985.
122. Ekmekcioglu C, Thalhammer T, Humpeler S et al. The melatonin receptor subtype MT2 is present in the human cardiovascular system. J Pineal Res 2003; **35**:40–44.
123. Jockers R, Maurice P, Boutin JA et al. Melatonin receptors, heterodimerization, signal transduction and binding sites: what's new?. Br J Pharmacol 2008; **154**:1182–1195.
124. Staiger H, Machicao F, Schäfer SA et al. Polymorphisms within the novel type 2 diabetes risk locus MTNR1B determine beta-cell function. PLoS ONE 2008; **3**:e3962.
125. Langenberg C, Pascoe L, Mari A et al. Common genetic variation in the melatonin receptor 1B gene (MTNR1B) is associated with decreased early-phase insulin response. Diabetologia 2009; **52**:1537–1542.
126. Prokopenko Y, Langenberg C, Florez JC et al. Variants in MTNR1B influence casting glucose levels. Nat Genet 2009; **41**:77–81.
127. Lyssenko V, Nagorny CL, Erdos MR et al. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet 2009; **41**:82–88.
128. Ha E, Choe BK, Jung KH et al. Positive relationship between melatonin receptor type 1B polymorphism and rheumatoid factor in rheumatoid arthritis patients in the Korean population. J Pineal Res 2005; **39**:201–205.
129. Melatonin receptor 1B (MTNR1B); SNP rs1387153; SNP rs10830963. SciBX 2009, doi:10.1038/scibx.2009.57.
130. Hills SA, Balkau B, Coppack SW et al. The EGIR-RISC STUDY (The European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease risk): I. Methodology and objectives. Diabetologia 2004; **47**:566–570.
131. Sekine A, Saito S, Iida A et al. Identification of single-nucleotide polymorphisms (SNPs) of human N-acetyltransferase genes NAT1, NAT2, AANAT, ARD1 and L1CAM in the Japanese population. J Hum Genet 2001; **46**:314–319.
132. Clarke R, Peden JF, Hopewell JC et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009; **361**:2518–2528.
133. Bhattacharyya S, Luan J, Challis B et al. Sequence variants in the melatonin-related receptor gene (GPR50) associate with circulating triglyceride and HDL levels. J Lipid Res 2006; **47**:761–766.
134. Wakatsuki A, Okatani Y, Ikenoue N et al. Effects of short-term melatonin administration on lipoprotein metabolism in normolipidemic postmenopausal women. Maturitas 2001; **38**:171–177.
135. Reiter RJ, Tan DX, Sainz RN, Mayo JC. Melatonin protects the heart against both ischemia/reperfusion injury and chemotherapeutic drugs. Cardiovasc Drugs Ther 2002; **16**:5–6.
136. Korkmaz A, Reiter RJ. Epigenetic regulation: a new research area for melatonin? J Pineal Res 2008; **44**:41–44.