MELATONIN, MITOCHONDRIA AND THE METABOLIC SYNDROME

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Adenosine monophosphate kinase (AMPK); cyclic adenosine monophosphate (cAMP); glutathione (GSH); glycated hemoglobin (HbA1C); insulin receptor substrate 1 (IRS-1); interleukin (IL); mammalian target of rapamycin (mTOR); metabolic syndrome (MS); mitochondrial permeability transition pore (mPTP); nicotinamide adenine dinucleotide+ (NAD+); nitric oxide (NO); reactive nitrogen species (RNS); reactive oxygen species (ROS); single nucleotide polymorphisms (SNPs); tumor necrosis factor (TNF).

Abstract

A number of risk factors for cardiovascular disease including hyperinsulinemia, glucose intolerance, dyslipidemia, obesity, and elevated blood pressure are collectively known as metabolic syndrome (MS). Since mitochondrial activity is modulated by the availability of energy in cells, the disruption of key regulators of metabolism in MS not only affects the activity of mitochondria but also their dynamics and turnover. Therefore, a link of MS with mitochondrial dysfunction has been suspected since long. As a chronobiotic/cytoprotector agent, melatonin has a special place in prevention and treatment of MS. Melatonin levels are reduced in diseases associated with insulin resistance like MS. Melatonin improves sleep efficiency and has antioxidant and anti-inflammatory properties, partly for its role as a metabolic regulator and mitochondrial protector. This article analyzes the multiple protective actions of melatonin that are relevant to the attenuation of inflammatory responses in MS and how melatonin is effective to curtail MS in animal models of hyperadiposity. The clinical data supporting the possible therapeutical use of melatonin in human MS are also reviewed.

Introduction

A number of risk factors for cardiovascular disease including hyperinsulinemia, glucose intolerance, dyslipidemia, obesity, and elevated blood pressure are collectively known as metabolic syndrome (MS). MS prevalence ranges from 15 to 30 % depending on the world region considered [1,2]. A 1.5 to 2.5-fold increase in cardiovascular mortality occurs when MS is present, representing one of the major public health problems nowadays.

The link of MS and mitochondrial dysfunction has been suspected since long. Mitochondrial activity is modulated by the availability of energy in cells and the disruption of key regulators of metabolism not only affect the activity of mitochondria but also their dynamics and turnover [3,4]. Mitochondrial dysfunction is associated with the functional decline found in tissues and organs during many age-related diseases such as MS and diabetes. Recently, a study carried out in non-diabetic participants from the Baltimore Longitudinal Study of Aging has associated impaired mitochondrial capacity with greater insulin resistance [5].

MS is preventable. The excessive fat accumulation, either in white adipose tissue or other organs, is the consequence of hypertrophy and hyperplasia of white adipocytes in a context of positive energy balance. Without question, poor diet, lack of exercise and chronic insulin resistance are major contributing factors to excessive fat accumulation [6,7]. The abnormal nutritional balance is controlled mainly at the hypothalamic level by a complex circuitry of orexigenic and anorexigenic signals and by an endogenous clock that sets a circadian rhythm of appetite-satiety, a function highly affected by modern life habits.

In the last decade, there has been a considerable increase in our understanding of the cellular and molecular factors that contribute to MS development. One basic function that appears to be heavily influenced by (and also influences) obesity and metabolic disease is the internal timing system [8-10]. The correlation between increased occurrence of obesity and the ubiquity of modern social habits, such as light at night, unusual meal timing, irregular sleep/ wake schedules and traveling between different time zones, all encompassed by a “24 /7” lifestyle, strongly suggests that impairment of sleep and the circadian system is involved in the etiology of MS. Several clinical surveys have shown increased prevalence of MS in night-shift workers, indicating that artificial lighting may contribute to the increased prevalence of metabolic disorders [11-14]. Thus, both animal and human data have clearly proved that circadian and sleep disruption leads to insulin resistance and MS. In a study performed with 593 type 2 diabetes mellitus patients sleep debt was associated with long-term metabolic disruption, which may promote the progression of the disease. For every 30 min of weekday sleep debt, the risk of obesity and insulin resistance at 12 months increased by 18 and 41%, respectively [15]. Collectively, these findings indicate the need for improving sleep quality to prevent the development of obesity and insulin resistance as well as its progression to diabetes.

As a chronobiotic/cytoprotector agent, melatonin has a special place in prevention and treatment of MS [16,17]. Melatonin improves sleep efficiency and has antioxidant and anti-inflammatory properties, partly for its role as a metabolic regulator and mitochondrial protector [18-20]. This review summarizes what is

known about a putative therapeutic role of melatonin concerning MS prevention and treatment. Medical literature was identified by searching databases including (MEDLINE, EMBASE), bibliographies from published literature and clinical trial registries / databases. Searches were last updated on April 30, 2017.

Mitochondria, Inflammation and the Metabolic Syndrome

Obesity in MS is associated with low-grade inflammation of the white adipose tissue, which can subsequently lead to insulin resistance, impaired glucose tolerance and diabetes [21,22] (Fig.1). Adipocytes actively secrete proinflammatory cytokines such as tumor necrosis factor (TNF) - α , interleukin (IL) -1 β and IL-6, resistin and leptin, triggering a vicious circle which leads to additional fat deposition. Increased circulating levels of C-reactive protein and other inflammatory biomarkers support also the occurrence of inflammation in obesity [23,24].

Early MS is characterized by the increased systemic markers of lipid oxidation, such as oxidized low density lipoproteins and isoprostanes, which contribute to the development of insulin resistance [3-5]. In the mitochondria, lipid peroxidation particularly affects cardiolipin, a phospholipid located at the level of inner mitochondrial membrane, which is required for several mitochondrial bioenergetic processes as well as in mitochondrial-dependent steps of apoptosis (e.g. it prevents the opening of the mitochondrial permeability transition pore (mPTP). Alterations in cardiolipin structure, content and acyl chain composition have been associated with mitochondrial dysfunction in various tissues under a variety of pathophysiological conditions [25].

Among mitochondrial regulators, the mammalian target of rapamycin (mTOR), which is activated by high calorie intake or high levels of amino acids, plays an important role [26]. The signaling pathway triggered by mTOR competes against other regulators of the cell metabolism such as adenosine monophosphate kinase (AMPK) and sirtuins, nicotinamide adenine dinucleotide⁺ (NAD⁺)-dependent deacetylases that induce more efficient energy consumption in situations of low intake, starvation or calorie restriction [27].

Several studies have shown that altered production of proinflammatory cytokines in obesity modulate adipocyte size and number through paracrine mechanisms that exert an important role in the regulation of fat mass [28-30]. The amounts of proinflammatory molecules derived from adipose tissue in obese patients diminishes after weight loss [31]. Therefore, the fat cells are both a source as well as a target for proinflammatory cytokines. When white adipose tissue mass increases by adipocyte hypertrophy, the large-size adipocytes develop a secretory dysfunction characterized by overproduction (synthesis and release) of adipocytokines that decrease tissue sensitivity to insulin, promote oxidative stress, and display proinflammatory effects (leptin, resistin, TNF- α , plasminogen activator inhibitor-1, IL-1, IL-6). In addition, lower amounts of adiponectin (an insulin-sensitizing adipokine) are released by adipocytes (Fig. 1). Consequently, obesity is the result of a multifactorial combination of genetic background, metabolic, endocrine, inflammatory and circadian dysfunctions, whose long-term maintenance is favored by behavioral disorders [32].

PLEASE INSERT FIGURE 1 ABOUT HERE

The levels of inflammatory mediators typically increase with age, even in the absence of acute infection or physiological stress. Such stress leads to inflammatory damage of cellular components, including proteins, lipids and DNA, and contributes to the age-related decline in physiological functions. The term "inflammaging" was introduced to underscore the importance of inflammation in senescence and its role in the development of age-related diseases such as MS [33-36]. The slowly progressing, persistent type of oxidative stress resulting from the increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which is enhanced by damage to the mitochondria, is typical of inflammaging [36-38].

Melatonin and Mitochondria

This subject is covered in depth by other reviews in this issue. Melatonin is a powerful scavenger of ROS and RNS and naturally acts on mitochondria, the site with the highest ROS/RNS production into the cell. Melatonin improves glutathione (GSH) redox cycling and increases GSH content by stimulating its synthesis in the cytoplasm, mitochondria depending on the GSH uptake from cytoplasm to maintain the GSH redox cycling [39]. Lastly, melatonin exerts important antiapoptotic effects and most of the apoptotic signals originate from the mitochondria (for ref. see [20,40,41]).

Melatonin plays an important role in antioxidant defense via the regulation of enzymes involved in the redox pathway and directly through the non-enzymatic, radical scavenger effect that melatonin and some of its metabolites, notably *N*¹-acetyl-*N*²-formyl-5-methoxykynuramine and *N*¹-acetyl-5-methoxykynuramine, have to scavenge ROS, RNS and organic radicals [42,43]. Safeguarding of respiratory electron flux, reduction of oxidant formation by lowering electron leakage and inhibition of mPTP events are among the most important effects on melatonin in mitochondria. Melatonin was reported to protect the mitochondria from oxidative damage in part by preventing cardiolipin oxidation [25,44].

Melatonin can also act on mitochondrial biogenesis via sirtuins. Sirtuins promote longevity in numerous organisms. The 7 mammalian subforms, sirtuin 1 to sirtuin 7, are involved in mitochondrial function. Sirtuins also stimulate mitochondrial biogenesis [45]. Several studies have reported upregulation of sirtuin 1 by melatonin (for ref. see [46,47]).

Melatonin and Inflammation

Counteraction of inflammaging by melatonin occurs at different levels. One of them concerns the correction of metabolic dysregulation including the prevention of insulin resistance [48-50]. Although in the studies summarized in Table 1 several regulatory pathways have been found to be modulated by melatonin treatment, the decisive effect at which the relevant routes converge seems to be the reduced serine phosphorylation of insulin receptor substrate 1 (IRS-1), accompanied by an upregulation of IRS-1 expression [51]. Melatonin and the melatonergic agonist piromelatin have been shown to reverse the blockade of this key step in insulin signal transduction [48,50,52].

PLEASE INSERT TABLE 1 ABOUT HERE

An additional level of action of melatonin concerns the prevention of processes that favor or lead to inflammation. These include calcium overload and excessive nitric oxide (NO) release that result in the formation of peroxynitrite, peroxynitrite-derived free radicals and tyrosine nitration and mitochondrial dysfunction [19]. All these changes are known to initiate low-grade inflammation in various organs.

Immunological effects of melatonin represent a third area relevant to inflammaging. Melatonin's multiple roles as an immune modulatory agent comprise both proinflammatory and antiinflammatory actions (acting as a "buffer" of the immune system) [19,38,90]. In the liver of aged, ovariectomized female rats (an animal model of MS), melatonin down-regulated proinflammatory cytokines, such as TNF- α , IL-1 β and IL-6, and up-regulated the anti-inflammatory cytokine IL-10 [91]. Reductions of TNF- α and IL-1 β and increased levels of IL-10 were observed in liver [62], pancreas [92] and heart [93] of the senescence-accelerated mouse strain SAMP8.

Peripheral oscillators exist in cells relevant to MS, such as pancreatic β -cells [94], hepatocytes, adipocytes, cardiomyocytes [95] and leukocytes [96,97]. In all these cell types melatonin modulates factors involved in metabolic sensing of the circadian apparatus like peroxisome proliferator-activated receptor- γ coactivator-1 α , peroxisome proliferator-activated receptor- γ , phosphoinositide 3-kinase, protein kinase B, and the accessory oscillator components AMPK, nicotinamide phosphoribosyl transferase and sirtuin 1 [38,98]. Melatonin reduced proinflammatory factors by suppressing the expression of nuclear factor- κ B via recruitment of a histone deacetylase to its promoter [99]. Other aspects of epigenetic modulation by melatonin via circadian oscillators have been summarized by [100].

Evidence of Melatonin Therapeutic Value in Metabolic Syndrome. Animal Studies

Treatment with melatonin in rats can reduce obesity, type 2 diabetes and hepatic steatosis [101,102]. In several animal models of hyperadiposity melatonin injection could normalize most observed alterations and to correct the altered biochemical pro-inflammatory profile (Table 1).

Melatonin treatment of streptozotocin-induced type 1 diabetic rats induces the regeneration and proliferation of β -cells in the pancreas leading to a decrease in blood glucose [103]. Loss of melatonin in circulation after pinealectomy results in hyperinsulinemia and accumulation of triglycerides in the rat liver [104]. The long-term administration of melatonin improves lipid metabolism in type 2 diabetic rats via restoring insulin sensitivity [105]. Melatonin treatment increases glycogen content in the liver of rats [106] while in high fat diet-induced diabetic mice the intraperitoneal injection of 10 mg/kg melatonin improved glucose utilization and insulin sensitivity and ameliorated hepatic steatosis [107].

As shown in Table 1, melatonin administration is usually very effective in reversing hyperadiposity in animal models of MS. The reasons for the decrease in

body weight after melatonin in the absence of significant differences in food intake is worth to be explored. A key piece of evidence in this regard is the observation that melatonin plays a role in seasonal changes in adiposity by increasing the activity of the sympathetic nervous system innervating white and brown fat [108]. Melatonin not only affects white adipose tissue, but also increases the recruitment of brown adipocytes and increases their metabolic activity in mammals (see [109]). It was speculated that the hypertrophic effect and functional activation of brown adipose tissue induced by melatonin can likely be applied to treatment of human obesity.

Collectively, the results indicate that the administration of melatonin effectively counteracts some of disrupting effects seen in diet-induced obesity in animals, in particular, insulin resistance, dyslipidemia and obesity. However, it must be noted that most experimental research has been carried out in nocturnal species like rats and mice, which are nocturnal animals, and therefore care needs to be taken when extrapolating data to humans. In both humans and rodents, melatonin levels rise during the evening, peak in the middle to latter half of the night and decline by morning. However, the dark phase is a time of energy expenditure in rodents, coincident with a peak in insulin sensitivity, while in humans, the dark phase is a time of energy deficit or fasting, with elevated glycogen breakdown and gluconeogenesis and decreased insulin sensitivity. These divergences may be even more profound because melatonin does not only affect physiological functions directly, but also modulates phasing and amplitudes of the circadian master clock and various peripheral circadian oscillators.

Evidence of Melatonin Therapeutic Value in the Metabolic Syndrome.

Clinical Studies

Table 2 summarizes the results of clinical studies on melatonin activity relevant to human MS. Type 2 diabetic patients have low circulating levels of melatonin [110] with a concurrently and expected upregulation of mRNA expression of melatonin membrane receptor [111]. Furthermore, allelic variants for melatonin receptors were associated with increased levels of fasting blood glucose and / or increased risk of type 2 diabetes [112-114] and with polycystic ovary syndrome [115]. These findings strongly bind melatonin to glucose homeostasis in blood.

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Patients with coronary artery disease show decreased melatonin secretion [128-131] and among elderly hypertensive individuals, nocturnal urinary melatonin excretion was inversely associated with the non-dipper pattern [132]. In turn, administered melatonin proved capable of reducing nocturnal blood pressure in hypertensives [135-138] and attenuated age-dependent disturbances of cardiovascular rhythms [139]. A meta-analysis of randomized controlled trials suggest that a controlled release preparation of melatonin is effective and safe in improving nocturnal hypertension [162]. As a pleiotropic molecule, melatonin can exert its antihypertensive and anti-remodeling effects through its antioxidant and scavenging properties, preserving the availability of nitric oxide and having sympathoplegic effects that provide cardiovascular protection in MS.

Resembling animal experiments, clinical studies have shown that melatonin improves lipid profiles in MS patients. Melatonin treatment (1 mg / kg for 30 days) increased levels of high-density lipoprotein-cholesterol in peri- and postmenopausal women [163]. Several mechanisms may explain the hypolipidemic effects of melatonin, such as reduced intestinal absorption of cholesterol [164] or an inhibited cholesterol biosynthesis [165].

Catecholamine-induced hypercoagulability in acute stress that contributes to the growth of thrombus after rupture of coronary plaque was prevented by the administration of melatonin [140]. This was probably mediated by the reported inhibitory effects of melatonin on platelet aggregation [141-143]. Considering these results melatonin may have a protective effect in reducing atherothrombotic risk in MS.

Several studies support the beneficial role of melatonin in patients with MS. Melatonin treatment ameliorates MS in obese patients [144,145] as well as in bipolar and schizophrenic patients after treatment with second generation antipsychotics [146-148]. Melatonin administration normalizes MS in elder hypertensive patients [149] and improves enzymatic profile in patients with on alcoholic liver steatosis [151,152]. The combination of melatonin and zinc acetate, when used alone or in combination with metformin improved glycemic control in type 2 diabetic patients [153] and an inverse relationship between urinary 6-sulfatoxy melatonin excretion and insulin levels and insulin resistance was reported in healthy women in the Nurses' Health Study cohort [166]. Overall, the results discussed above suggest that melatonin therapy can be beneficial for patients with MS, although more studies are clearly needed to evaluate an appropriate time / duration of treatment / dose relationship administration of melatonin in patients with MS.

It must be noted that several results deny the capacity of melatonin to improve glucose tolerance and to reduce insulin resistance in humans. Melatonin administration decreased glucose tolerance, already in nondiabetic young individuals [166], an observation confirmed by other recent studies [155,167]. In vitro, melatonin inhibits insulin secretion, an effect that is logical in humans if one presumes that melatonin suppresses insulin during the night to sensitize the pancreatic β -cells in preparation for breakfast, but is more difficult to explain in nighttime eating rodents.

Additional information concerning a glucose tolerance-reducing property of melatonin in humans came from the detection of melatonin receptor polymorphisms. To date, several single nucleotide polymorphisms (SNPs) located near or inside the gene encoding MTNR1B with an association with type 2 diabetes mellitus have been identified in Asian (Indian, Sri Lankan, Chinese, Korean, Japanese) and European ethnicities [112,122-127]. Among these SNPs, rs10830963 appears the most strongly associated with an increase in fasting plasma glucose, glucose area under the curve and glycated hemoglobin (HbA1C) and a decrease in pancreatic β -cell function, basal insulin secretion and plasma insulin [168]. This G allele that carries the SNP rs10830963 is prodiabetic and is overexpressed in pancreatic β -cells, causing a more intense decrease in cyclic adenosine monophosphate (cAMP) upon melatonin stimulation and consequently suppressing more strongly the cAMP-dependent secretion of insulin [169]. It appears to affect β -cell function directly and is associated with a defective early

insulin response and a decreased β -cell glucose sensitivity [169-171]. In clinical studies, the presence of the G allele worsens the decrease in glucose tolerance induced by melatonin [172].

The rs10830963 G-allele may have a greater risk on the transition from normal glucose tolerance to prediabetes than on prediabetes to type 2 diabetes mellitus and is thought to have an important influence on glucose levels from childhood onwards [173]. Individuals older than 45 years of age who are carrying the rs10830963 G allele, show a higher expression of MTNR1B in pancreatic islets [169]. This has been reported in diabetic rats as well as diabetic humans. It is not known whether this is a physiological adaptive response to reduced melatonin levels or whether it is part of the pathology of diabetes. It has been proposed that an increase in MT₂ receptor expression could increase the inhibitory downstream signaling leading to an overall decrease in insulin release in type 2 diabetes mellitus [169].

Increased MTNR1B expression occurred in human islets from risk G-allele carriers. Melatonin treatment reduced insulin secretion and raised glucose levels more extensively in risk G-allele carriers indicating that an increased melatonin signaling may be a risk factor for type 2 diabetes [157]. Since the presence of the G allele was shown to worsen the reduction in glucose tolerance by melatonin [172] strategies of blocking melatonergic signaling in patients with diabetes have been proposed [174].

However, it must be noted that a reduction in insulin secretion is not necessarily associated with insulin resistance in the target organs, clearly improved by melatonin in most studies. In addition, other MT₂ receptor variants with entirely different properties have been found to be also associated with type 2 diabetes. Some of them are entirely dysfunctional because of their incapability of binding melatonin, and others were found to be unable to interact with G_i proteins [175,176]. Thus, the absence of melatonin signaling is presumably also diabetogenic.

A further important aspect concerns the contrasting findings of impairments of insulin secretion by the overexpressed MT₂ G allele and the observed reduced melatonin levels in patients with diabetes [110,116-120]. The reduction in melatonin levels should presumably be considered as a primary change that is associated with the initiation and/or progression of the disease. In fact, the decrease in melatonin has been regarded as a risk factor for type 2 diabetes.

In young adults, the expression levels of the G allele showed a higher variability, but were not statistically different from those of noncarriers, whereas a strong increase in G allele expression was observed in individuals above 45 years [169]. Based on these findings, Hardeland recently proposed an aging-related deterioration of the circadian system, which may lead to losses of rhythm amplitudes, presumably also in the pancreatic β -cell oscillators, and additionally to decreases in nocturnal melatonin secretion [47]. This suggestion gives rise to the interesting question on whether exogenous melatonin administered to carriers of the G allele or to other adults before the age of 40 years might protect the circadian system from losses in amplitudes and, thus, prevent or delay the development of type 2 diabetes. Another important point to consider in human studies is the discrimination of core symptoms (glucose homeostasis) from diabetes-associated

pathologies, including those derived from an enhanced oxidative stress like liver steatosis, cardiovascular disease, retinopathy, nephropathy or osteoporosis. In most of these associated pathologies melatonin has a demonstrated therapeutic efficacy.

Conclusions

Clinical management of type 2 diabetes includes rigorous lifestyle modifications, insulin therapy, drug treatments that promote insulin sensitization (such as metformin) and insulin secretion (such as glibenclamide), novel glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose cotransporter 2 inhibitors [177]. These approaches are designed to manage the symptoms of insulin resistance/ β -cell dysfunction and are either used alone or in combination. Many drug therapies for diabetes are costly and in some cases have been associated with adverse events, including possible pancreatitis, hypoglycemia and osteoporosis [178]. Thus, there remains a need for new and cost-effective pharmacotherapies for diabetes that have limited additional health risks.

Obesity is a preventable disease, but its prevalence is continuously increasing worldwide, and because it is frequently associated with other cardiovascular risk factors and high mortality, obesity has become an important public health problem and a heavy socioeconomic burden for the overall society. Environmental factors or stressors of the so-called contemporary “24/7” societies have pronounced effects on metabolism producing circadian clock disruption. Furthermore, people whose work involves irregular time schedules and forced exposure to bright light at night (night/shift workers) show significant disruptions in sleep architecture, and increased prevalence of MS. These lines of evidence indicate that the system fails to adjust properly to environmental and/or stressor changes disrupting overall metabolic homeostasis.

Melatonin can provide an innovative strategy in MS by combining its chronobiotic effect on the circadian rhythm with their cytoprotective properties. Melatonin protects against several MS comorbidities, such as diabetes and concomitant oxyradical mediated damage, inflammation, microvascular disease and atherothrombotic risk. Melatonin may have thus a place since the initial phases of MS treatment. It has a high safety profile and shows a reduced toxicity, thus differing from most many pharmaceutical agents used in MS patients.

Moreover, melatonin is usually remarkably well tolerated at very high doses [179]. As melatonin is a short-lived molecule that has a limited duration of action (half-life from 0.54 to 0.67 h) analogs with a high affinity for melatonin receptors and a longer duration of action have synthesized to treat circadian disorders[180]. To what extent the new melatonergic agents approved by the US Food and Drug Administration or the European Medicines Agency (ramelteon, agomelatine, tasimelteon) share the protective activity of melatonin in MS remains to be defined. There is evidence that one of these analogs, ramelteon, given daily in drinking water (8 mg/ kg) for 8 weeks to spontaneously hypertensive male Wistar-Kyoto rats significantly attenuated systolic blood pressure and body weight gain associated with age [181]. In addition, an investigational melatonergic

agonist, piromelatine (NEU-P11) has been reported to be similarly effective as or even superior to melatonin in improving some MS-associated parameters [52,71,182]. Given higher binding affinities, longer half-life and high relative potencies of the various melatonin agonists, studies using 2 or 3 mg / day of melatonin are probably inadequate to provide adequate comparison with the effects of the natural compound.

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References

1. Smith CJ, Ryckman KK (2015) Epigenetic and developmental influences on the risk of obesity, diabetes, and metabolic syndrome. *Diabetes Metab Syndr. Obes.* 8: 295-302.
2. O'Neill S, O'Driscoll L (2015) Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes. Rev.* 16: 1-12.
3. Bhatti JS, Kumar S, Vijayan M, Bhatti GK, Reddy PH (2017) therapeutic strategies for mitochondrial dysfunction and oxidative stress in age-related metabolic disorders. *Prog. Mol. Biol. Transl. Sci.* 146: 13-46.
4. Bhatti JS, Bhatti GK, Reddy PH (2016) Mitochondrial dysfunction and oxidative stress in metabolic disorders - A step towards mitochondria based therapeutic strategies. *Biochim. Biophys. Acta* doi: 10.1016/j.bbadis.2016.11.010. [Epub ahead of print]
5. Fabbri E, Chia CW, Spencer RG, Fishbein KW, Reiter DA, Cameron D, Zane AC, Moore ZA, Gonzalez-Freire M, Zoli M, Studenski SA, Kalyani RR, Egan JM, Ferrucci L (2017) Insulin resistance is associated with reduced mitochondrial oxidative capacity measured by 31P-magnetic resonance spectroscopy in participants without diabetes from the Baltimore Longitudinal Study of Aging. *Diabetes* 66: 170-176.
6. Di Daniele N., Noce A, Vidiri MF, Moriconi E, Marrone G, Annicchiarico-Petruzzelli M, D'Urso G, Tesaro M, Rovella V, De Lorenzo A. (2017) Impact of Mediterranean diet on metabolic syndrome, cancer and longevity. *Oncotarget.* 8: 8947-8979.
7. de la Iglesia R, Loria-Kohen V, Zulet MA, Martinez JA, Reglero G, Ramirez de MA (2016) Dietary strategies implicated in the prevention and treatment of metabolic syndrome. *Int. J. Mol. Sci.* 17:
8. Kalsbeek A, la FS, Fliers E (2014) Circadian control of glucose metabolism. *Mol. Metab* 3: 372-383.
9. Huang W, Ramsey KM, Marcheva B, Bass J (2011) Circadian rhythms, sleep, and metabolism. *J. Clin. Invest* 121: 2133-2141.
10. Karthikeyan R, Marimuthu G, Spence DW, Pandi-Perumal SR, Bahammam AS, Brown GM, Cardinali DP (2014) Should we listen to our clock to prevent type 2 diabetes mellitus? *Diabetes Res. Clin. Pract.* 106: 182-190.
11. McFadden E, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ (2014) The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the Breakthrough Generations Study. *Am. J. Epidemiol.* 180: 245-250.
12. Molzof HE, Wirth MD, Burch JB, Shivappa N, Hebert JR, Johnson RL, Gamble KL (2017) The impact of meal timing on cardiometabolic syndrome indicators in shift workers. *Chronobiol. Int.* 34: 337-348.
13. Lin YC, Hsieh IC, Chen PC (2015) Utilizing the metabolic syndrome component count in workers' health surveillance: An example of day-time vs. day-night rotating shift workers. *Int. J. Occup. Med. Environ. Health* 28: 675-688.
14. Kawabe Y, Nakamura Y, Kikuchi S, Murakami Y, Tanaka T, Takebayashi T, Okayama A, Miura K, Okamura T, Ueshima H (2014) Relationship between shift work and clustering of the metabolic syndrome diagnostic components. *J. Atheroscler. Thromb.* 21: 703-711.
15. Arora T, Chen MZ, Cooper AR, Andrews RC, Taheri S (2016) The impact of sleep debt on excess adiposity and insulin sensitivity in patients with early type 2 diabetes mellitus. *J. Clin. Sleep Med.* 12: 673-680.
16. Cardinali DP, Cano P, Jimenez-Ortega V, Esquifino AI (2011) Melatonin and the metabolic syndrome: physiopathologic and therapeutical implications. *Neuroendocrinology* 93: 133-142.
17. Cardinali DP, Hardeland R (2017) Inflammaging, metabolic syndrome and melatonin: a call for treatment studies. *Neuroendocrinology* 104:382-339

18. Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z, Reiter RJ (2015) Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism. *Molecules*. 20: 18886-18906.
19. Hardeland R, Cardinali DP, Brown GM, Pandi-Perumal SR (2015) Melatonin and brain inflammaging. *Prog. Neurobiol.* 127-128: 46-63.
20. Sharafati-Chaleshtori R, Shirzad H, Rafieian-Kopaei M, Soltani A (2017) Melatonin and human mitochondrial diseases. *J. Res. Med. Sci.* 22: 2
21. Balistreri CR, Caruso C, Candore G (2010) The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators. Inflamm.* 2010: 802078
22. Makki K, Froguel P, Wolowczuk I (2013) Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN. Inflamm.* 2013: 139239
23. Welty FK, Alfaddagh A, Elajami TK (2016) Targeting inflammation in metabolic syndrome. *Transl. Res* 167: 257-280.
24. Esser N, Paquot N, Scheen AJ (2015) Inflammatory markers and cardiometabolic diseases. *Acta Clin. Belg.* 70: 193-199.
25. Paradies G, Petrosillo G, Paradies V, Reiter RJ, Ruggiero FM (2010) Melatonin, cardiolipin and mitochondrial bioenergetics in health and disease. *J. Pineal Res.* 48: 297-310.
26. Crino PB (2016) The mTOR signalling cascade: paving new roads to cure neurological disease. *Nat. Rev. Neurol.* 12: 379-392.
27. Zhao D, Yang J, Yang L (2017) Insights for oxidative stress and mTOR signaling in myocardial ischemia/reperfusion injury under diabetes. *Oxid. Med. Cell Longev.* 2017: 6437467
28. Arpaci D, Gurkan TA, Yilmaz S, Ergenc H, Tamer A, Keser N, Gunduz H (2015) The relationship between epicardial fat tissue thickness and visceral adipose tissue in lean patients with polycystic ovary syndrome. *J Ovarian. Res* 8: 71
29. Sarvari AK, Vereb Z, Uray IP, Fesus L, Balajthy Z (2014) Atypical antipsychotics induce both proinflammatory and adipogenic gene expression in human adipocytes in vitro. *Biochem. Biophys. Res Commun.* 450: 1383-1389.
30. Zhang Y, Zitsman JL, Hou J, Fennoy I, Guo K, Feinberg J, Leibel RL (2014) Fat cell size and adipokine expression in relation to gender, depot, and metabolic risk factors in morbidly obese adolescents. *Obesity. (Silver. Spring)* 22: 691-697.
31. Tchernof A, Despres JP (2013) Pathophysiology of human visceral obesity: an update. *Physiol Rev.* 93: 359-404.
32. Pereira-Miranda E, Costa PR, Queiroz VA, Pereira-Santos M, Santana ML (2017) Overweight and obesity associated with higher depression prevalence in adults: a systematic review and meta-analysis. *J. Am. Coll. Nutr.* 1-11.
33. Franceschi C, Bonafe M, Valensin S, Olivieri F, De LM, Ottaviani E, De BG (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* 908: 244-254.
34. Boren E, Gershwin ME (2004) Inflamm-aging: autoimmunity, and the immune-risk phenotype. *Autoimmun. Rev.* 3: 401-406.
35. Cevenini E, Monti D, Franceschi C (2013) Inflamm-ageing. *Curr. Opin. Clin. Nutr. Metab Care* 16: 14-20.
36. Catrysse L, van LG (2017) Inflammation and the metabolic syndrome: the tissue-specific functions of NF-kappa β . *Trends Cell Biol.* doi: 10.1016/j.tcb.2017.01.006. [Epub ahead of print]
37. De la Fuente M, Miquel J (2009) An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. *Curr. Pharm. Des* 15: 3003-3026.
38. Hardeland R (2013) Melatonin and the theories of aging: a critical appraisal of melatonin's role in antiaging mechanisms. *J. Pineal Res.* 55: 325-356.
39. Tan DX, Manchester LC, Qin L, Reiter RJ (2016) Melatonin: a mitochondrial targeting molecule involving mitochondrial protection and dynamics. *Int. J. Mol. Sci.* 17:

- 40 . Cardinali DP, Pagano ES, Scacchi Bernasconi PA, Reynoso R, Scacchi P (2013) Melatonin and mitochondrial dysfunction in the central nervous system. *Horm. Behav.* 63: 322-330.
- 41 . Tan DX, Manchester LC, Liu X, Rosales-Corral SA, Acuña-Castroviejo D, Reiter RJ (2013) Mitochondria and chloroplasts as the original sites of melatonin synthesis: a hypothesis related to melatonin's primary function and evolution in eukaryotes. *J. Pineal Res.* 54: 127-138.
- 42 . Reiter RJ, Paredes SD, Manchester LC, Tan DX (2009) Reducing oxidative/nitrosative stress: a newly-discovered genre for melatonin. *Crit Rev Biochem. Mol. Biol.* 44: 175-200.
- 43 . Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR (2011) Melatonin--a pleiotropic, orchestrating regulator molecule. *Prog. Neurobiol.* 93: 350-384.
- 44 . Petrosillo G, Fattoretti P, Matera M, Ruggiero FM, Bertoni-Freddari C, Paradies G (2008) Melatonin prevents age-related mitochondrial dysfunction in rat brain via cardiolipin protection. *Rejuvenation. Res* 11: 935-943.
- 45 . Guarente L (2008) Mitochondria--a nexus for aging, calorie restriction, and sirtuins? *Cell* 132: 171-176.
- 46 . Mayo JC, Sainz RM, Gonzalez MP, Cepas V, Tan DX, Reiter RJ (2017) Melatonin and sirtuins: A "not-so unexpected" relationship. *J. Pineal Res.* 62:
- 47 . Hardeland R (2017) Melatonin and the pathologies of weakened or dysregulated circadian oscillators. *J. Pineal Res.* doi: 10.1111/jpi.12377. Epub 2016 Nov 24
- 48 . She M, Hou H, Wang Z, Zhang C, Laudon M, Yin W (2014) Melatonin rescues 3T3-L1 adipocytes from FFA-induced insulin resistance by inhibiting phosphorylation of IRS-1 on Ser307. *Biochimie* 103: 126-130.
- 49 . Teodoro BG, Baraldi FG, Sampaio IH, Bomfim LH, Queiroz AL, Passos MA, Carneiro EM, Alberici LC, Gomis R, Amaral FG, Cipolla-Neto J, Araujo MB, Lima T, Uyemura SA, Silveira LR, Vieira E (2014) Melatonin prevents mitochondrial dysfunction and insulin resistance in rat skeletal muscle. *J. Pineal Res.* 57:155-156
- 50 . Quan X, Wang J, Liang C, Zheng H, Zhang L (2015) Melatonin inhibits tunicamycin-induced endoplasmic reticulum stress and insulin resistance in skeletal muscle cells. *Biochem. Biophys. Res. Commun.* 463: 1102-1107.
- 51 . Du Y, Wei T (2014) Inputs and outputs of insulin receptor. *Protein Cell* 5: 203-213.
- 52 . She M, Deng X, Guo Z, Laudon M, Hu Z, Liao D, Hu X, Luo Y, Shen Q, Su Z, Yin W (2009) NEU-P11, a novel melatonin agonist, inhibits weight gain and improves insulin sensitivity in high-fat/high-sucrose-fed rats. *Pharmacol. Res.* 59: 248-253.
- 53 . Prunet-Marcassus B, Desbazeille M, Bros A, Louche K, Delagrangé P, Renard P, Casteilla L, Penicaud L (2003) Melatonin reduces body weight gain in Sprague Dawley rats with diet-induced obesity. *Endocrinology* 144: 5347-5352.
- 54 . Puchalski SS, Green JN, Rasmussen DD (2003) Melatonin effect on rat body weight regulation in response to high-fat diet at middle age. *Endocrine.* 21: 163-167.
- 55 . Sartori C, Dessen P, Mathieu C, Monney A, Bloch J, Nicod P, Scherrer U, Duplain H (2009) Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. *Endocrinology* 150: 5311-5317.
- 56 . Ladizesky MG, Boggio V, Albornoz LE, Castrillon PO, Mautalen C, Cardinali DP (2003) Melatonin increases oestradiol-induced bone formation in ovariectomized rats. *J. Pineal Res.* 34: 143-151.
- 57 . Sanchez-Mateos S, Alonso-Gonzalez C, Gonzalez A, Martinez-Campa CM, Mediavilla MD, Cos S, Sanchez-Barcelo EJ (2007) Melatonin and estradiol effects on food intake, body weight, and leptin in ovariectomized rats. *Maturitas* 58: 91-101.
- 58 . Ciortea R, Costin N, Braicu I, Haragas D, Hudacsko A, Bondor C, Mihu D, Mihu CM (2011) Effect of melatonin on intra-abdominal fat in correlation with endometrial proliferation in ovariectomized rats. *Anticancer Res.* 31: 2637-2643.

- 59 . Raskind MA, Burke BL, Crites NJ, Tapp AM, Rasmussen DD (2007) Olanzapine-induced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. *Neuropsychopharmacology* 32: 284-288.
- 60 . De Pedro N, Martinez-Alvarez RM, Delgado MJ (2008) Melatonin reduces body weight in goldfish (*Carassius auratus*): effects on metabolic resources and some feeding regulators. *J. Pineal Res.* 45: 32-39.
- 61 . Rios-Lugo MJ, Cano P, Jimenez-Ortega V, Fernandez-Mateos MP, Scacchi PA, Cardinali DP, Esquifino AI (2010) Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat-fed rats. *J. Pineal Res.* 49: 342-348.
- 62 . Cuesta S, Kireev R, Forman K, Garcia C, Escames G, Ariznavarreta C, Vara E, Tresguerres JA (2010) Melatonin improves inflammation processes in liver of senescence-accelerated prone male mice (SAMP8). *Exp. Gerontol.* 45: 950-956.
- 63 . Cuesta S, Kireev R, Garcia C, Rancan L, Vara E, Tresguerres JA (2013) Melatonin can improve insulin resistance and aging-induced pancreas alterations in senescence-accelerated prone male mice (SAMP8). *Age (Dordr.)* 35: 659-671.
- 64 . Nduhirabandi F, du Toit EF, Blackhurst D, Marais D, Lochner A (2011) Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of diet-induced obesity. *J. Pineal Res.* 50: 171-182.
- 65 . Agil A, Navarro-Alarcon M, Ruiz R, Abuhamad S, El-Mir MY, Vazquez GF (2011) Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. *J. Pineal Res.* 50: 207-212.
- 66 . Kitagawa A, Ohta Y, Ohashi K (2012) Melatonin improves metabolic syndrome induced by high fructose intake in rats. *J. Pineal Res.* 52: 403-413.
- 67 . Cardinali DP, Bernasconi PA, Reynoso R, Toso CF, Scacchi P (2013) Melatonin may curtail the metabolic syndrome: studies on initial and fully established fructose-induced metabolic syndrome in rats. *Int. J. Mol. Sci.* 14: 2502-2514.
- 68 . Bernasconi PA, Cardoso NP, Reynoso R, Scacchi P, Cardinali DP (2013) Melatonin and diet-induced metabolic syndrome in rats: impact on the hypophysial-testicular axis. *Horm. Mol. Biol. Clin. Investig.* 16: 101-112.
- 69 . Demirtas CY, Pasaoglu OT, Bircan FS, Kantar S, Turkozkan N (2015) The investigation of melatonin effect on liver antioxidant and oxidant levels in fructose-mediated metabolic syndrome model. *Eur. Rev Med. Pharmacol. Sci.* 19: 1915-1921.
- 70 . Ewida SF, Al-Sharakly DR (2016) Implication of renal aquaporin-3 in fructose-induced metabolic syndrome and melatonin protection. *J. Clin. Diagn. Res.* 10: CF06-CF11
- 71 . Huang L, Zhang C, Hou Y, Laudon M, She M, Yang S, Ding L, Wang H, Wang Z, He P, Yin W (2013) Blood pressure reducing effects of piromelatine and melatonin in spontaneously hypertensive rats. *Eur. Rev Med. Pharmacol. Sci.* 17: 2449-2456.
- 72 . Vinogradova I, Anisimov V (2013) Melatonin prevents the development of the metabolic syndrome in male rats exposed to different light/dark regimens. *Biogerontology.* 14: 401-409.
- 73 . Hatzis G, Ziakas P, Kavantzias N, Triantafyllou A, Sigalas P, Andreadou I, Ioannidis K, Chatzis S, Filis K, Papalampros A, Sigala F (2013) Melatonin attenuates high fat diet-induced fatty liver disease in rats. *World J. Hepatol.* 5: 160-169.
- 74 . Diez ER, Renna NF, Prado NJ, Lembo C, Ponce Zumino AZ, Vazquez-Prieto M, Miatello RM (2013) Melatonin, given at the time of reperfusion, prevents ventricular arrhythmias in isolated hearts from fructose-fed rats and spontaneously hypertensive rats. *J. Pineal Res.* 55: 166-173.
- 75 . Agil A, Reiter RJ, Jimenez-Aranda A, Iban-Arias R, Navarro-Alarcon M, Marchal JA, Adem A, Fernandez-Vazquez G (2013) Melatonin ameliorates low-grade inflammation and oxidative stress in young Zucker diabetic fatty rats. *J. Pineal Res.* 54: 381-388.

- 76 . Bibak B, Khalili M, Rajaei Z, Soukhtanloo M, Hadjzadeh MA, Hayatdavoudi P (2014) Effects of melatonin on biochemical factors and food and water consumption in diabetic rats. *Adv. Biomed. Res.* 3: 173
- 77 . Hidayat M, Maha Y, Wasim H (2015) Effect of melatonin on serum glucose and body weight in streptozotocin induced diabetes in albino rats. *J. Ayub. Med. Coll. Abbottabad.* 27: 274-276.
- 78 . Pai SA, Majumdar AS (2014) Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats. *J. Pharm. Pharmacol.* 66: 1710-1721.
- 79 . Cano BP, Pagano ES, Jimenez-Ortega V, Fernandez-Mateos P, Esquifino AI, Cardinali DP (2014) Melatonin normalizes clinical and biochemical parameters of mild inflammation in diet-induced metabolic syndrome in rats. *J. Pineal Res.* 57: 280-290.
- 80 . Rios-Lugo MJ, Jimenez-Ortega V, Cano-Barquilla P, Mateos PF, Spinedi EJ, Cardinali DP, Esquifino AI (2015) Melatonin counteracts changes in hypothalamic gene expression of signals regulating feeding behavior in high-fat fed rats. *Horm. Mol. Biol. Clin. Investig.* 21: 175-183.
- 81 . Favero G, Stacchiotti A, Castrezzati S, Bonomini F, Albanese M, Rezzani R, Rodella LF (2015) Melatonin reduces obesity and restores adipokine patterns and metabolism in obese (ob/ob) mice. *Nutr. Res.* 35: 891-900.
- 82 . Winiarska K, Dzik JM, Labudda M, Focht D, Sierakowski B, Owczarek A, Komorowski L, Bielecki W (2015) Melatonin nephroprotective action in Zucker diabetic fatty rats involves its inhibitory effect on NADPH oxidase. *J. Pineal Res.*
- 83 . Doddigarla Z, Ahmad J, Parwez I (2016) Effect of chromium picolinate and melatonin either in single or in a combination in high carbohydrate diet-fed male Wistar rats. *Biofactors* 42: 106-114.
- 84 . Salmanoglu DS, Gurpinar T, Vural K, Ekerbicer N, Dariverenli E, Var A (2016) Melatonin and L-carnitin improves endothelial dysfunction and oxidative stress in Type 2 diabetic rats. *Redox. Biol.* 8: 199-204.
- 85 . Gao L, Zhao YC, Liang Y, Lin XH, Tan YJ, Wu DD, Li XZ, Ye BZ, Kong FQ, Sheng JZ, Huang HF (2016) The impaired myocardial ischemic tolerance in adult offspring of diabetic pregnancy is restored by maternal melatonin treatment. *J. Pineal Res.* 61: 340-352.
- 86 . Thomas AP, Hoang J, Vongbunyong K, Nguyen A, Rakshit K, Matveyenko AV (2016) Administration of melatonin and metformin prevents deleterious effects of circadian disruption and obesity in male rats. *Endocrinology* 157: 4720-4731.
- 87 . Sun H, Wang X, Chen J, Song K, Gusdon AM, Li L, Bu L, Qu S (2016) Melatonin improves non-alcoholic fatty liver disease via MAPK-JNK/P38 signaling in high-fat-diet-induced obese mice. *Lipids Health Dis.* 15: 202
- 88 . Sheen JM, Chen YC, Hsu MH, Tain YL, Huang YH, Tiao MM, Li SW, Huang LT (2016) Melatonin alleviates liver apoptosis in bile duct ligation young rats. *Int. J. Mol. Sci.* 17:
- 89 . Xu P, Wang J, Hong F, Wang S, Jin X, Xue T, Jia L, Zhai Y (2017) Melatonin prevents obesity through modulation of gut microbiota in mice. *J. Pineal Res.* doi: 10.1111/jpi.12399. Epub 2017 Mar 10.
- 90 . Carrillo-Vico A, Lardone PJ, Alvarez-Sanchez N, Rodriguez-Rodriguez A, Guerrero JM (2013) Melatonin: buffering the immune system. *Int. J. Mol. Sci.* 14: 8638-8683.
- 91 . Kireev RA, Tresguerres AC, Garcia C, Ariznavarreta C, Vara E, Tresguerres JA (2008) Melatonin is able to prevent the liver of old castrated female rats from oxidative and pro-inflammatory damage. *J. Pineal Res.* 45: 394-402.
- 92 . Cuesta S, Kireev R, Garcia C, Forman K, Escames G, Vara E, Tresguerres JA (2011) Beneficial effect of melatonin treatment on inflammation, apoptosis and oxidative stress on pancreas of a senescence accelerated mice model. *Mech. Ageing Dev.* 132: 573-582.
- 93 . Forman K, Vara E, Garcia C, Kireev R, Cuesta S, Escames G, Tresguerres JA (2011) Effect of a combined treatment with growth hormone and melatonin in the cardiological aging on male SAMP8 mice. *J. Gerontol. A Biol. Sci. Med. Sci.* 66: 823-834.

- 94 . Muhlbauer E, Wolgast S, Finckh U, Peschke D, Peschke E (2004) Indication of circadian oscillations in the rat pancreas. *FEBS Lett.* 564: 91-96.
- 95 . Hardeland R, Madrid JA, Tan DX, Reiter RJ (2012) Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. *J. Pineal Res.* 52: 139-166.
- 96 . Boivin DB, James FO, Wu A, Cho-Park PF, Xiong H, Sun ZS (2003) Circadian clock genes oscillate in human peripheral blood mononuclear cells. *Blood* 102: 4143-4145.
- 97 . Bollinger T, Leutz A, Leliavski A, Skrum L, Kovac J, Bonacina L, Benedict C, Lange T, Westermann J, Oster H, Solbach W (2011) Circadian clocks in mouse and human CD4+ T cells. *PLoS. One.* 6: e29801
- 98 . Hardeland R (2015) Melatonin and circadian oscillators in aging--a dynamic approach to the multiply connected players. *Interdiscip. Top. Gerontol.* 40: 128-140.
- 99 . Jung KH, Hong SW, Zheng HM, Lee HS, Lee H, Lee DH, Lee SY, Hong SS (2010) Melatonin ameliorates cerulein-induced pancreatitis by the modulation of nuclear erythroid 2-related factor 2 and nuclear factor-kappa β in rats. *J. Pineal Res.* 48: 239-250.
- 100 . Hardeland R (2014) Melatonin, noncoding RNAs, messenger RNA stability and epigenetics-evidence, hints, gaps and perspectives. *Int. J. Mol. Sci.* 15: 18221-18252.
- 101 . Pan M, Song YL, Xu JM, Gan HZ (2006) Melatonin ameliorates nonalcoholic fatty liver induced by high-fat diet in rats. *J. Pineal Res.* 41: 79-84.
- 102 . Stumpf I, Bazwinsky I, Peschke E (2009) Modulation of the cGMP signaling pathway by melatonin in pancreatic beta-cells. *J. Pineal Res.* 46: 140-147.
- 103 . Kanter M, Uysal H, Karaca T, Sagmanligil HO (2006) Depression of glucose levels and partial restoration of pancreatic beta-cell damage by melatonin in streptozotocin-induced diabetic rats. *Arch. Toxicol.* 80: 362-369.
- 104 . Nishida S, Sato R, Murai I, Nakagawa S (2003) Effect of pinealectomy on plasma levels of insulin and leptin and on hepatic lipids in type 2 diabetic rats. *J. Pineal Res.* 35: 251-256.
- 105 . Nishida S, Segawa T, Murai I, Nakagawa S (2002) Long-term melatonin administration reduces hyperinsulinemia and improves the altered fatty-acid compositions in type 2 diabetic rats via the restoration of Delta-5 desaturase activity. *J. Pineal Res.* 32: 26-33.
- 106 . Mazepa RC, Cuevas MJ, Collado PS, Gonzalez-Gallego J (2000) Melatonin increases muscle and liver glycogen content in nonexercised and exercised rats. *Life Sci.* 66: 153-160.
- 107 . Shieh JM, Wu HT, Cheng KC, Cheng JT (2009) Melatonin ameliorates high fat diet-induced diabetes and stimulates glycogen synthesis via a PKCzeta-Akt-GSK3 β pathway in hepatic cells. *J. Pineal Res.* 47: 339-344.
- 108 . Bartness TJ, Demas GE, Song CK (2002) Seasonal changes in adiposity: the roles of the photoperiod, melatonin and other hormones, and sympathetic nervous system. *Exp. Biol. Med.* (Maywood.) 227: 363-376.
- 109 . Tan DX, Manchester LC, Fuentes-Broto L, Paredes SD, Reiter RJ (2011) Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity. *Obes. Rev* 12: 167-188.
- 110 . Tutuncu NB, Batur MK, Yildirim A, Tutuncu T, Deger A, Koray Z, Erbas B, Kabakci G, Aksoyek S, Erbas T (2005) Melatonin levels decrease in type 2 diabetic patients with cardiac autonomic neuropathy. *J. Pineal Res.* 39: 43-49.
- 111 . Peschke E, Stumpf I, Bazwinsky I, Litvak L, Dralle H, Muhlbauer E (2007) Melatonin and type 2 diabetes - a possible link? *J. Pineal Res.* 42: 350-358.
- 112 . Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, Loos RJ, Manning AK, Jackson AU, Aulchenko Y, Potter SC, Erdos MR, Sanna S, Hottenga JJ, Wheeler E, Kaakinen M, Lyssenko V, Chen WM, Ahmadi K, Beckmann JS, Bergman RN, Bochud M, Bonnycastle LL, Buchanan TA, Cao A, Cervino A, Coin L, Collins FS, Crisponi L, de Geus EJ, Dehghan A, Deloukas P, Doney AS, Elliott P, Freimer N, Gateva V, Herder C, Hofman A, Hughes TE, Hunt S, Illig T, Inouye M,

Isomaa B, Johnson T, Kong A, Krestyaninova M, Kuusisto J, Laakso M, Lim N, Lindblad U, Lindgren CM, McCann OT, Mohlke KL, Morris AD, Naitza S, Orru M, Palmer CN, Pouta A, Randall J, Rathmann W, Saramies J, Scheet P, Scott LJ, Scuteri A, Sharp S, Sijbrands E, Smit JH, Song K, Steinthorsdottir V, Stringham HM, Tuomi T, Tuomilehto J, Uitterlinden AG, Voight BF, Waterworth D, Wichmann HE, Willemsen G, Witteman JC, Yuan X, Zhao JH, Zeggini E, Schlessinger D, Sandhu M, Boomsma DI, Uda M, Spector TD, Penninx BW, Altshuler D, Vollenweider P, Jarvelin MR, Lakatta E, Waeber G, Fox CS, Peltonen L, Groop LC, Mooser V, Cupples LA, Thorsteinsdottir U, Boehnke M, Barroso I, Van Duijn C, Dupuis J, Watanabe RM, Stefansson K, McCarthy MI, Wareham NJ, Meigs JB, Abecasis GR (2009) Variants in MTNR1B influence fasting glucose levels. *Nat Genet* 41: 77-81.

113 . Huber M, Treszl A, Reibis R, Teichmann C, Zergibel I, Bolbrinker J, Scholze J, Wegscheider K, Voller H, Kreutz R (2013) Genetics of melatonin receptor type 2 is associated with left ventricular function in hypertensive patients treated according to guidelines. *Eur. J. Intern. Med.* 24: 650-655.

114 . Zheng C, Dalla MC, Cobelli C, Groop L, Zhao H, Bale AE, Shaw M, Duran E, Pierpont B, Caprio S, Santoro N (2015) A common variant in the MTNR1b gene is associated with increased risk of impaired fasting glucose (IFG) in youth with obesity. *Obesity. (Silver. Spring)* 23: 1022-1029.

115 . Song X, Sun X, Ma G, Sun Y, Shi Y, Du Y, Chen ZJ (2015) Family association study between melatonin receptor gene polymorphisms and polycystic ovary syndrome in Han Chinese. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 195: 108-112.

116 . O'Brien IA, Lewin IG, O'Hare JP, Arendt J, Corral RJ (1986) Abnormal circadian rhythm of melatonin in diabetic autonomic neuropathy. *Clin. Endocrinol. (Oxf)* 24: 359-364.

117 . Hikichi T, Tateda N, Miura T (2011) Alteration of melatonin secretion in patients with type 2 diabetes and proliferative diabetic retinopathy. *Clin. Ophthalmol.* 5: 655-660.

118 . Mantele S, Otway DT, Middleton B, Bretschneider S, Wright J, Robertson MD, Skene DJ, Johnston JD (2012) Daily rhythms of plasma melatonin, but not plasma leptin or leptin mRNA, vary between lean, obese and type 2 diabetic men. *PLoS. One.* 7: e37123

119 . McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP (2013) Melatonin secretion and the incidence of type 2 diabetes. *JAMA* 309: 1388-1396.

120 . Reutrakul S, Siwasaranond N, Nimitphong H, Saetung S, Chirakalwasan N, Chailurkit LO, Srijaruskul K, Ongphiphadhanakul B, Thakkinstian A (2017) Associations between nocturnal urinary 6-sulfatoxymelatonin, obstructive sleep apnea severity and glycemic control in type 2 diabetes. *Chronobiol. Int.* 1-11.

121 . Shimada M, Seki H, Samejima M, Hayase M, Shirai F (2016) Salivary melatonin levels and sleep-wake rhythms in pregnant women with hypertensive and glucose metabolic disorders: A prospective analysis. *Biosci. Trends* 10: 34-41.

122 . Matuszek MA, Anton A, Thillainathan S, Armstrong NJ (2015) Increased Insulin following an Oral Glucose Load, Genetic Variation near the Melatonin Receptor MTNR1B, but No Biochemical Evidence of Endothelial Dysfunction in Young Asian Men and Women. *PLoS. One.* 10: e0133611

123 . Zhan Y, Li C, Gao Q, Chen J, Yu S, Liu SG (2015) Association between the rs4753426 polymorphism in MTNR1B with fasting plasma glucose level and pancreatic beta-cell function in gestational diabetes mellitus. *Genet. Mol. Res.* 14: 8778-8785.

124 . Tarnowski M, Malinowski D, Safranow K, Dziedziejko V, Pawlik A (2017) MTNR1A and MTNR1B gene polymorphisms in women with gestational diabetes. *Gynecol. Endocrinol.* 1-4.

125 . Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, Wheeler E, Glazer NL, Bouatia-Naji N, Gloyn AL, Lindgren CM, Magi R, Morris AP, Randall J, Johnson T, Elliott P, Rybin D, Thorleifsson G, Steinthorsdottir V, Henneman P, Grallert H, Dehghan A, Hottenga JJ, Franklin CS, Navarro P, Song K, Goel A, Perry JR, Egan JM, Lajunen T, Grarup N, Sparso T, Doney A, Voight BF, Stringham HM, Li M, Kanoni S, Shrader P, Cavalcanti-Proenca C, Kumari M, Qi L, Timpson NJ, Gieger C, Zabena C, Rocheleau G, Ingelsson E, An P, O'Connell J, Luan J, Elliott A, McCarroll SA, Payne F, Roccascella RM, Pattou F, Sethupathy P, Ardlie K, Ariyurek Y, Balkau B, Barter P, Beilby JP, Ben Shlomo Y, Benediktsson R, Bennett AJ, Bergmann S, Bochud M, Boerwinkle E, Bonnefond A, Bonnycastle LL, Borch-Johnsen K, Bottcher Y, Brunner E, Bumpstead SJ, Charpentier G, Chen YD, Chines P, Clarke R, Coin LJ, Cooper MN, Cornelis M, Crawford G, Crisponi L, Day IN, de Geus EJ, Delplanque J, Dina C, Erdos MR, Fedson AC, Fischer-Rosinsky A, Forouhi NG, Fox CS, Frants R,

Franzosi MG, Galan P, Goodarzi MO, Graessler J, Groves CJ, Grundy S, Gwilliam R, Gyllenstein U, Hadjadj S, Hallmans G, Hammond N, Han X, Hartikainen AL, Hassanali N, Hayward C, Heath SC, Herberg S, Herder C, Hicks AA, Hillman DR, Hingorani AD, Hofman A, Hui J, Hung J, Isomaa B, Johnson PR, Jorgensen T, Julia A, Kaakinen M, Kaprio J, Kesaniemi YA, Kivimaki M, Knight B, Koskinen S, Kovacs P, Kyvik KO, Lathrop GM, Lawlor DA, Le Bacquer O, Lecoeur C, Li Y, Lyssenko V, Mahley R, Mangino M, Manning AK, Martinez-Larrad MT, McAteer JB, McCulloch LJ, McPherson R, Meisinger C, Melzer D, Meyre D, Mitchell BD, Morken MA, Mukherjee S, Naitza S, Narisu N, Neville MJ, Oostra BA, Orru M, Pakyz R, Palmer CN, Paolisso G, Pattaro C, Pearson D, Peden JF, Pedersen NL, Perola M, Pfeiffer AF, Pichler I, Polasek O, Posthuma D, Potter SC, Pouta A, Province MA, Psaty BM, Rathmann W, Rayner NW, Rice K, Ripatti S, Rivadeneira F, Roden M, Rolandsson O, Sandbaek A, Sandhu M, Sanna S, Sayer AA, Scheet P, Scott LJ, Seedorf U, Sharp SJ, Shields B, Sigurdsson G, Sijbrands EJ, Silveira A, Simpson L, Singleton A, Smith NL, Sovio U, Swift A, Syddall H, Syvanen AC, Tanaka T, Thorand B, Tichet J, Tonjes A, Tuomi T, Uitterlinden AG, van Dijk KW, van Hoek M, Varma D, Visvikis-Siest S, Vitart V, Vogelzangs N, Waeber G, Wagner PJ, Walley A, Walters GB, Ward KL, Watkins H, Weedon MN, Wild SH, Willemssen G, Witteman JC, Yarnell JW, Zeggini E, Zelenika D, Zethelius B, Zhai G, Zhao JH, Zillikens MC, Borecki IB, Loos RJ, Meneton P, Magnusson PK, Nathan DM, Williams GH, Hattersley AT, Silander K, Salomaa V, Smith GD, Bornstein SR, Schwarz P, Spranger J, Karpe F, Shuldiner AR, Cooper C, Dedoussis GV, Serrano-Rios M, Morris AD, Lind L, Palmer LJ, Hu FB, Franks PW, Ebrahim S, Marmot M, Kao WH, Pankow JS, Sampson MJ, Kuusisto J, Laakso M, Hansen T, Pedersen O, Pramstaller PP (2010) New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 42: 105-116.

126 . Liao S, Liu Y, Tan Y, Gan L, Mei J, Song W, Chi S, Dong X, Chen X, Deng S (2012) Association of genetic variants of melatonin receptor 1B with gestational plasma glucose level and risk of glucose intolerance in pregnant Chinese women. *PLoS. One.* 7: e40113

127 . Liu C, Wu Y, Li H, Qi Q, Langenberg C, Loos RJ, Lin X (2010) MTNR1B rs10830963 is associated with fasting plasma glucose, HbA1C and impaired beta-cell function in Chinese Hans from Shanghai. *BMC. Med. Genet.* 11: 59

128 . Sakotnik A, Liebmann PM, Stoschitzky K, Lercher P, Schauenstein K, Klein W, Eber B (1999) Decreased melatonin synthesis in patients with coronary artery disease. *Eur. Heart J.* 20: 1314-1317.

129 . Girotti L, Lago M, Ianovsky O, Carbajales J, Elizari MV, Brusco LI, Cardinali DP (2000) Low urinary 6-sulphatoxymelatonin levels in patients with coronary artery disease. *J. Pineal Res.* 29: 138-142.

130 . Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia MJ, Sanchez J, Marrero F, de Armas-Trujillo D (2002) Decreased nocturnal melatonin levels during acute myocardial infarction. *J. Pineal Res.* 33: 248-252.

131 . Yaprak M, Altun A, Vardar A, Aktoz M, Ciftci S, Ozbay G (2003) Decreased nocturnal synthesis of melatonin in patients with coronary artery disease. *Int. J. Cardiol.* 89: 103-107.

132 . Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, Ikada Y, Kurumatani N (2013) Nocturnal urinary melatonin excretion is associated with non-dipper pattern in elderly hypertensives. *Hypertens. Res.* 36: 736-740.

133 . Cavallo A, Daniels SR, Dolan LM, Bean JA, Khoury JC (2004) Blood pressure-lowering effect of melatonin in type 1 diabetes. *J. Pineal Res.* 36: 262-266.

134 . Cavallo A, Daniels SR, Dolan LM, Khoury JC, Bean JA (2004) Blood pressure response to melatonin in type 1 diabetes. *Pediatr. Diabetes* 5: 26-31.

135 . Cagnacci A, Cannolella M, Renzi A, Baldassari F, Arangino S, Volpe A (2005) Prolonged melatonin administration decreases nocturnal blood pressure in women. *Am. J. Hypertens.* 18: 1614-1618.

136 . Scheer FA, Van Montfrans GA, Van Someren EJ, Mairuhu G, Buijs RM (2004) Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension* 43: 192-197.

137. Grossman E, Laudon M, Yalcin R, Zengil H, Peleg E, Sharabi Y, Kamari Y, Shen-Orr Z, Zisapel N (2006) Melatonin reduces night blood pressure in patients with nocturnal hypertension. *Am. J. Med.* 119: 898-902.
138. Mozdzan M, Mozdzan M, Chalubinski M, Wojdan K, Broncel M (2014) The effect of melatonin on circadian blood pressure in patients with type 2 diabetes and essential hypertension. *Arch. Med. Sci.* 10: 669-675.
139. Gubin DG, Gubin GD, Gapon LI, Weinert D (2015) Daily melatonin administration attenuates age-dependent disturbances of cardiovascular rhythms. *Curr. Aging Sci.*
140. Wirtz PH, Bartschi C, Spillmann M, Ehlert U, von Kanel R (2008) Effect of oral melatonin on the procoagulant response to acute psychosocial stress in healthy men: a randomized placebo-controlled study. *J Pineal Res* 44: 358-365.
141. Del Zar MM, Martinuzzo M, Cardinali DP, Carreras LO, Vacas MI (1990) Diurnal variation in melatonin effect on adenosine triphosphate and serotonin release by human platelets. *Acta Endocrinol. (Copenh)* 123: 453-458.
142. Del Zar MM, Martinuzzo M, Falcon C, Cardinali DP, Carreras LO, Vacas MI (1990) Inhibition of human platelet aggregation and thromboxane-B2 production by melatonin: evidence for a diurnal variation. *J. Clin. Endocrinol. Metab* 70: 246-251.
143. Vacas MI, Del Zar MM, Martinuzzo M, Falcon C, Carreras LO, Cardinali DP (1991) Inhibition of human platelet aggregation and thromboxane B2 production by melatonin. Correlation with plasma melatonin levels. *J. Pineal Res.* 11: 135-139.
144. Kozirog M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M (2011) Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. *J. Pineal Res.* 50: 261-266.
145. Goyal A, Terry PD, Superak HM, Nell-Dybdahl CL, Chowdhury R, Phillips LS, Kutner MH (2014) Melatonin supplementation to treat the metabolic syndrome: a randomized controlled trial. *Diabetol. Metab Syndr.* 6: 124
146. Romo-Nava F, Alvarez-Icaza GD, Fresan-Orellana A, Saracco AR, Becerra-Palars C, Moreno J, Ontiveros Uribe MP, Berlanga C, Heinze G, Buijs RM (2014) Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. *Bipolar. Disord.* 16: 410-421.
147. Modabbernia A, Heidari P, Soleimani R, Sobhani A, Roshan ZA, Taslimi S, Ashrafi M, Modabbernia MJ (2014) Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. *J. Psychiatr. Res.* 53: 133-140.
148. Mostafavi A, Solhi M, Mohammadi MR, Hamed M, Keshavarzi M, Akhondzadeh S (2014) Melatonin decreases olanzapine induced metabolic side-effects in adolescents with bipolar disorder: a randomized double-blind placebo-controlled trial. *Acta Med. Iran* 52: 734-739.
149. Shatilo VB, Bondarenko EV, Antoniuk-Shcheglova IA (2010) [Pineal gland melatonin-producing function in elderly patients with hypertensive disease: age peculiarities]. *Adv. Gerontol.* 23: 539-542.
150. Garfinkel D, Zorin M, Wainstein J, Matas Z, Laudon M, Zisapel N (2011) Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study. *Diabetes Metab Syndr. Obes.* 4: 307-313.
151. Gonciarz M, Gonciarz Z, Bielanski W, Mularczyk A, Konturek PC, Brzozowski T, Konturek SJ (2012) The effects of long-term melatonin treatment on plasma liver enzymes levels and plasma concentrations of lipids and melatonin in patients with nonalcoholic steatohepatitis: a pilot study. *J. Physiol Pharmacol.* 63: 35-40.
152. Gonciarz M, Gonciarz Z, Bielanski W, Mularczyk A, Konturek PC, Brzozowski T, Konturek SJ (2010) The pilot study of 3-month course of melatonin treatment of patients with nonalcoholic steatohepatitis: effect on plasma levels of liver enzymes, lipids and melatonin. *J. Physiol Pharmacol.* 61: 705-710.

- 153 . Hussain SA, Khadim HM, Khalaf BH, Ismail SH, Hussein KI, Sahib AS (2006) Effects of melatonin and zinc on glycemic control in type 2 diabetic patients poorly controlled with metformin. *Saudi. Med. J.* 27: 1483-1488.
- 154 . Mesri AN, Mahdavi R, Roshanravan N, Lotfi YN, Ostadrahimi AR, Faramarzi E (2015) A double-blind, placebo-controlled trial related to the effects of melatonin on oxidative stress and inflammatory parameters of obese women. *Horm. Metab Res* 47: 504-508.
- 155 . Rubio-Sastre P, Scheer FA, Gomez-Abellan P, Madrid JA, Garaulet M (2014) Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. *Sleep* 37: 1715-1719.
- 156 . Chojnacki C, Walecka-Kapica E, Klupinska G, Pawlowicz M, Blonska A, Chojnacki J (2015) Effects of fluoxetine and melatonin on mood, sleep quality and body mass index in postmenopausal women. *J. Physiol Pharmacol.* 66: 665-671.
- 157 . Tuomi T, Nagorny CL, Singh P, Bennet H, Yu Q, Alenkvist I, Isomaa B, Ostman B, Soderstrom J, Pesonen AK, Martikainen S, Raikkonen K, Forsen T, Hakaste L, Almgren P, Storm P, Asplund O, Shcherbina L, Fex M, Fadista J, Tengholm A, Wierup N, Groop L, Mulder H (2016) Increased melatonin signaling is a risk factor for type 2 diabetes. *Cell Metab* 23: 1067-1077.
- 158 . Amstrup AK, Sikjaer T, Pedersen SB, Heickendorff L, Mosekilde L, Rejnmark L (2016) Reduced fat mass and increased lean mass in response to 1 year of melatonin treatment in postmenopausal women: A randomized placebo-controlled trial. *Clin. Endocrinol. (Oxf)* 84: 342-347.
- 159 . Dominguez-Rodriguez A, Abreu-Gonzalez P, de la Torre-Hernandez JM, Gonzalez-Gonzalez J, Garcia-Camarero T, Consuegra-Sanchez L, Garcia-Saiz MD, Aldea-Perona A, Virgos-Aller T, Azpeitia A, Reiter RJ (2017) Effect of intravenous and intracoronary melatonin as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: Results of the Melatonin Adjunct in the acute myocardiAl Infarction treated with Angioplasty trial. *J. Pineal Res.* 62:
- 160 . Dominguez-Rodriguez A, Abreu-Gonzalez P, de la Torre-Hernandez JM, Gonzalez-Gonzalez J, Garcia-Camarero T, Consuegra-Sanchez L, Garcia-Saiz MD, Aldea-Perona A, Virgos-Aller T, Azpeitia A, Reiter RJ (2017) Early Treatment With Melatonin May Reduce Infarct Size in Patients With ST Segment Elevation Myocardial Infarction: Insights from the MARIA (Melatonin Adjunct in the acute myocardiAl Infarction treated with Angioplasty Trial. *Am J Cardiology*
- 161 . McMullan CJ, Rimm EB, Schernhammer ES, Forman JP (2017) A nested case-control study of the association between melatonin secretion and incident myocardial infarction. *Heart* 103: 694-701.
- 162 . Grossman E, Laudon M, Zisapel N (2011) Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. *Vasc. Health Risk Manag.* 7: 577-584.
- 163 . Tamura H, Nakamura Y, Narimatsu A, Yamagata Y, Takasaki A, Reiter RJ, Sugino N (2008) Melatonin treatment in peri- and postmenopausal women elevates serum high-density lipoprotein cholesterol levels without influencing total cholesterol levels. *J. Pineal Res.* 45: 101-105.
- 164 . Hussain SA (2007) Effect of melatonin on cholesterol absorption in rats. *J. Pineal Res.* 42: 267-271.
- 165 . Esquifino A, Agrasal C, Velazquez E, Villanua MA, Cardinali DP (1997) Effect of melatonin on serum cholesterol and phospholipid levels, and on prolactin, thyroid-stimulating hormone and thyroid hormone levels, in hyperprolactinemic rats. *Life Sci.* 61: 1051-1058.
- 166 . McMullan CJ, Curhan GC, Schernhammer ES, Forman JP (2013) Association of nocturnal melatonin secretion with insulin resistance in nondiabetic young women. *Am. J. Epidemiol.* 178: 231-238.
- 167 . Eckel RH, Depner CM, Perreault L, Markwald RR, Smith MR, McHill AW, Higgins J, Melanson EL, Wright KP, Jr. (2015) Morning Circadian Misalignment during Short Sleep Duration Impacts Insulin Sensitivity. *Curr. Biol.* 25: 3004-3010.

- 168 . Staiger H, Machicao F, Schafer SA, Kirchhoff K, Kantartzis K, Guthoff M, Silbernagel G, Stefan N, Haring HU, Fritsche A (2008) Polymorphisms within the novel type 2 diabetes risk locus MTNR1B determine beta-cell function. *PLoS. One.* 3: e3962
- 169 . Lyssenko V, Nagorny CL, Erdos MR, Wierup N, Jonsson A, Spegel P, Bugliani M, Saxena R, Fex M, Pulizzi N, Isomaa B, Tuomi T, Nilsson P, Kuusisto J, Tuomilehto J, Boehnke M, Altshuler D, Sundler F, Eriksson JG, Jackson AU, Laakso M, Marchetti P, Watanabe RM, Mulder H, Groop L (2009) Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. *Nat. Genet.* 41: 82-88.
- 170 . Langenberg C, Pascoe L, Mari A, Tura A, Laakso M, Frayling TM, Barroso I, Loos RJ, Wareham NJ, Walker M (2009) Common genetic variation in the melatonin receptor 1B gene (MTNR1B) is associated with decreased early-phase insulin response. *Diabetologia* 52: 1537-1542.
- 171 . Marchetti P, Syed F, Suleiman M, Bugliani M, Marselli L (2012) From genotype to human beta cell phenotype and beyond. *Islets.* 4: 323-332.
- 172 . Garaulet M, Gomez-Abellan P, Rubio-Sastre P, Madrid JA, Saxena R, Scheer FA (2015) Common type 2 diabetes risk variant in MTNR1B worsens the deleterious effect of melatonin on glucose tolerance in humans. *Metabolism* 64: 1650-1657.
- 173 . Barker A, Sharp SJ, Timpson NJ, Bouatia-Naji N, Warrington NM, Kanoni S, Beilin LJ, Brage S, Deloukas P, Evans DM, Grontved A, Hassanali N, Lawlor DA, Lecoeur C, Loos RJ, Lye SJ, McCarthy MI, Mori TA, Ndiaye NC, Newnham JP, Ntalla I, Pennell CE, St PB, Prokopenko I, Ring SM, Sattar N, Visvikis-Siest S, Dedoussis GV, Palmer LJ, Froguel P, Smith GD, Ekelund U, Wareham NJ, Langenberg C (2011) Association of genetic Loci with glucose levels in childhood and adolescence: a meta-analysis of over 6,000 children. *Diabetes* 60: 1805-1812.
- 174 . Espino J, Pariente JA, Rodriguez AB (2011) Role of melatonin on diabetes-related metabolic disorders. *World J. Diabetes* 2: 82-91.
- 175 . Bonnefond A, Clement N, Fawcett K, Yengo L, Vaillant E, Guillaume JL, Dechaume A, Payne F, Roussel R, Czernichow S, Herberg S, Hadjadj S, Balkau B, Marre M, Lantieri O, Langenberg C, Bouatia-Naji N, Charpentier G, Vaxillaire M, Rocheleau G, Wareham NJ, Sladek R, McCarthy MI, Dina C, Barroso I, Jockers R, Froguel P (2012) Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes. *Nat. Genet.* 44: 297-301.
- 176 . Karamitri A, Renault N, Clement N, Guillaume JL, Jockers R (2013) Minireview: Toward the establishment of a link between melatonin and glucose homeostasis: association of melatonin MT2 receptor variants with type 2 diabetes. *Mol. Endocrinol.* 27: 1217-1233.
- 177 . Lew KN, Wick A (2015) Pharmacotherapy of type 2 diabetes mellitus: navigating current and new therapies. *Medsurg. Nurs.* 24: 413-9, 438.
- 178 . Nauck MA, Friedrich N (2013) Do GLP-1-based therapies increase cancer risk? *Diabetes Care* 36 Suppl 2: S245-S252
- 179 . Weishaupt JH, Bartels C, Polking E, Dietrich J, Rohde G, Poeggeler B, Mertens N, Sperling S, Bohn M, Huther G, Schneider A, Bach A, Siren AL, Hardeland R, Bahr M, Nave KA, Ehrenreich H (2006) Reduced oxidative damage in ALS by high-dose enteral melatonin treatment. *J. Pineal Res.* 41: 313-323.
- 180 . Cardinali DP, Srinivasan V, Brzezinski A, Brown GM (2012) Melatonin and its analogs in insomnia and depression. *J. Pineal Res.* 52: 365-375.
- 181 . Oxenkrug GF, Summergrad P (2010) Ramelteon attenuates age-associated hypertension and weight gain in spontaneously hypertensive rats. *Ann. N. Y. Acad. Sci.* 1199: 114-120.
- 182 . She M, Hu X, Su Z, Zhang C, Yang S, Ding L, Laudon M, Yin W (2014) Piromelatine, a novel melatonin receptor agonist, stabilizes metabolic profiles and ameliorates insulin resistance in chronic sleep restricted rats. *Eur. J. Pharmacol.* 727: 60-65.

Figure Legends

Figure 1. The MS is the consequence of obesity-induced changes in adipocytokine secretion that lead to the development of systemic insulin resistance, type 2 and 3 diabetes mellitus, and cardiovascular disorders. Overnutrition that results from a combination of increased food intake and reduced energy expenditure leads to adipose tissue expansion, increased adipocyte size and number, and increased macrophage infiltration that, together, lead to increased free fatty acid release, dysregulated secretion from adipocytes of a variety of adipocytokines, including adiponectin, leptin and resistin and increased release from resident macrophages of the inflammatory cytokines (TNF- α , IL-6.) Dysregulated secretion of these adipokines elicits a variety of adverse effects on numerous tissues.

Table 1. Effects of melatonin in animal models of MS

Observation	Reference(s)
In rats fed from weaning with a high-fat diet melatonin decreased body weight gain, feed efficiency and plasma glucose, leptin and triglyceride levels	[53]
In middle-aged rats receiving a high caloric liquid diet, melatonin reduced weight gain and plasma insulin and leptin levels	[54]
In high-fat diet-fed mice, melatonin improved insulin sensitivity and glucose tolerance	[55]
In ovariectomized rats, melatonin was effective to reduce obesity	[56-58]
In olanzapine-treated rats, melatonin was effective to reduce obesity	[59]
In goldfish body weight gain and specific growth rate were reduced by melatonin treatment	[60]
Melatonin and its analog piromelatonin inhibited weight gain and improves insulin sensitivity in high-fat fed rats	[52]
In high-fat fed rats, melatonin attenuated body weight increase, the increase in plasma glucose, insulin, adiponectin, leptin, triglycerides and cholesterol levels, and counteracted disrupted 24 h patterns	[61]
Melatonin improves inflammation processes in liver and pancreas of senescence-accelerated prone male mice (SAMP8)	[62,63]
Melatonin reduced body weight gain, visceral adiposity, blood triglyceride and insulin levels and TBARS under a high calorie diet in rats.	[64]
In young male Zucker diabetic fatty rats melatonin treatment reduced mean weight gain without affecting food intake, decreased in a non-significant way blood pressure, and improved dyslipidemia	[65]
Melatonin improves MS induced by high fructose intake in rats without affecting food intake	[66-70]
Melatonin and its analog piromelatonin reduced blood pressure in spontaneously hypertensive rats	[71]
Melatonin prevents the development of the MS in male rats exposed to different light/dark regimens	[72]
Melatonin attenuates high fat diet-induced fatty liver disease in rats	[73]
Melatonin, given at the time of reperfusion, prevents ventricular arrhythmias in isolated hearts from fructose-fed rats and spontaneously hypertensive rats	[74]

Melatonin ameliorates low-grade inflammation and oxidative stress in young Zucker diabetic fatty rats	[75]
Melatonin improves hyperglycemia, hypertriglyceridemia, polyphagia, and polydipsia in streptozotocin diabetic rats	[76,77]
Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats	[78]
Melatonin normalizes clinical and biochemical parameters of mild inflammation in diet-induced MS syndrome in rats	[79]
Melatonin counteracts changes in hypothalamic gene expression of signals regulating feeding behavior in high-fat fed rats	[80]
Melatonin reduces obesity and restores adipokine patterns and metabolism in obese (ob/ob) mice	[81]
Melatonin nephroprotective action in Zucker diabetic fatty rats involves an inhibitory effect on NADPH oxidase	[82]
Melatonin prevents type 2 diabetes in high carbohydrate diet-fed male Wistar rats	[83]
Melatonin decreases fasting blood glucose, total cholesterol, LDL levels and MDA levels, and restores the vascular responses and endothelial dysfunction in diabetic, high-fat diet fed rats	[84]
Maternal melatonin supplementation during rat diabetic pregnancy improves the tolerance to myocardial ischemia/reperfusion injury in the offspring, via restoring cardiac IRS-1/Akt signaling	[85]
In rats with diet-induced obesity exposed to circadian disruption, treatment with melatonin alone or in combination with metformin modifies progression of metabolic dysfunction through improved adiposity, circadian activity, insulin sensitivity, and islet cell failure	[86]
Melatonin prevents non-alcoholic fatty liver disease in high-fat diet induced obese mice by decreasing body weight and reducing inflammation via modulation of the MAPK-JNK/P38 signaling pathway	[87]
Melatonin reverses liver apoptosis, mainly through intrinsic pathway and reversed endoplasmic reticulum stress and mitochondrial function in rats subjected to bile duct ligation	[88]
Melatonin reduces body weight, liver steatosis, and low-grade inflammation, and improves insulin resistance and gut microbiota in high-fat diet fed mice	[89]

Table 2. Clinical observations on melatonin relevance in MS.

FINDINGS	REF.
Low plasma melatonin levels in type 2 diabetic patients	[110,116-120]
Low plasma melatonin levels in pregnant women with hypertensive or glucose metabolic disorder complications	[121]
Increased number of melatonin receptors in type 2 diabetic patients	[111]
Melatonin receptor gene polymorphism associated with high risk of type 2 diabetes	[112,122-127]
Genetics of melatonin receptor type 2 is associated with left ventricular function in hypertensive patients and with increased risk of impaired fasting glucose in youth with obesity	[113,114]
Family association study between melatonin receptor gene polymorphisms and polycystic ovary syndrome	[115]
Low melatonin production in coronary disease independently of β -adrenoceptor blocker treatment	[128-131]
Among elderly hypertensive individuals, nocturnal urinary melatonin excretion is inversely associated with the non-dipper pattern	[132]
Melatonin treatment decreases nocturnal BP in type 1 adolescent diabetics	[133,134]
Melatonin treatment decreases high nocturnal BP in hypertensives	[135-138]
Melatonin administration attenuates age-dependent disturbances of cardiovascular rhythms	[139]
Melatonin treatment prevents catecholamine-induced hypercoagulability in normal volunteers	[140]
Melatonin inhibits human platelet aggregation in vivo and in vitro	[141-143]
Melatonin treatment ameliorates MS in obese patients	[144,145]
Melatonin treatment improves MS after treatment of bipolar and schizophrenic patients with 2 nd generation antipsychotics	[146-148]
Melatonin administration normalizes MS in elder hypertensive patients	[149]
Short-term use of prolonged-release melatonin improves sleep maintenance in type 2 diabetic patients with insomnia without affecting glucose and lipid metabolism. Long-term prolonged-release melatonin	[150]

administration has a beneficial effect on HbA1c, suggesting improved glycemic control	
Melatonin treatment improves enzymatic profile in patients with non-alcoholic liver esteatosis	[151,152]
The combination of melatonin and zinc acetate, when used alone or in combination with metformin improved glycemic control in type 2 diabetic patients	[153]
Melatonin treatment ameliorated oxidative stress and inflammatory parameters of obese women	[154]
Acute melatonin administration in healthy women impairs glucose tolerance	[155]
The combined administration of melatonin and fluoxetine was effective to treat mood, sleep and obesity in postmenopausal women	[156]
Increased MTNR1B expression occurred in human islets from risk G-allele carriers. Melatonin treatment in a human recall-by-genotype study reduced insulin secretion and raised glucose levels more extensively in risk G-allele carriers indicating that an increased melatonin signaling may be a risk factor for type 2 diabetes	[157]
Reduced fat mass and increased lean mass in response to 1 year of melatonin treatment in postmenopausal women	[158]
Evaluation of the efficacy and safety of melatonin for the reduction of reperfusion injury in patients undergoing revascularization for ST-elevation myocardial infarction indicated that intracoronary melatonin administration (median time >3.3 h earlier) was not associated with a reduction in infarct size	[159]
In a post-hoc analysis of the previously reported trial to assess whether the effect of melatonin was affected by the timing of reperfusion the main finding was that melatonin, when given <2.5 h after symptom onset, could reduce infarct size significantly by approximately 40%	[160]
A prospective nested case-control study of participants from the Nurses' Health Study cohorts I and II indicated that a lower melatonin secretion was significantly associated with a higher risk of myocardial infarct in women with augmented body mass index	[161]