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Role of melatonin in metabolic regulation

Ahmet Korkmaz · Turgut Topal · Dun-Xian Tan · Russel J. Reiter

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Abstract Although the human genome has remained unchanged over the last 10,000 years, our lifestyle has become progressively more divergent from those of our ancient ancestors. This maladaptive change became apparent with the Industrial Revolution and has been accelerating in recent decades. Socially, we are people of the 21st century, but genetically we remain similar to our early ancestors. In conjunction with this discordance between our ancient, genetically-determined biology and the nutritional, cultural and activity patterns in contemporary Western populations, many diseases have emerged. Only a century ago infectious disease was a major cause of mortality, whereas today non-infectious chronic diseases are the greatest cause of death in the world. Epidemics of metabolic diseases (e.g., cardiovascular diseases, type 2 diabetes, obesity, metabolic syndrome and certain cancers) have become major contributors to the burden of poor health and they are presently emerging or accelerating, in most developing countries. One major lifestyle consequence is light at night and subsequent disrupted circadian rhythms commonly referred to as circadian disruption or chronodisruption. Mounting evidence reveals that particularly melatonin rhythmicity has crucial roles in a variety of metabolic functions as an anti-oxidant, anti-inflammatory chronobiotic and possibly as an epigenetic regulator. This paper provides a brief outline about metabolic dysregulation in conjunction with a disrupted melatonin rhythm.

Keywords Syperglycemia · Hyperlipidemia · Dysmetabolism · Melatonin · Circadian rhythm

A. Korkmaz · T. Topal
Department of Physiology, School of Medicine,
Gulhane Military Medical Academy,
Ankara, Turkey

A. Korkmaz · D.-X. Tan · R. J. Reiter (✉)
Department of Cellular and Structural Biology,
The University of Texas, Health Science Center at San Antonio,
Mail Code 7762, 7703 Floyd Curl Drive,
San Antonio, TX 78229-3900, USA
e-mail: reiter@uthscsa.edu

1 Introduction

From a physiologic perspective, all living organisms have several common features including a high level of robustness against external and internal perturbations. Robustness is one of the fundamental organizational principles of biological systems and the robust design of biological systems mediates adaptation, survival and reproduction. Metabolic diseases are viewed as a breakdown of robustness in biological systems, with the disease becoming persistent if the damage cannot be repaired. Consequently, the concept of robustness can be defined as "continuous maintenance of physiologic functions" despite external and internal perturbations. Metabolic diseases including diabetes, cardiovascular diseases and obesity may involve a highly complex breakdown of normal physiology and share a "common pathway" behind the clinical manifestations, i.e., the "insulin variable" [1]. Consequently, insulin resistance (IR) caused by hyperglycemia and dyslipidemia seems to be linked to many features of the metabolic diseases.

2 Hyperglycemia, dyslipidemia and postprandial dysmetabolism

What happens during the postprandial period is well known since many biochemical parameters including plasma

glucose and lipid profiles are systematically measured during the fasting state and after eating. Furthermore, in terms of the number of waking hours, the postprandial state is relatively a long period for modern humans. Before the abundant availability of food, both fasting and postprandial biochemical measures were in physiologic range. In modern societies food consumption is more frequent and in spite of the fact that fasting biochemistry may be normal (e.g., fasting euglycemia and normal lipid profile), what occurs in the blood postprandially can insidiously devastate metabolism and may eventually disrupt homeostasis. Thus, postprandial dysmetabolism maybe a major, unrecognized, fundamental disturbance involved in the metabolic diseases.

A significant proportion of these at-risk subjects would go undetected when screened with fasting glucose levels but would demonstrate hyperglycemia after meals or during an oral glucose tolerance test [2]. Emerging data indicate that even borderline high (100 to 140 mg/dl) postprandial glycemia (PPG) (the earliest measurable abnormality of glucose homeostasis) may predispose to cardiovascular disease (CVD) events. Large prospective observational studies consistently show that the 1- or 2-hour post-glucose challenge levels are better predictors of CVD risk than either fasting glucose or even HbA_{1c} levels [3, 4]. A recent study also found that postprandial hyperglycemia occurs very frequently, even in the setting of good diabetic control as assessed by HbA_{1c} and fasting glucose levels [5]. Population studies have shown that a fasting glucose level as low as 90 mg/dl can be associated with a 2-hour postprandial glucose level > 200 mg/dl [4–6]. In early stages of type 2 diabetes, when fasting glucose and HbA_{1c} are usually within acceptable ranges, postprandial hyperglycemia can cause macrovascular (e.g., myocardial infarction) and microvascular complications (e.g., retinopathy, nephropathy) [2–4]. Data indicating that postprandial glucose contributes to >70% of the overall glycemic load in patients who have a fairly well controlled HbA_{1c} (<7.3%) [7] lend support to this concept. Casual PPG levels provide clinically relevant guidance to glycemic control [8], and therapies that target PPG (e.g., rapid-acting insulin analogues, which reach maximal concentration approximately twice as fast as regular human insulin) can lower HbA_{lc} as effectively or more effectively than therapies that target fasting plasma glycemia (e.g., long-acting basal insulin) [9].

These observations suggest the notion that postprandial dysmetabolism is present during the normoglycemic years and precedes both fasting hyperglycemia and the typical diagnosis of type 2 diabetes (T2D). Theoretically, it seems logical that, during the years of postprandial dysmetabolism, physicians continue to measure physiologically normal plasma glucose and lipid levels during the fasting state. As a result, in the United Kingdom Prospective Diabetes Study (UKPDS), about 50% of subjects had already experienced diabetic complications by the time they were first diagnosed with diabetes [10].

A consistent body of data demonstrates a strong association between postprandial glucose levels and cardiovascular risk [11]. Large epidemiologic studies have shown a continuously graded direct relation between the level of the post-glucose challenge glycemia and risk for pathophysiological events, including CVD death, stroke, sudden cardiac death, and peripheral arterial disease [12]. Even in patients classified as having normal glucose tolerance, as documented by post-load glucose levels <140 mg/dl, the level of post-load glycemia correlates with risk of the cardiovascular death and all-cause mortality [13]. The risks from glycemia begin at levels >80 mg/dl; by 140 mg/dl, the point at which traditionally patients are classified as glucose intolerant or pre-diabetic, cardiovascular risk is already elevated by 58% [12].

Hyperglycemia is generally accompanied by dyslipidemia in most circumstances and apart from hyperglycemia, dyslipidemia is a well known contributor to cell dysfunction (e.g., endothelial and β-cells). Moreover, postprandial hyperlipidemia with elevated levels of triglycerides (TG), chylomicron remnants, and free-fatty acids (FFA) results in oxidative stress and inflammation and may independently potentiate the adverse effects of postprandial hyperglycemia [14]. Given this information, the postprandial period is more understandable when referred as “postprandial dysmetabolism” interval. Like fasting plasma glucose, TG are traditionally measured in the fasting state, typically the lowest triglyceride values of the day [12]. Levels of fasting and postprandial TG are highly variable depending in part on the content of the last meal and the duration of the fasting period prior to eating. Several studies reported that elevated postprandial TG levels independently increased the incidence of myocardial infarction by 40% per 100 mg/dl rise [15]. Postprandial TG levels have also been shown to be proportional to the angiographic progression of coronary atherosclerosis and carotid artery intimal thickness [16]. Furthermore, lipids are persistently harmful when stored in abdominal region and abdominal fat is more closely correlated with insulin resistance than with overall obesity.

3 Light at night (LAN) and prolonged sympathetic activation; adding fuel to the postprandial fire

Day, night and seasons originated from the fact that, our planet has rotated on its axis every 24 hr and annually moves around the sun for centuries. The 24 h day controls circadian rhythms, which are synchronized by external day/night Zeitgebers. The circadian clock, which measures time on about a 24-hr, basis exists in virtually all living creatures. The core oscillator is located in the supra-

chiasmatic nuclei (SCN) which generate a rhythmic oscillation of roughly 25 h. A retinal component of this system allows the biological clock to be entrained by external cues, synchronizing circadian time with the environment. Finally, the output component is required to use time information for controlling circadian gene expression, physiology and behaviors. The overt circadian rhythms of temperature, cortisol, wake-sleep, blood pressure, heart rate and plasma glucose levels with which we are familiar can be viewed as the hands of this clock system. Further characterization of these molecular cogwheels revealed the existence of numerous peripheral clocks working harmonically with the central clock [17].

In mammals, information on environmental lighting conditions that is neurally perceived by the retina is finally converted into nocturnally elevated synthesis of the pineal secretory product, melatonin. In the photo-responsive mammalian pineal gland, the message of darkness relies on the master circadian pacemaker in the SCN. SCN contains the unique mammalian clock controlling circadian rhythmicity in peripheral tissues via neural (autonomic nervous system; ANS) and indirectly via humoral (pineal melatonin secretion) signals (Fig. 1). Mammalian clock genes have revealed that they are expressed in a circadian manner throughout the tissues of the body. It is accepted that virtually all peripheral cells contain a circadian clock which is similar to that present in SCN neurons [17]. Among others (e.g., social signs, environmental factors), the light/dark cycle has the most marked influence on the SCN and thereby at the periphery as well.

Urban development has brought the need for artificial lighting of roadways, shopping centers, stadiums, and homes. Some of this light strays and scatters into the atmosphere, bringing about a brightening of the natural sky beyond background levels; this is referred to as urban sky glow. In 2001, the percentage of the world's population living under sky brightness higher than baseline levels was 62%, with the percentages of US and European populations exposed to brighter than normal skies lying at 99% [18]. While humans live much of their lives based on artificially manipulated light cycles governed by electric lighting, this unnatural condition may exert slow, insidious but permanent pathophysiological outcomes.

Light at night (LAN) mimics day time leading to disturbances of the biological clock referred to as chronodisruption [19] and to a continuous flow of neural information from retina to the SCN; hence, the parasympathetic period is blunted by LAN. Features typically of the

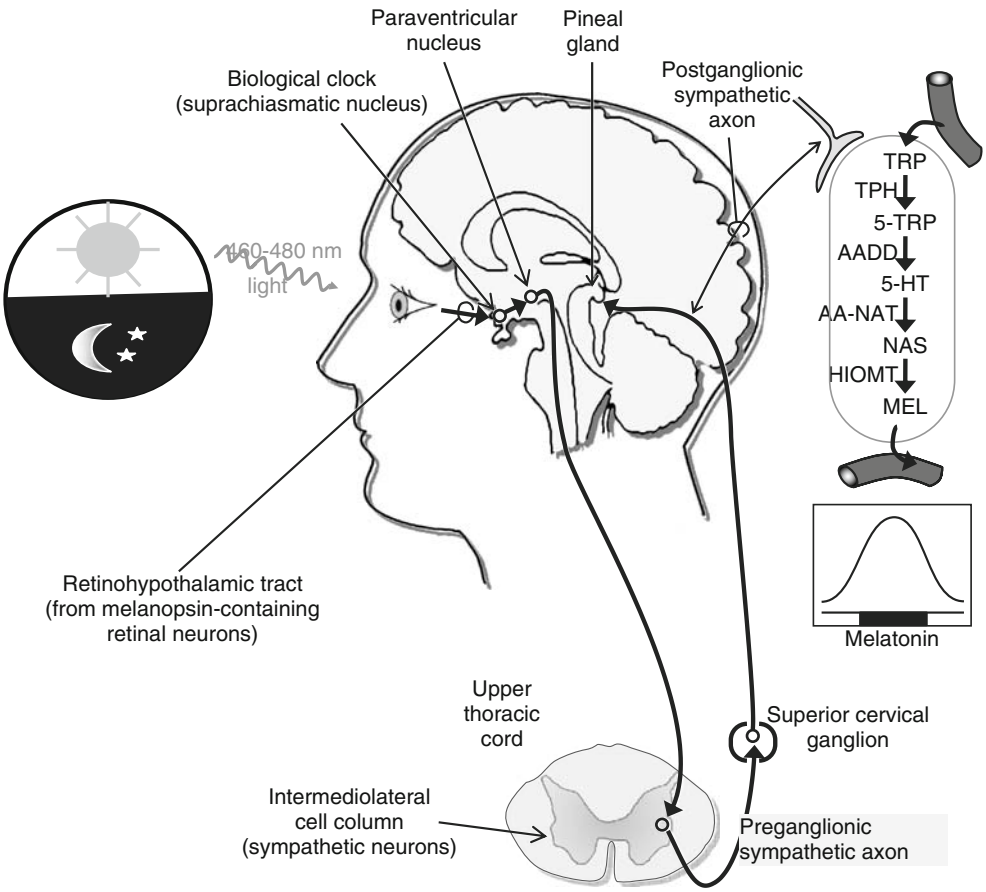

Fig. 1 A summary of the photo-neuroendocrine system as the neuroanatomical organization for circadian rhythms. The total pathway from the eyes to the pineal gland includes retinohypothalamic projections to the SCN and paraventricular nucleus (PVN), to the intermediolateral (IML) column of the thoracic spinal cord, to the superior cervical ganglia, and finally to the pineal gland. During the day, light perceived by the retinal melanopsin-containing ganglion cells signals the SCN to shutdown pineal melatonin synthesis. The circadian master-clock is situated in the SCN and orchestrates circadian rhythms by disseminating information on time via neuronal and humoral routes. The SCN shares the light:dark information with the IML column of the spinal cord and modulates rhythmic sympathetic activity for metabolic regulation. The mammalian pineal gland is inhibited by light during day and activated at night via a multisynaptic pathway from the SCN

sympathetic period including higher blood pressure, plasma glucose and heart rate remain relatively sustained for some additional time. Thus, the body receives a mixture of information from the ANS leading to "autonomic confusion" (Fig. 2) [20]. The nature of parasympathetic division is to permit organs (e.g., gut, heart or bladder) to be active on an individual basis while the sympathetic division functions system-wide including the regulation of vascular smooth muscle. Ambient LAN as well as several indoor factors (e.g., personal computers, TV) can further complicate the post-prandial period and worsen metabolism over many years before overt pathology appears [21]. Prolonged computer use and television watching, two major sedentary behaviors in many areas of the world, have been identified as risk factors for diabetes, obesity and metabolic syndrome (MS) [22]. Television watching is often associated with low physical activity and high energy intake; however, a clear and significant relationship between television watching and risk for MS, independent of physical activity and energy intake, was recently reported [23]. While blunting the postprandial period, extending light into the dark period also causes a delayed plasma melatonin peak and reduced total melatonin production. Exposure to an activated television set was recently shown to be associated with lower urinary melatonin metabolite concentrations [24].

4 Melatonin rhythm and plasma glucose regulation

The role of central nervous system in regulating plasma glucose has been demonstrated in SCN-lesion studies. Without a functioning SCN, cortisol and glucose do not rise before the beginning of the active period (morning arousal) and blood pressure does not dip in the inactive period (nocturnal dip) [25, 26]. Additionally, damaging the SCN also eliminates the circadian physiology of the pineal gland and loss of the pineal melatonin alters glucose homeostasis in pinealectomized rats [27]. Consequently, there is favorable evidence that the circadian rhythm of melatonin influences insulin secretion and the endocrine pancreas [28–30], reduces blood glucose, HbA_{1c} and plasma lipids and restores liver enzymes [30–32] in diabetic rats.

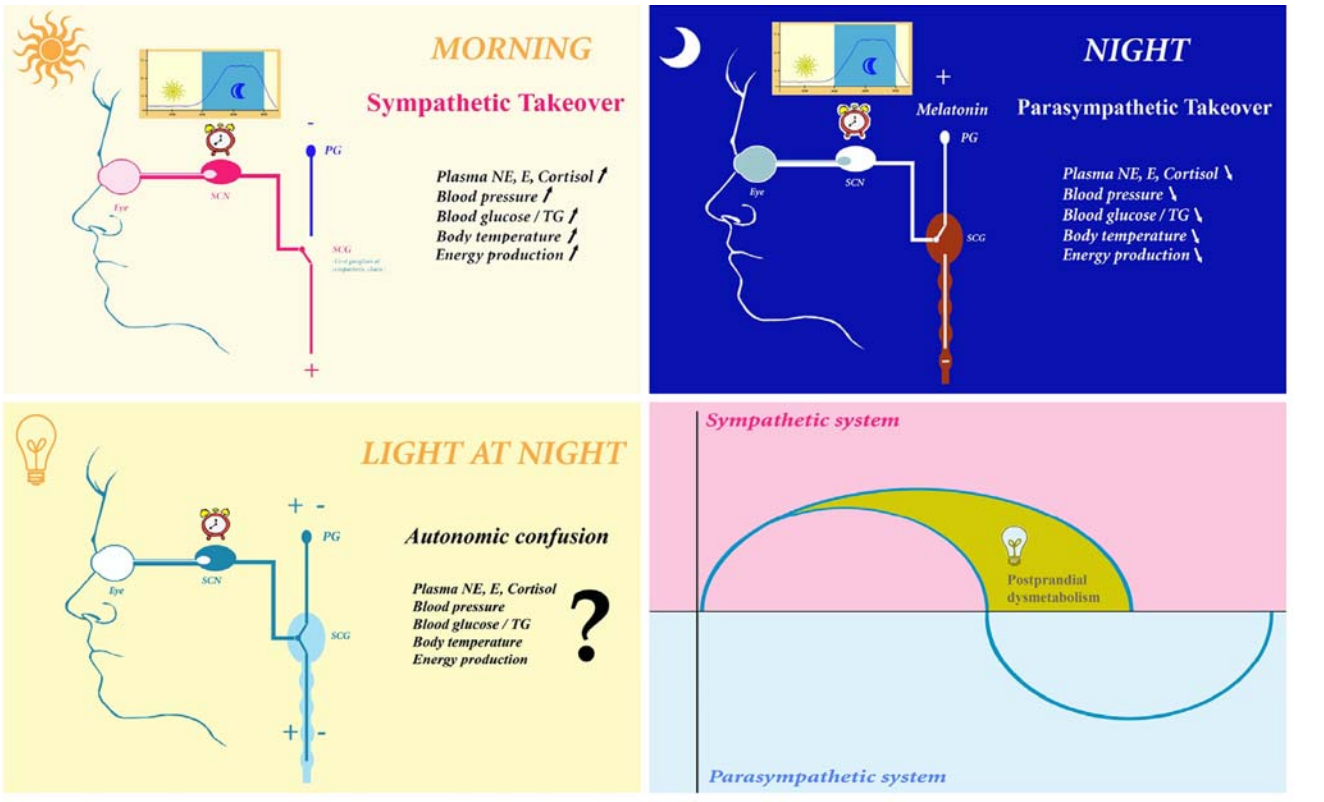

Fig. 2 During day, light detected by the retina inhibits the SCN and prevents melatonin synthesis. SCN modulates the autonomic nervous system and allows the sympathetic control of metabolism in the morning *(dawn phenomenon)*. At this time, plasma epinephrine, norepinephrine, cortisol and glucose levels are elevated. Overt cardiovascular changes include elevated blood pressure and heart rate. Apart from increasing plasma glucose, the photoneuroendocrine system renders tissues more tolerant to glucose and increases insulin sensitivity during the active period. At the end of the active period, retinas are exposed to darkness and the pineal is activated to secrete melatonin. At the same time, SCN blocks the sympathetic tonicity and allows parasympathetic control of metabolism *(dusk phenomenon)*. Light at night blunts the autonomic shift and causes autonomic confusion. SCN continues to inhibit pineal melatonin secretion and peak melatonin plasma levels are delayed

Although, little is known about how melatonin influences plasma glucose in humans, T2D patients show a reduced diurnal serum melatonin level and an increased pancreatic melatonin-receptors [29, 33]. Many beneficial actions of melatonin and its metabolites are related with its anti-oxidant and anti-inflammatory properties [34–37]. A clear role of pineal melatonin in preventing or delaying diabetic onset, however, is not clarified, since studies showing beneficial effects of melatonin have been conducted after onset of the clinical manifestation of diabetes [38, 39]. Nevertheless, a recent comprehensive review has documented a variety of actions of melatonin on physiology of endocrine pancreas which would be expected to reduce the incidence of diabetes [40].

5 Pineal melatonin and blood pressure regulation

It has been known for over a century that systemic blood pressure (BP) has a daily variation characterized by substantial reductions during sleep in humans. The circadian rhythm of BP was ultimately established by Millar-Craig et al. [41] using continuous intra-arterial monitoring. This seminal study showed that BP was highest mid-morning and then fell progressively throughout the remainder of the day; in addition, the study showed that BP was lowest at night (nocturnal dip), but rose before awakening (morning surge). These findings highlighted the importance of the circadian rhythm of BP with regard to the management of hypertension. During end of the activation period, a natural circadian rhythm of BP usually is associated with a nocturnal decrease of 10–20% in BP.

However, at least 30–35% of hypertensive patients exhibit a ‘non-dipper’ pattern. This is associated with insulin resistance [42], obesity [43] and coronary heart disease [44]. The evidence predominantly indicates the presence of a greater cardiovascular morbidity and mortality in hypertensive non-dippers as compared to dippers [26, 45]. Interestingly, many individuals with elevated clinical BP do not develop hypertensive complications and a large number of subjects may be treated with little or no benefit to the individual [45, 46].

Reports have suggested a possible influence of melatonin on circulatory functions. Reduced levels of melatonin have been found in the nocturnal serum of spontaneously hypertensive rats (SHR) [47] and the administration of melatonin reduced blood pressure to normal range in these animals [48]. It has been long known that hypertension is induced by pinealectomy in rats [49]. In SHR rats, however, BP decreased after 6 weeks of melatonin treatment (10 mg/kg), which was associated with a reduction of interstitial renal tissue inflammation, decreased oxidative stress and attenuation of pro-inflammatory transcription factors in the kidney [50]. In the same model of hypertension, melatonin, in addition to lowering mean BP and causing a heart rate reduction, restored plasma norepinephrine concentration and the proportion of β1/β2 receptors in the heart [51], enhanced maximal relaxation of mesenteric arteries [52] and improved baroreflex responses [53]. Similarly, in rats with nitric oxide-deficient hypertension, 5-day treatment with melatonin (10 mg/kg) reduced BP and ischemia–reperfusion injury of myocardial tissue [54].

Reduced levels of melatonin have also been found in subjects suffering from non-dipper hypertension [55]. When 3 mg melatonin is given to hypertensive patients 1 h before going to bed, improvements with the day–night rhythm of BP were apparent, particularly in women with a blunted nocturnal decline [56]. Similarly, daily intake of 2.5 mg melatonin at night reduces blood pressure to normal range in male subjects with essential hypertension [57]. Daily nighttime melatonin has also been shown to amplify the nocturnal decline in diastolic BP in patients with type 1 diabetes [58].

Melatonin may act on BP also via specific melatonin receptors localized in peripheral vessels or in parts of central nervous system participating in BP control. With a large clinical trial using melatonin as a hypertension treatment, many important questions could be answered, such as the dose of melatonin and regimen of its application and the choice of patients with greatest possible benefit from melatonin treatment. Consequently, melatonin seems to be a candidate drug for treatment of hypertension since the number of patients with well-controlled hypertension is alarmingly low worldwide [59].

6 Melatonin and body weight regulation

Daily administration of melatonin suppresses abdominal fat and plasma leptin levels of middle-age male rats [60]. Furthermore, melatonin has regulatory effects of body weight in a high fat-induced obese rat model and may prevent some of the side effects on glucose homeostasis such as decreased insulin sensitivity [61]. Supplementation of melatonin in middle-aged male rats was also shown to mimic some youthful energy regulatory responses by decreasing body weight, intra-abdominal adiposity, and plasma insulin and leptin concentrations while increasing core body temperature, physical activity, and plasma corticosterone levels. These results suggest that aging-associated reductions in endogenous melatonin secretion may alter energy regulation in middle age, resulting in elevated body weight and adiposity and their associated

detrimental metabolic consequences [62]. In the same study, the authors crossed-over the control and daily melatonin-treated groups; the rats initially treated with melatonin that were now not receiving the indole for an additional 12 weeks rapidly gained weight, whereas the control rats that were crossed over to melatonin rapidly lost weight, reversing their precross-over weight trends. The final weights of rats that were crossed over from control to melatonin were similar to those of the melatonin group before cross-over [62]. This study also revealed that an inappropriate time schedule (e.g., day-time) for the administration of melatonin may reduce its ability to control body weight. Appropriate melatonin supplementation (e.g., night-time), however, may potentially provide therapy or prophylaxis not only for the insulin resistance, increased intra-abdominal fat and resulting pathologies that occur with aging, but also for some age-associated behavioral changes [60].

It is now known that at least 10% of all cellular transcripts oscillate in a circadian manner, underscoring the global regulatory capacity of the circadian transcriptional machinery [63]. Molecular studies reveal the direct coupling of clock genes and the regulation of metabolism including the control of glucose homeostasis [64], lipid synthesis [65] and adipogenesis [66]. Since two essential components of the circadian clock (*Clock/Bmal*) are involved in the diurnal variation of glucose and TG [64] and *Bmal1* regulates adipogenesis and lipid synthesis [66], melatonin seems to be a player in adipocyte physiology. Recently, it was shown that rhythmic exposure of cultured adipocytes to melatonin temporally influenced the rhythmic expression of the clock genes *Clock, Bmal1* and *Per 1* and the peaks occurred during the induced night [67]. Insulin, a major player in the energy metabolism, has a close connection with melatonin in the regulation of energy metabolism. It was documented that pinealectomy causes glucose intolerance and decreases daily secretion of insulin stimulated by glucose intake [68] and insulin secretion by isolated pancreatic islets [69]. In support of this, melatonin enhances leptin expression and release by rat adipocytes in the presence of insulin [70], and it also enhances the insulin effects on leptin expression [71]. As result, prolonged melatonin administration at night has clearly shown that it reduces abdominal fat accumulation [60, 62] independent of food intake and total body fat in middle-age male [62] and obese rats [61]. Conversely, the diminution of the circadian amplitude of the endogenous melatonin signal (e.g., due to aging or LAN) may result in increased body weight, visceral adiposity, and associated adverse metabolic consequences. Restoration of the nocturnal melatonin signal decreases body weight, intraabdominal adiposity, plasma insulin and leptin levels without altering food intake or total adiposity [60, 62].

7 A summary of biochemical and pharmacological mechanisms of melatonin that influence physiological infrastructure

In mammals, melatonin is primarily secreted by the pineal gland. Synthesis also occurs, however, in many cells including those in the retina, ciliary body, lens, brain, airway epithelium, platelets, bone marrow, gut, placenta, lymphocytes, testes, ovary and skin [72]. The concentration of melatonin in the gut, for example, surpasses blood levels by 10–100 times and there is estimated to be at least 400x more melatonin in the gut than in the pineal gland [73]. The large quantity of extrapineal melatonin appears not to contribute significantly to the melatonin circadian rhythm in the circulation since surgical or chemical pinealectomy diminishes the circulating nighttime melatonin levels to low daytime values. Thus, extrapineal melatonin, despite its large quantity, does not serve as a chemical signal of light/dark and extrapineal melatonin synthesis, with the exception of the retina, is not known to exhibit a circadian rhythm. It was speculated that the locally generated melatonin in many tissues throughout the body is for protection against nitro-oxidative stress, given that melatonin, as well as its metabolites, are powerful free radical scavengers [35, 74–76]. This may be particularly valid in the gastrointestinal tract and skin [77–79], both of which are continuously exposed to toxins or damaging agents such as food pollutants, bacteria, parasites and ultraviolet or other irradiation. The function of locally-produced high levels of melatonin may assist these cells in coping with these stressors as a paracoid, antioxidant, and anti-inflammatory agent [74] including that caused by hyperglycemia [80] and other toxic reactants [81–83]. Melatonin has also been shown to ameliorate inflammation by blocking transcriptional factors [84–87] via several mechanisms [88]. The close association between nitro-oxidative stress, inflammation and aging as well as chronic diseases [89] is consistent with the idea that extrapineal melatonin may function intracellularly as a “healthy aging regulator” [90, 91].

Pineal-derived melatonin, however, even in small amounts, likely via receptor-mediated mechanisms induces circadian changes in organisms. Melatonin is not a conventional hormone, since it has both receptor-mediated and receptor-independent actions and virtually all cells are its target whether or not they possess receptors for the indolamine. This is highlighted by the fact that there are no morpho-physiological barriers to melatonin, e.g., cell membranes or the blood-brain barrier. Melatonin has membrane receptors (MT 1 and 2) as well as nuclear receptors (NMRs). Membrane receptor-mediated functions include the control of seasonal reproduction, modulation of sleep processes and influences on bone growth and

osteoporosis [92, 93]. Less is known of the physiological roles of NMRs. There is ample evidence, however, indicating that melatonin might be a crucial epigenetic regulator via a number of mechanisms including by means of its nuclear receptors [94].

The term epigenetics describes the study of heritable alterations in gene expression that occur in the absence of changes in genome sequence. This can be contrasted with genetics, which deals with the transmission of information based on differences in DNA sequence. The traditional view that gene and environmental interactions control disease susceptibility can now be expanded to include epigenetic reprogramming as a key determinant in the origin of human disease [95]. Our current understanding of epigenetic gene regulation involves basically two classes of molecular mechanisms: DNA methylation and histone modifications. A variety of enzymes are involved in this process including most importantly DNA methyltransferases, histone deacetylases and histone acetyl transferases [96]. Recent evidence revealed that melatonin influences cell physiology and metabolism via a variety of epigenetic mechanisms including nuclear receptors, co-regulators, histone acetylating and DNA methylating enzymes [97–101].

Disturbance of the circadian organization of physiology, endocrinology and metabolism, called chronodisruption [19], links light and particularly LAN, biological rhythms and the development of cancers with melatonin being a crucial and central biological intermediary [18]. In the Nurses' Health Study, 78,586 women were followed from 1988 through 1998 and reported an increased risk of colorectal cancer associated with working rotating night shifts [102]. Based on 13 studies, a recent meta-analysis [103] reported an increased breast cancer risk among women who work night shift. In regard to this, there is an obvious epidemiologic connection between the frequency of breast cancer and LAN and/or night-shift strongly relate to reduced melatonin production and a disrupted melatonin rhythm [104]. Consequently, environmental factors, especially when disturbed, are among the major determinants of genetic and epigenetic changes related to carcinogenesis. Mounting evidence reveals that epigenetic perturbations are as important as genetic mutations in the pathogenesis of the human diseases.

8 Concluding remarks

Melatonin is a pleiotropic, nocturnally peaking and systemically acting chronobiotic. Several generalizations can be proposed in regard to melatonin; its receptors are widespread in mammals and it readily passes all biological membranes to reach intracellular organelles [105, 106]. Its membrane receptors mediate some of melatonin's actions, some of which are well known. Although, less is known about NMRs, a majority of species-specific regulatory effects of melatonin seem to be related to its nuclear action [107]. Many cells can synthesize melatonin, presumably to scavenge the oxygen and nitrogen based reactants produced in these cells. Elevated blood melatonin levels are always correlated with darkness and it is referred to as the "chemical expression of darkness" [108]. Once synthesized in the pineal gland during the dark period, it is released into the bloodstream as well as other body fluids including the cerebrospinal fluid; it also eventually enters the bile, seminal fluid and amniotic fluid [109, 110]. Furthermore, nocturnal third ventricular cerebrospinal and biliary fluid melatonin levels are several orders of magnitude higher than simultaneously-measured concentrations in the peripheral blood [111, 112]. Melatonin seems to be involved in a variety of physiologic and metabolic processes as a multitasking indolamine via receptor-mediated and receptor-independent mechanisms. Disturbances of the melatonin rhythm, which are a reflection of generalized chronodisruption, have a variety of potential consequences as summarized herein and elsewhere [113].

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