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**Melatonin and metabolic regulation: a review**

**Miguel Navarro-Alarcón,\*,a Francisco J. Ruiz-Ojeda,a Rosa M. Blanca-Herrera,a María Mohamad-Akeel Serrano,b Dario Acuña-Castroviejo,c Gumersindo Fernández-Vázquezd and Ahmad Agil\*,b**

aDepartment of Nutrition and Food Chemistry, Faculty of Pharmacy, University of Granada E-18071 Granada, Spain .

bInstitute of Neurosciences, Department of Pharmacology, School of Medicine, University of Granada, E-18071 Granada, Spain

cInstitute of Biotechnology, Department of Physiology, School of Medicine, University of Granada, E-18071 Granada, Spain

dService of Endocrinology, Carlos III Hospital, Madrid, Spain

Correspondence to: Miguel Navarro-Alarcón & Ahmad Agil at Department of Nutrition and Food Science, School of Pharmacy, University of Granada, Spain (address to which request for reprints should be sent).

Tel. 34-958249766

Fax. 34-95829577

e-mail: [nalarcon@ugr.es](mailto:nalarcon@ugr.es) & [aagil@ugr.es](mailto:aagil@ugr.es)

Human life expectancy has increased over the past 50 years due to scientific and medical advances and higher food availability. However, overweight and obesity affect more than 50% of adults and 15% of infants and adolescents. There has also been a marked increase in the prevalence of the metabolic syndrome in recent decades, which has been associated with a reduction in nocturnal pineal production of melatoninwith aging and an increased risk of coronary diseases, type 2 diabetes mellitus (T2DM) and death. Melatonin is currently under intensive investigation in experimental animal models of diabetes, obesity and MS at pharmacological doses (between 5 to 20 mg kg-1 body weight), demonstrating its capacity to ameliorate the total metabolic profile and its potential as an alternative to conventional drug therapies for the disorders associated with the MS, i.e., elevated systolic blood pressure, and impairment of glucose homeostasis, plasma lipid profile, inflammation, oxidative stress, and increased body weight. An especially significant finding is the induction by melatonin of white adipose tissue browning, which may be related to its effects against oxidative stress, uncoupling the mitochondrial bioenergetic process by enhancing the expression of uncoupled-protein-1 (UCP-1), which has been related to body weight reduction in experimental animals. Further research is required to improve knowledge of this mechanism. Clinical studies are needed with the administration of pharmacological melatonin doses, because the dose has ranged between 0.050 and 0.16 mg kg-1 bw in most studies to date. Melatonin is a natural phytochemical, and it is also important to test its beneficial metabolic effects when consumed in functional foods.

**Introduction**

Metabolic diseases represent a failure of the body to resist persistent internal and external disturbances in biological systems.1 Metabolic diseases related to this complex breakdown of the normal body physiology include diabetes, cardiovascular disease (CVD), obesity and the metabolic syndrome, among others.

Life expectancy has markedly increased in Western countries over the past 50 years, largely attributable to scientific and medical advances and an increase in food availability. However, overweight and obesity now affect more than 50% of adults and 15% of children and adolescents worldwide, and this increase has been especially alarming in southern European countries.2,3 Changes in the behavior of European children include the adoption of unhealthy dietary habits and a decrease in physical activity.4 A sedentary lifestyle and the lack of sleep have also been described as risk factors for childhood obesity, with a report that the risk of obesity is increased in children sleeping <9 hrs/day.4

The premature infant obesity related to the above changes has been associated with the early development of diseases characteristic of older ages, including the metabolic syndrome, type 2 diabetes mellitus (T2DM), and CVD4,5 Hence there is a need for research-based preventive strategies aimed at inappropriate dietary habits and life style patterns during childhood, which is a critical period for the development of adiposity. The development of obesity and metabolic syndrome during childhood and adolescence is also influenced by genetic and psycho-social factors, which require further investigation to improve our understanding of the susceptibility to these disorders and their etiology.6 Thus, several genetic polymorphisms, such as those for peroxisome proliferator-activated receptor-gamma” (PPARg) and beta 3-adrenergic receptors (Adrb3), have been related to body weight loss7 and the metabolic syndrome.8 There is also scientific evidence that the gene for the dopamine receptor d4 (DRD4) plays a role in overfeeding.9

Once excessive fat deposition is established, it is highly resistant to treatment, and there is a clear tendency for overweight and obesity in childhood and adolescence to persist into adulthood.10 For this reason, it is crucial to prevent excessive fat deposits in early childhood. Hypertrophy and hyperplasia of adipocytes are characteristic during this period of life and are enhanced when fat deposition, with a tendency for this fat deposition to continue in adult life.10

Recent decades have seen a considerable increase in the prevalence of the metabolic syndrome, which is defined by the presence of at least three of the following: visceral obesity, hypertriacylglycerolemia, reduced high-density–lipoprotein cholesterol (HDL-c) levels, high systemic blood pressure (BP), and elevated fasting blood levels of glucose.11 The metabolic syndrome is associated with increased oxidative stress and the activation of pro-inflammatory cytokines and prothrombotic mediators.5,12-13 An extended oxidative status also diminishes antioxidant enzymes, producing lipid peroxidation. It has been reported that metabolic syndrome patients have a three-fold higher risk of coronary disease and two-fold higher risk of T2DM and death.12,14 Other researchers observed significantly reduced nocturnal melatonin in women with the metabolic syndrome.15

Various authors have demonstrated that melatonin has multiple beneficial effects on the organism. Thus, it is an important regulator of the circadian rhythm and is a potent antioxidant and anti-inflammatory hormone that enhances the activity of antioxidant enzymes and diminishes oxidative injury.16-18 Other trials reported that it reduces the BP, benefiting patients with the metabolic syndrome and inflammatory processes.19-20

Melatonin is a neurohormone synthesized nocturnally in mammals, mainly in the pineal gland1 but also in many other organs, such as the retina, ciliary body, brain, crystalline, aerial epithelium, platelets, bone marrow, bowel, placenta, lymphocytes, testes, ovary, and skin.1,21 Nevertheless, despite high extrapineal concentrations of melatonin,22 these do not participate in regulation of the circadian rhythm, given that surgical or chemical pinealectomy reduces nocturnal circulating melatonin levels to the low values observed during the day.

Melatonin participates in many other biological functions, including energy balance control.5,23 This indolamine and its metabolites also act as efficient radical scavengers, behaving as antioxidant and anti-inflammatory agents through the blockade of transcription factors by various mechanisms.24-38 Recent studies demonstrated that melatonin supplementation can diminish the body weight of rodents with melatonin deficiency due to pinealectomy, the extension of light periods, or aging.39-43 It has also been reported that melatonin administration diminishes the weight of middle-aged rats and those with diet-induced obesity 5,40,42, accompanied by a reduction in the associated visceral obesity, hyperinsulinemia, and hyperleptinemia.42,44 Melatonin has also been found to exert hypolipidemic effects in rats 5,45 and humans46-48, and melatonin treatment (10 mg/kg bw) significantly decreased cholesterol absorption in rats on a high-cholesterol diet.45 Melatonin has also been reported to reduce low-density–lipoprotein cholesterol (LDL-c) and triglyceride levels in diabetic patients and concomitantly raise their high- density–lipoprotein cholesterol (HDL-c) levels.46-49 Other researchers50 found that melatonin administration in peri- and post-menopausal women enhanced their HDL-c levels without affecting their concentrations of total cholesterol.

Melatonin is a non-conventional molecule whose action is mediated by receptors but is also independent of them and is not impeded by morpho-physiological barriers, e.g., cell membranes or the blood-brain barrier. Specifically, the melatonin has two membrane receptors (MTR1 and MTR2) that control seasonal reproduction, sleep modulation, bone growth, and osteoporosis.1,16,21,30,35-36,51 It also has other nuclear receptors whose physiological significance is poorly understood, although they appear to have a crucial role as regulators of epigenetic changes through the acetyl-binding of histones and/or methyl-binding of DNA enzymes.1,52-54

The chrono-disruption or breakdown of the circadian organization of physiology, endocrinology, and metabolism is associated with the increased lighting conditions that characterize advanced societies.55 This alteration produces an imbalance of biological rhythms and can participate in the development of certain cancers, with melatonin being a crucial and central biological mediator.56-57 Additionally, the disruption of the circadian rhythm and the associated diminishment of melatonin production at night by the pineal gland have been related to an increased breast cancer risk in epidemiological studies.58-59 It has been reported that melatonin levels diminish in rats during aging and suffering from circadian disruption, originating metabolic disturbances similar to those associated with the metabolic syndrome.60-61 These researchers found that the nocturnal administration of melatonin diminished age-related metabolism disorders in rats, namely abdominal obesity, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, hypo*-*beta*-*lipoproteinemia*,* and glycosuria.60 A case-control study nested in the Nurses’ Health Study Cohort (2000 participants monitored from 2000 to 2010)62reported that lower melatonin secretion was independently associated with a higher risk of developing T2DM.

Previous studies demonstrated the role of melatonin in the circadian rhythm at neurological level 63-68 and in diseases related to sleep disturbance, such as traumatic brain injury.64 Melatonin can prevent apoptosis and diminish oxidative stress.36-37,64,70 Stem cells are able to express the MTR1 specific receptor and/or MTR2, which participates in neuroprotection.71-72 The intra-cerebral transplant of melatonin secreted by the pineal gland ameliorated behavior disturbances in rats with cerebrovascular disease and may indicate a possible therapeutic approach to this disease. Treatment with exogenous melatonin also improved the survival of glia cells in brain ischemia. These and similar findings have led to research into the role of melatonin in the differentiation, proliferation and neuroprotection of stem cells.72 These novel findings have implications for the use of melatonin in neuroprotective strategies against Parkinson’s disease.72 Other researchers73 reported that physiological and pharmacological concentrations of melatonin act against oxidative stress and against the age-related decrease in nocturnal melatonin levels.

Melatonin is a natural component of some vegetables (e.g., alfalfa, almonds, black and white mustard, feverfew leaves, turmeric tuber, celery, flax, fennel, fenugreek, cherries, poppies, etc.), and there have been reports of its concentration in a number of plant-derived foodstuffs74-77 and on the beneficial effects of the melatonin alone or in combination with other components of vegetable origin.78 Elevated melatonin concentrations have been observed in beverages, such as coffee, tea, beer, and wine, as well as in corn, rice, wheat, and oats.75 It has been proposed that the antioxidant effects attributed to polyphenolic compounds (proanthocyanidins) in plants and by-products (e.g., wine, nuts, etc.) may also be due in part to other components, such as melatonin.74,79-81 Increased interest in the potential benefits of melatonin has led to studies on the optimal timing of cow milking to obtain the highest melatonin concentration in milk82 and on brewing methods to increase its concentration in beer.83 It is therefore an important research task to determine the concentrations of melatonin in plants and their by-products and the influential factors and to explore enhancement of their melatonin content by genetic engineering.

**Melatonin and body weight regulation**

Obesity has been described as the cigarette of the 21st century.78 Primary or exogenous obesity is a multi-factorial disorder that results from interaction between an unfavorable socio-cultural environment and polygenic predisposition in an individual. A positive energetic balance translates into excessive body fat, generally associated with an increased caloric intake favored by an obesogenic environment.84

Adipose tissue has classically been considered the main fat storage organ but is now also considered as an endocrine organ involved in the immune response, satiation, and insulin sensitivity, among others. Thus, adipocytes not only play a crucial role in the synthesis and regulation of triglycerides but also synthesize a series of adipocytokines, including; leptin, a hormone that regulates caloric intake; adiponectin, which increases insulin sensitivity,44 and hemodynamic vascular factors, such as cytokine-like tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) and chemokines, including macrophage chemotactic protein-1 (MCP-1).85-86 Obesity is characterized by low-grade inflammation generated by the activity of adipocytes and other cells, including macrophages and T-lymphocytes that infiltrate and are recruited by adipose tissue.87-88

The worldwide increase in the incidence of obesity over recent decades has been accompanied by a rise in the incidence of insulin resistance by two main mechanisms. One is antagonism of insulin action by high non-sterified-fatty-acids (NEFAs) and/or free-fatty-acids (FFAs), because the augmentation of adipose tissue increases the concentration of FFAs in the bloodstream, generating insulin resistance in the muscle and promoting serine phosphorylation. This leads to a lower translocation of GLUT-4 glucose transporters dependent on the phosphatidylinositol kinase-3, producing hyperglycemia and compensatory hyperinsulinemia that increase glycated protein concentrations (advanced glycated end products [AGEs]) and methylglyoxal (MG), whose levels are biochemical markers of T2DM.89 The excess of plasma FFA and glucose stimulates pancreatic insulin secretion, aggravating the hyper-insulinemia and leading to insulinopenia, due to the accumulation of pancreatic lipids in the blood and their toxic, apoptosis-promoting effects;90 T2DM is produced when this situation becomes chronic.90 The other main mechanism is antagonism of insulin action by adipocytokines derived from adipose tissue, such as TNF-α, which promotes insulin resistance in several tissues by inhibiting autophosphorylation of tyrosine residues of the beta subunit of the insulin receptor. Elevated leptin levels are characteristic of individuals with insulin resistance, obesity, and/or dyslipidemia, whereas plasma levels of adiponectin are inversely correlated with insulin resistance and glucose tolerance*.* Study of animal models of obesity and T2DM found that melatonin administration enhances FFA oxidation in the muscle, thereby reducing the hepatic glucose production that promotes weight loss and ameliorating insulin sensitivity and glucose tolerance.44 It was also reported that the administration of melatonin (25 µg/ml in drinking water) to male Wistar rats produced a significant weight loss in those with fully-developed fructose-induced metabolic syndrome.91

Daily melatonin administration was found to reduce abdominal fat and plasma leptin levels in middle-age male rats.40,44 It also affected body weight regulation in young rats with obesity induced by a high-fat diet (Table 1) and showed a preventive effect against the reduction in insulin sensitivity.42,44 It has been reported that melatonin reduces body weight gain without influencing the food intake,5,42,92-93 attributed to an increase in energy expenditure, especially in brown adipose tissue (BAT)23,43 or an increase in physical activity or even in the basal metabolic rate (BMR). However, findings on the influence of melatonin on locomotor activity in rats have been inconsistent,92 and its existence has not been established.93

Other studies in rodents have reported that melatonin increases the activity and mass of BAT; the mechanisms underlying these effects have not been elucidated, but various possible explanations have been proposed.23 Thus, it has been suggested that melatonin affects body adipose tissue mass a) via MTR1 and MTR2 membrane receptors; b) by central action on noradrenaline turnover; c) by direct activation of kinase C, which drives regulation of the growth factors responsible for adipocyte differentiation and mitochondrial biogenesis*; d*) *via* nuclear receptors in brown adipose cells; e) by mitochondrial activation of the uncoupled protein-1 (UCP1) or tyrosine 5’-diodinase type 2 activation, enhancing triiodothyronine (T3) levels.1,33,94-95

It was recently reported that the chronic oral administration of melatonin induces browning of inguinal white adipose tissue in Zücker diabetic fatty (ZDF) rats, a model of obesity-related type 2 diabetes, and their lean littermates (ZL). Melatonin was also found to increase uncoupling protein 1 (UCP1) and PGC-1α (thermogenic proteins) in extracts from beige inguinal areas in ZL rats. Hence, chronic oral melatonin treatment gives white adipose tissue a BAT-like function in ZDF rats.96

Observations in middle-aged male rats have suggested that the aging-related reduction in endogenous melatonin secretion can alter the regulation of energy, producing an increase in body weight and adiposity with their undesirable metabolic consequences.92 However, adequate nocturnal melatonin supplementation may be a prophylactic measure against aging-related changes in insulin resistance, intra-abdominal fat, and behavior.40,60 Administration of NEU-P11, a melatonin agonist, inhibited weight gain and improved insulin sensitivity in rats on a high-fat/high-sucrose diet.97

Although the link between obesity and T2DM is not fully understood, hypothalamic signaling pathways have been implicated. Gyte et al. (2007)98 compared Zücker fatty (ZF) and ZFD rats with ZL rats and found a reduced expression of the proopiomelacortin (POMC) gene in the fatty (ZF and ZDF) *versus* lean rats at all ages; they also observed a reduced expression of the channel component ATP-dependant K+ (KATP), known as Kirk 6.2 protein, in the obese rats. In a later study,99 it was found that the glucose excitation of hypothalamic neurons that synthesize melanin is also mediated by the KATP channel and is downregulated by UCP2 and that the glucose sensitization of these neurons plays a major role in the regulation of glucose homeostasis.

It is known that at least 10% of cellular transcription varies in a circadian manner. Molecular studies have reveal the direct coupling between clock genes and metabolism regulation, including the control of glucose homeostasis,100 lipid synthesis,101 and adipogenesis.102 It was observed that pinealectomy produces glucose intolerance and a daily decrease in insulin secretion by isolated pancreatic islets.1 In this regard, melatonin was found to increase the expression of leptin and its release from rat adipocytes in the presence of insulin and to enhance the effects of insulin on leptin expression.103

**(a) Role of melatonin and POMC-derived peptides in energy expenditure regulation**

POMC-derived melanocortin peptides are produced in various brain regions, especially in the hypothalamus, and have been related to energy homeostasis in studies of mice with and without the POMC system.104-106 This system comprises endogenous agonists and antagonists, melanocortin receptors, and accessory receptor proteins107 and is known to mediate in the regulation of energy homeostasis through hormones and other factors such as leptin, insulin, bowel hormones, and cytokines. Knowledge of all peptides derived from the POMC system is incomplete, although some are known to be related to the inhibition of food intake (adrenocorticotropin [ACTH], desacetyl-α-melanocyte-stimulating hormone [α-MSH], β -MSH and γ-MSH) as observed in rodents when these peptides were exogenously administered and their direct action in the brain were observed.

Obese POMC-null mice were not diabetic, although they showed impaired glucagon regulation,108 indicating that POMC-derived peptides may play a critical role in the regulation of glucagon production by pancreatic-α-cells. In addition, the central administration of α-MSH and β-MSH or γ-MSH peptides diminished hunger in POMC-null mice, but only α-MSH peptide significantly reversed the obesity.109 However, humans are unable to stay alive without adrenal glands and glucocorticoid hormones and those with a POMC-null mutation could only survive if supplemented with glucocorticoids since birth, and they would still suffer from hyperphagia and obesity.110 A significant increase in fatty and lean tissue and 23% reduction in basal energy expenditure were observed in POMC-null mice in comparison to normal wild mice of the same age;105 hence, the obesity phenotype of POMC-null mice may result from a reduced BMR as well an increased dietary intake.

Mechanisms underlying the regulation of obesity and T2DM by the POMC system also involve melanocortin 3 and 4 receptors (MC3R and MC4R, respectively), which are of critical importance in the hunger control of mammals111 and in their body weight regulation.112 It has been observed that a higher BMR due to MC4R is consistent with a higher protection against obesity in humans.107 Action of the agouti protein in obese animals and humans has been related to MC4R inhibition. Thus, MC4R regulates the food intake by increasing intracellular Ca2+, activating c-Fos expression and releasing oxytocin. In relation to energy expenditure, the weight gain was greater in POMC-null mice than in normal wild mice receiving the same amount of food, attributable to a lower energy expenditure in the former.113 Blockade of the central MC4R signal was found to promote insulin resistance in skeletal muscle and in BAT but not in WAT, in which glucose uptake and lipogenesis were stimulated.107

Much less is known about the role of MC3R in the regulation of energy homeostasis. MC3R-null mice had a moderate obesity phenotype and insulin resistance in comparison to MC4R-null mice. Interestingly, a deficiency in MC3R deficiency produces a worse synchronization of clock genes in the circadian rhythm. The highest density of messenger ribonucleic acid (mRNA) expression for MC3R synthesis is found in the forebrain and half habenular nucleus; the role of MC3R at these localizations is unknown, but these brain regions are additional sites of melatonin synthesis besides the pineal gland.114 Hence, MC3R may possibly be involved in the circadian rhythm and food intake regulation. It was also reported that MC3R may be one of the melanocortin peptides most responsible for their anti-inflammatory properties, which could also influence energy homeostasis.107 Thus, obesity is associated with a chronic low-grade inflammation due to an imbalance between pro- and anti-inflammatory cytokines synthesized in the adipocytes and macrophages that infiltrate adipose tissue, liver, and muscle.115

Agouti-related peptide (AgRP) acts as an antagonist of both MC3R and MC4R, and its administration and over-expression in the brain rat promotes weight gain by enhancing food intake and decreasing energy expenditure.116

The POMC system can be peripherally regulated by leptin, insulin, and bowel hormones (e.g., hunger hormone ghrelin or satiety hormone cholecystokinin), nutrients (e.g., glucose, leucine, etc), and cytokines (IL-18).107 When circulating levels of leptin are high, it is known to activate its receptor in POMC neurons responsible for releasing melanocortin peptides such as α-MSH, which inhibits food intake except in obese individuals with leptin resistance.117 Leptin also decreases food intake *via* a mechanism that involves increased sensitivity to satiety signals.118

Insulin can regulate energy homeostasis by acting on POMC neurons or AgRP, as shown in a study119 on insulin signaling in the hypothalamus in relation to energy expenditure and glucose production. Insulin signaling in AgRP neurons was found to reduce liver production of glucose, whereas insulin signaling in POMC neurons increased this production and enhanced the melanocortin-mediated enhancement of energy expenditure.

In the normal metabolism of neurons, glucose ATP interacts with and closes KATP channels, producing decreased depolarization, external K+ flow, membrane depolarization of POMC neurons, enhancement of electric activity, and stimulation of α-MSH release.120 However, in wild mice fed with a high-fat diet for 20 weeks whose UCP2 activity was also enhanced, the glucose did not produce sufficient ATP to stimulate α-MSH release from the POMC neurons.121

Recent studies reported the capacity of melatonin to positively regulate leptin, adiponectin, insulin, and glucose levels (Table 2), improving the global energy metabolism in obese and diabetic Zucker rats.44 As reported above, the metabolism and effects of these hormones is related to the POMC system. Therefore, future studies are required to investigate whether the action of melatonin on hormones and the melanocortin system and therefore on the positive regulation of the glucose metabolism characteristic of T2DM is exerted *via* these hormones and/or directly by its effect on the POMC system, taking into account its ability to cross the blood-brain barrier, given its small size and amphiphilic character.

# Melatonin and regulation of hyperglycemia, dyslipidemia and postprandial dysmetabolism

Food is consumed more frequently in advanced modern societies, and events in the postprandial period can promote homeostasis disruption or dysmetabolism1, directly related to metabolic diseases, even when fasting biochemical processes are normal and individuals have euglycemic levels and a normal lipid profile.1 Several studies have identified patients with normal fasting glucose levels (90 mg/dL) who show postprandial glucose levels >200 mg/dL at 2 hrs after intake.122 It is generally considered that dysmetabolism in the first years of life increases the risk of postprandial hyperglycemia and the onset of T2DM.

Postprandial glucose levels of around 140 mg/dL reveal a certain glucose intolerance or pre-diabetic status in individuals, which can predispose to CVD.123 Glucose intolerance leads to hyperglycemia,124 usually associated with dyslipidemia development, which eventually contributes to endothelial and pancreatic β-cell dysfunction,33,125 various inflammatory processes, and the enhancement of oxidative stress.

T2DM is characterized by chronic hyperglycemia and the development of micro- and macro-vascular complications.126 Researchers found that hyperglycemia can increase reactive oxygen species (ROS) production from the mitochondrial electron transport chain, concluding that this event may be a key to the development of diabetic alterations. They also reported that the inhibitor complex II (tenoil trifluoracetone and uncoupling of carbonyl cyanide-chlorophenyl hydrazone) completely prevents the effect of hyperglycemia on ROS production. This effect was also inhibited by overexposure to UCP1 or manganese superoxide dismutase-dependent (Mn-SOD) antioxidant enzyme.127-128 Another group studied the impact of single nucleotide polymorphisms on glucose metabolism and insulin secretion in a Chinese population; they found that genotypes of the 2-catalytic subunit of glucose-6-phosphatase (G6PC2) and of melatonin receptor 1B (MTR1B) modulated fasting glucose levels in normo-glycemic individuals, while variants of G6PC2 and glucokinase regulatory protein (GCKR) were associated with T2DM.129 Likewise, other researchers associated common variants of MTNR1B, G6PC2 and GCKP genotypes with elevated fasting glucose plasma levels and reduced insulin secretion, showing that these alleles can trigger or perpetuate hyperglycemia in predisposed individuals.130

In mouse experiments, removal of the receptor was associated with increased insulin resistance and insulin metabolism impairment.131 The authors concluded that MTR1 may be involved in the pathogenesis of T2DM, opening the way for further investigation on mechanisms by which MTR1 signaling can affect glucose metabolism.

Melatonin exerts its influence in the periphery through activation of two specific receptors: MTR1 and MTR2. Both isoforms are expressed in islets of Langerhans and are involved in modulating insulin secretion from β-cells and glucagon secretion from α-cells. The desynchrony of receptor signaling may lead to the development of T2DM, and genome-wide association studies have identified MTR2 activation as a risk factor for melatonin disturbance. Melatonin also has a diurnal impact on the blood glucose-regulating function of the islets, and a study in diabetic rat models found an inverse relationship between melatonin and insulin, with an increase in melatonin leading to a downregulation of insulin secretion and *vice-versa* .132

It has not been established whether mitochondrial ROS are associated with T2DM complications. However, the association between 8-hydroxideoxyguanosine (8-OHdG) and the severity of diabetic alterations has been studied, because 8-OHdG is a product of oxidative DNA damage and can therefore serve as a sensitive mitochondrial biomarker of *in vivo* oxidative stress, being around 16-fold more abundant in the mitochondrial *versus* nuclear DNA.133 Other researchers126 found a positive and significant correlation in T2DM patients between the urinary excretion of 8-OHdG and glycated haemoglobin (HbA1c), suggesting that hyperglycemia may increase their mitochondrial ROS production. They reported that glycemic control with intensive insulin therapy can normalize mitochondrial ROS production and thereby delay the onset and progression of early stages of micro- and macro-vascular complications, finding a lesser thickness of intimal and medial layers of the carotid and a 2- to 3-fold reduction in urinary elimination of 8-OHdG.

The effects of melatonin on glucose body metabolism remains controversial. Several authors reported a close relationship between insulin and melatonin due to the effect of melatonin on pancreatic islets, specifically on their insulin secretion capacity.44,134 Various studies have found that melatonin decreases glucose-induced insulin release in mice and rats.135-136 In this context, studies in rats found that the nocturnal increase in melatonin synthesis was reduced with elevated insulin and leptin levels, and that melatonin can prevent the aging-related increase in insulin resistance.41 A significant reduction of melatonin secretion was observed in an animal model of T2DM (Goto-kakizaki rats),137 as also reported in humans with T2DM.138 Experiments in diabetic rats have reported that melatonin influences insulin secretion through effects on the circadian rhythm, leading to a decrease in glucose blood levels,44,137,139-140 (Table 2). It was recently reported that the administration of melatonin to ZDF rats diminished their plasma Cr and V levels,141 which may be one of the mechanisms by which it ameliorates glucose and insulin metabolism.44

A reduction in melatonin has been associated with T2DM genesis, and it has been proposed that pancreatic receptors of β-cells for melatonin are coupled to three parallel signaling pathways with different influences on insulin secretion: (a) cyclic adenosine monophosphate (cAMP) pathway, leading to the inhibition of insulin secretion; (b) MTNR2 pathway, inhibiting the guanylate cyclase/cyclic guanosine monophosphate pathway and therefore insulin secretion; (c) inositol triphosphate (IP3) pathway, which augments insulin by mobilizing calcium.134

It would be of interest to determine whether melatonin can exert a preventive effect against T2DM *via* a similar mechanism similar to that of nicotinamide and aminoguanidine, which prevent nitric oxide synthase expression in the pancreatic islets, decreasing β-cell dysfunction and breakdown and reducing hyperglycemia in ZDF rats,142 I*n vivo* and *in vitro* studies have reported that melatonin attenuates metabolic disorders and oxidative stress in T2DM.143-147 (Table 2). It has been reported that oxidative stress significantly decreased insulin cell signaling and glucose uptake by the adipocytes, which are both characteristic features of T2DM. The positive effects of melatonin against oxidative stress are likely attributable to its action as oxy-radical scavenger.

Neurogenic differentiation factor (NeuroD) is a transcription factor involved in the differentiation of neurons and in the control of energy balance and metabolism, and it plays a key role in type 1 and 2 diabetes. Neurogenic differentiation factor (NeuroD) mRNA levels show a day/night variation that is independent of the molecular clock gene mPER1 but depends on MTR1. Melatonin affects NeuroD expression in the gastrointestinal tract by acting on MTR1 receptors and may therefore contribute to the circadian regulation of metabolic functions.148

In T2DM, hyperglycemia is accompanied by dyslipidemia, which is a known contributor to endothelial cellular β-cell dysfunction. It has been suggested that postprandial hyperglycemia, with high triglyceride levels, chylomicron remnants, and FFAs, is implicated in the development of inflammation and especially oxidative stress, which can in turn exacerbate the adverse effects of postprandial hyperglycemia.149 One of the characteristic features of T2DM is the elevation of blood FFA levels, which are significantly diminished after melatonin supplementation due to its stimulation of non-shivering thermogenesis in the BAT. Melatonin appears to produce a greater entry of FFAs into the mitochondria, significantly reducing their plasma levels.

In regard to dyslipidemia, melatonin administration significantly ameliorated the lipid profile (Table 3) in a ZDF rat model of T2DM and significantly reduced the characteristic hypertriglyceridemia in this disease.5,150 Similar results were obtained in Sprague-Dawley rats on an obesity-inducing diet.41 Melatonin would act by suppressing visceral fat without affecting subcutaneous deposits,40,92 ameliorating insulin sensitivity by enhancing protein lipase activity and reducing lipolytic activity in visceral adipose tissue.40 Other effects associated with melatonin administration include a reduction in blood levels of LDL-cholesterol and its protection from oxidation,125,151-153 supporting the role of this indolamine in the prevention of atherogenesis. Mechanisms proposed to underlie this effect include: inhibition of cholesterol absorption,45 enhancement of LDLc receptor activity, inhibition of cholesterol synthesis, and increase of cholesterol catabolism into bile acids.154-156 In the clinical setting, the therapeutic aim in obese and diabetic patients is to decrease LDLc and triglyceride levels and to increase HDLc levels. Melatonin has been reported to have a hypolipidemic effect in diabetic patients with dyslipidemia46-48 and to enhance plasma HDLc levels in peri- and post-menopausal women without altering total cholesterol concentrations.48 (Table 3). A study in patients with the metabolic syndrome157 found that a high melatonin:insulin ratio was negatively correlated with LDL-cholesterol and T-cholesterol and positively correlated with HDL-cholesterol.

The role of pineal melatonin in preventing and delaying the onset of the T2DM has not been fully elucidated, although it has been reported to have beneficial effects after the development of clinical diabetes features.44,158 Further research is warranted in pre-diabetic stages, before the clinically evident onset of T2DM and using young animals or humans (infants or adolescents), in order to support the development of preventive approaches to this disease.

Gonzalez-Flores et al. (2012)78 published an interesting study on the potential of melatonin as a component of functional foods, finding that the consumption by young, middle-aged, and elderly subjects of the juice of red grapes (Tempranillo variety; 200 ml, twice daily for 5 days), stabilized by high hydrostatic pressure, increased their urinary 6-sulfatoxymelatonin levels and total urinary antioxidant capacity.

With regard to the physiological effects of melatonin on the organism, most studies administered a high dose, and the usual pharmacological dose in animal models is 100-fold higher than physiological plasma levels in humans. This makes it difficult to distinguish between the pharmacological and physiological effects of melatonin, which needs to be addressed in future studies. In this context, various authors have recently measured melatonin levels in vegetables, as the main dietary source of this indolamine, which are also associated with antioxidant effects that have been exclusively attributed to their polyphenolic compound content until now.74-76,78-81,159-160 Therefore, the therapeutic potential of melatonin is a great interest, especially from dietary sources. Epidemiological studies are required across countries to test the correlation between the dietary intake of melatonin and the prevalence of diabetes and obesity, among other diseases related to oxidative-stress and circadian rhythm disorders related. To date, most studies of melatonin supplementation have been performed using supra-physiological doses in animal models of diabetes and obesity.

**Melatonin and oxidative stress regulation**

Generally, melatonin reduces oxidative stress through several mechanisms such as hydroxyl (OH●), peroxyl (LOO●) and/or nitric oxide (NO●) radical scavenging or by the stimulation of antioxidant enzymes, namely superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase or glutathione reductase (GSH);161-164 It has been reported that the antioxidant effect of melatonin and its derivatives can detoxify harmful reactants and decrease molecular damage, which has clinical implications, given the considerable number of aging-related diseases with a major free radical component.33,35 One theory proposed to explain the aging processes implicates ROS and reactive nitrogen species (RNS) and their derivatives as causative agents.165 In a study of lipid peroxidation in aging, Dimitrev and Titov89 (2010) described two opposite trends: an anti-aging effect attributable to the anti-radical action of melatonin; and a pro-aging effect based on the action of toxic aldehydes.

The findings of basic research have suggested that melatonin administration might be useful to modify progression of some diseases and prevent some aging signs, and further research is warranted to develop the clinical relevance of these observations. Thus, it has been reported that melatonin is highly effective to attenuate oxidative stress biomarkers in neonates.33

Several authors have argued that melatonin is not likely to be a relevant antioxidant *in vivo,* because its physiological concentration is too low in comparison with other antioxidants to detoxify radical products and by-products.33 They assumed a balance between the low blood concentrations of this indolamine, even at night, when they reach the nanomolar range, with concentrations in tissues and cells.159 However, other body fluids, including ovarian follicular, biliary, and cerebrospinal fluids contain much higher concentrations of melatonin,166-167 and numerous tissues and cells have the capacity for its production.159

Various studies have reported that melatonin acts as a free radical scavenger.143,168 In one *in vitro* study in primary human muscle cells, oxidative stress strongly decreased insulin signaling and therefore glucose uptake, and both effects were markedly ameliorated by melatonin in its role as ROS scavenger. Konar et al.169 (2007) performed a supplementation study with melatonin and other antioxidants (vitamin E and C, and Se) reporting a protective effect against the oxidative damage induced by a high cadmium dose in rats. Venkataraman et al.170 (2010) also found that melatonin supplementation significantly reversed the neuronal damage associated with the enhanced oxidative stress produced by neurotoxic substances such as polychlorinated biphenyls (PCBs). Specifically, the supplementation increased the activity of antioxidant enzymes such as total SOD, Zn/Cu-dependent SOD (cytoplasmic Zn/Cu-SOD), Mn-dependent SOD (mitochondrial Mn-SOD) and GSH-Px, and enhanced the mRNA of these enzymes in brain regions (cerebral cortex, cerebellum, and hippocampus) of adult rats exposed to the aforementioned neurotoxic substances. Melatonin supplementation was found to augment plasma Se levels in ZDF and ZL rats as a previous step to the enhancement of GSH-Px activity.171 Melatonin was also reported to reduce oxidative stress by decreasing lipid peroxidation in plasma, erythrocytes, and the cortical region in ovariectomized rats172 and ZDF rats, with an especially marked reduction in erythrocyte GSH-Px levels in comparison to controls.44 Likewise, Chang et al.173 (2008) observed that melatonin preserves SOD oxidative reactivity, suggesting that it might serve as a potent agent to treat oxidative damage in peripheral nerves.

Another group171 found that melatonin enhanced the longevity of aging (10-month-old) female mice, decreasing lipid peroxidation and enhancing GSH-Px and GSH enzyme activities. Specifically, the study highlighted an increased mitochondrial vulnerability to oxidation in these mice that was counteracted by melatonin treatment. The researchers reported that melatonin regulated oxidative stress by ameliorating the mitochondrial respiratory chain and ATP production under different experimental conditions174 and by decreasing O2 consumption as a function of its concentration, inhibiting increased O2 flux in the presence of ADP excess and decreasing the membrane electrochemical potential, thereby inhibiting O2●- and H2O2 production. At the same time, melatonin maintained the efficiency of oxidative phosphorylation and ATP synthesis and enhanced the activity of respiratory complexes (mainly complexes I, II and III). These effects appeared to be attributable to the presence of melatonin and support the hypothesis that melatonin and T3 participate jointly in the physiological regulation of mitochondrial homeostasis.175 As previously noted, melatonin administration induced the browning of inguinal WAT in ZDF rats.96 It enhances UCP1 expression and therefore reduces O2•- production in the electron transport chain in the mitochondria, eventually producing a reduction in total peroxidation and malonaldehyde levels.36

With regard to the oxidative stress produced by anticancer agents,176 Abraham et al. (2010), in a rat study, found that melatonin attenuated the oxidative stress induced by methotrexate (used in chemotherapy) and the kidney damage by significantly reducing malonaldehyde levels and increasing the activity of antioxidant enzymes (SOD, GSH-Px, catalase, GSH and glutathione S transferase [GST]) in the kidney. These biomarkers were also improved by melatonin treatment in other experimental studies (Table 4). Other researchers27 found that co-administration of melatonin with the chemotherapeutic agent adriamycin normalized catalase and GSH-Px activities and reduced levels of thiobarbituric acid reactive substances (TBARS) and protein carbonyls in comparison to rats treated with adriamycin alone. In a previous study,177 reported that melatonin protects against the DNA adduct formation induced by the carcinogen safrole, partly through its hydroxyl radical scavenging capacity. Others178 reported the antioxidant effect of N-acetyl-5-methoxykynuramine, a melatonin metabolite that is a potent singlet oxygen scavenger.

A study in platelets of human origin treated with oxidized-LDL found that melatonin supplementation significantly decreased malonaldehyde, protein carbonyl, and phosphatidylserine levels.153 Melatonin was also shown to enhance the antioxidant action of α-tocopherol and ascorbate against Fe-dependent lipid peroxidation and nicotinamide adenine dinucleotide phosphate (NADPH) in human placental mitochondria in a concentration-dependent manner,179 exerting its antioxidant action as a free radical scavenger rather than metal chelator. It was found that the antioxidant activity of melatonin was synergistic with that of ascorbate and additive with that of vitamin E. It was also observed180 that melatonin treatment before the injection of kainic acid had a protective effect on catalase and SOD activities in the rat cerebral cortex and increased the nitrite:nitrate ratio.

Another group181 reported that an elevated concentration of melatonin inhibits *in vitro* LDL peroxidation but does oxidize LDL in cultured endothelial cells, concluding that melatonin *per se* appears to have little antiatherogenic action in the *in vitro* oxidation of LDL. Markedly larger atherosclerotic lesions were observed in the proximal aorta of hypercholesterolemic mice on an atherogenic diet supplemented with melatonin,182 suggesting that caution should be taken in prescribing high melatonin doses to hypercholesterolemic patients. In another study, the same authors182 reported that the capacity of melatonin (among other molecules) to inhibit atherogenic lipoprotein oxidation *in vitro* does not predict their capacity to inhibit atherosclerosis development *in vivo*. Others observed an inverse relationship between urinary 6-sulfatoxymelatonin level and independent risk factors for CVD, including uric acid and high–sensitivity C reactive protein (CRP).183

A study184 in hypoxic rats found significantly increased serum and hippocampus malonaldehyde levels, apoptotic cell death and mRNA levels of inflammatory mediators (TNF-α or inducible nitric oxide synthase [iNOS]) and reduced mRNA levels of SOD-Zn/Cu and catalase in hypoxic *versus* normoxic rats. However, in comparison to vehicle-treated hypoxic rats, melatonin-treated hypoxic rats showed significantly reduced serum and hippocampus malonaldehyde levels and expression of inflammatory mediators, with an absence of apoptosis and enhanced activity of the aforementioned antioxidant enzymes.

In summary, multiple direct and indirect mechanisms underlie the antioxidant capacity of melatonin,65,159,185-186 including: induction of antioxidant enzymes (GSH-Px, catalase and SOD);162 inhibition of nitric oxide synthase, by which it also exerts an important anti-inflammatory activity;165,175 and amelioration of the mitochondrial electron transport chain: These multiple actions have been associated with oncostatic, immune-modulatory, anti-aging and neuroprotective effects.44,54,125 A study of rats treated with adriamycin found that melatonin regulated oxidative stress by modulating plasma levels of free Fe through chelation and soluble complex formation,27 suggesting a potential role in cancer chemotherapy. However this effect was not observed in melatonin-supplemented ZDF rats.162

Bertuglia and Reiter147 (2009) observed that a 4-week melatonin supplementation of hamsters with intermittent hypoxia (characteristic of obstructive sleep apnea) diminished their ROS and nitrate/nitrite levels, which play a major role in micro-vascular dysfunction in intermittent hypoxia.

*In vitro* and *in vivo* studies in experimental animals (Table 4) have proposed various mechanisms by which antioxidant effects are exerted. Antioxidant systems include non-enzymatic proteins (transferrin, ferritin, *c*eruloplasmin, albumin, etc), enzymes (Cu,Zn-SOD, Mn-SOD, catalase, and GSH-Px), oxidizable molecules (GSH, vitamins A, E and C, carotenoids, flavonoids), and trace elements (Cu, Zn, Se and Fe). However, these systems can be overwhelmed under pathological conditions, e.g., CVD,187 explaining the research interest in novel antioxidant molecules able to inhibit oxidative stress by restoring the balance between ROS and antioxidants. The main advantage of melatonin in comparison to the above antioxidant systems is precisely its capacity to restore the oxidative balance and to ameliorate oxidative stress-related disease due to its amphipathic character, allowing it to cross the cell membrane and reach the mitochondria, where it exerts a direct antioxidant effect against free radical generation during oxidative metabolism (Table 4).96,171,174-175 However, most of the available evidence derives from animal or laboratory studies, and there is a need to test this effect with clinical trials in humans in different physiological and pathological conditions. In addition, given its beneficial metabolic effects and preventive actions, further data are required on the levels of melatonin in food, determining the main dietary sources and influential factors, such as climate, plant species, growing conditions, technological and culinary treatment, and storage conditions, among others.

As noted above, various studies159,171,174-175 have addressed the role of melatonin as an antioxidant molecule against ROS and NOS and its support for the activity of antioxidant enzymes (Table 4). However very little information is available on the possible influence of melatonin on the tissue and blood levels of minerals involved in the oxidative metabolism, i.e., Zn, Cu, Mn, Se, and Fe.162,169,188 These minerals act as enzymatic cofactors of the antioxidant enzymes reported above, and an increase in blood Cu and Fe levels is related to increased oxidative stress. Our research group measured plasma levels of the five minerals in ZDF and ZL rats,5,44,162 finding that plasma Fe, Cu and Mn levels were significantly lower in ZL rats than in ZDF rats, related to the increased oxidative stress in diabetes and obesity. Melatonin administration significantly enhanced plasma Se levels in both groups (M-ZDF and M-ZL),157 probably as a previous step to the enhancement of GSH-Px activity.162

It was recently reported that intestinal Ca2+ absorption is inhibited by menadione, through oxidative and apoptosis mechanisms,70 and restored by melatonin treatment. This finding underscores the importance of Ca2+ metabolism in the regulation of cellular oxidative stress and apoptosis, and further research is warranted on the effects of melatonin administration on Ca2+ homeostasis.

**Melatonin and blood pressure control**

It has long been known that the systemic BP is variable and reduced (by 10-20%) during sleep in humans. It rises after waking until mid-morning and then progressively declines throughout the rest of the day.1,189-190 However, the nocturnal fall in BP does not take place in 30-35% of hypertensive patients, which has been related to insulin resistance, obesity, and coronary heart disease191-192 and an increase in cardiovascular mortality and morbidity.189

Melatonin has been found to ameliorate hypertension in studies in rats, rabbits and humans. It reduced BP to normal ranges in hypertensive rats,193 rats with hypertension due to NO deficiency,194 and female rabbits with food-induced obesity.195 Melatonin administration lowered the BP196 of hypertensive women, a dose of 2.5 mg/day normalized the BP in men with essential hypertension,190 and nocturnal melatonin supplementation had a positive effect on the diastolic BP of women with type 1 diabetes mellitus (T1DM).197 For these reasons, indolamine has been proposed as an anti-hypertensive drug. Melatonin may also have a greater effect in patients with whose BP is not reduced at night.1 Melatonin administration for 6 weeks (10 mg/kg) reduced inflammation of the interstitial kidney tissue and oxidative stress in spontaneous hypertensive rats, associated with an attenuation of kidney transcription factors193 and BP reduction. Melatonin was also reported to restore the norepinephrine concentration and proportion of heart β1/β2 receptors in animals198 and to improve the maximum relaxation of mesenteric arteries. However, our research group found that melatonin supplementation (10 mg/day) only tended to reduce the systolic blood pressure (p= 0.056) in middle-aged male ZDF rats.5

A study in hypertensive humans reported that the melatonin administration (2.5 mg/day) decreased nocturnal systolic BP and diastolic BP.190 Among the various BP-lowering mechanisms of melatonin, its antioxidant effects appear to be the most important. Several animal studies suggest that melatonin can exert hypotensive action *via* melatonin receptors in the hypothalamus by influencing the release of catecholamine, modulating the response of beta-receptors and enhancing Endotelial nitric oxide synthase enzyme (eNOS) activation and NO synthesis.199 This enhancement in eNOS activity may be associated with a rise in the Ca concentration of endothelial cells. In contrast, *in vitro* studies found that high melatonin concentrations can neutralize NO.200

Continuous light exposure is known to lead to melatonin deficiency and complex neurohormonal activation, resulting in the development of hypertension in rats. In one study, rats were supplemented with melatonin (10 mg/kg/24 h) and captopril (100 mg/kg/24 h) and exposed to continuous light; the authors concluded that melatonin may reduce the stiffness of the aorta and small arteries, pulse wave and peripheral vascular resistance in continuous light-induced hypertension.201

In male Witsar rats treated for four weeks, melatonin evidenced similar renoprotective effects against doxorubicin-induced nephrotoxicity to those shown by captopril, olmesartan, and angiotensin II type 2 receptor agonist compound 21.202

Melatonin can influence the BP *via* the specific pathways of receptors in peripheral vessels or in parts of the central nervous system. Key questions remain to be answered about the prolonged use of melatonin to treat hypertension, such as the dose and administration route and the selection of the patients most likely to benefit. However, this indolamine appears to be a promising candidate to treat arterial hypertension.203 Thus, after two months of melatonin (5 mg/day, 2 h before bedtime), a significant fall in systolic blood pressure (SBP) was observed in patients with the metabolic syndrome.204

Both piromelatine (a melatonin agonist) and melatonin were found to exert an antihypertensive effect on systolic BP in spontaneously hypertensive Wistar-Kyoto rats during the morning and during the evening,20 and melatonin reported that melatonin counteracted systolic BP elevation in rats with fully established fructose-induced metabolic syndrome.91

**Conclusion**

Chronic melatonin administration counteracts various metabolic disorders in experimental animals, especially attributable to the browning of WAT, as found in ZDF rats. The ameliorative effects of melatonin on the total metabolic profile indicate that it may constitute an alternative to classic drugs used to treat the metabolic syndrome, besides its current indication for sleep disorders. In addition, pharmacological doses of melatonin in animal models of T2DM, obesity and/or metabolic syndrome reduced body weight gain, improved the lipid profile and glucose homeostasis, reduced low-grade inflammation, oxidative stress levels and systolic BP. Melatonin is a natural phytochemical with beneficial effects on the total metabolic profile and there is a need for studies into its levels in food and by-products in different countries to determine the dietary intake of this indolamine by distinct populations. These data would support epidemiological studies on the relationship between the metabolic syndrome and melatonin intake. An area of special interest is the development of functional foods, and research is also warranted into the benefits of enriching foods with melatonin.

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**Abbreviations**

ACTH Adrenocorticotropin

AGEs Advanced glycated end products

Adrb3 Beta 3-adrenergic receptors

AgRP Agouti-related peptide

cAMP Cyclic adenosine monophosphate

BAT Brown adipose tissue

BP Blood pressure

BMR Basal metabolic rate

CAT Catalase

CRP C reactive protein

CVD Cardiovascular disease

DNADeoxyribonucleic acid

DRD4 Dopamine receptor d4

FFAs Free-fatty-acids (FFAs)

G6PC2 Glucose -6-phosphatase

GCKR Glucokinase regulatory protein

GSH Glutathione reductase

GSH-Px Glutathione peroxidase enzyme

GST Glutathione S transferase

HbA1c Glycated haemoglobin

HDL-c High-density–lipoprotein cholesterol

IL-1 Interleukin-1

IP3 Inositol triphosphate

LDL-c Low-density–lipoprotein cholesterol

LOO● Peroxyl radical

MCP-1 Macrophage chemotactic protein-1

MC3R Melanocortin 3 receptor

MC4R Melanocortin 4 receptor

MG Methylglyoxal

Mn-dependent SOD Mitochondrial Mn-SOD

α-MSH Desacetyl-α-melanocyte-stimulating hormone

β -MSH Desacetyl-β-melanocyte-stimulating hormone

γ -MSH Desacetyl-γ-melanocyte-stimulating hormone

MTR1 Melatonin receptor-1

MTR2 Melatonin receptor-2

MTR1B Melatonin receptor 1B

NADPH Nicotinamide adenine dinucleotide phosphate

NEFAs Non-sterified-fatty-acids

NeuroD Neurogenic differentiation factor

NO Nitric oxide

NO● Nitric oxide radical

eNOS Endotelial nitric oxide synthase enzyme

iNOS Inducible nitric oxide synthase enzyme

OH● Hydroxyl radical

8-OHdG 8-Hydroxideoxyguanosine

PCBs Polychlorinated biphenyls

mPER1 Gen involved in the regulation of mammalian circadian clock

POMC Proopiomelacortin

PPARg Peroxisome proliferator-activated receptor-gamma

mRNA Messenger ribonucleic acid

RNS Reactive nitrogen species

ROS Reactive oxygen species

SBP Systolic blood pressure

SOD Superoxide dismutase enzyme

TBARS Thiobarbituric acid reactive substances

T1DM Type 1 diabetes mellitus

T2DM Type 2 diabetes mellitus (T2DM)

T3 Triiodothyronine

TNF-α Tumor necrosis factor-α

UCP1 Uncoupled protein-1

UCP2 Uncoupled protein-2

ZDF Zücker diabetic fatty

ZL Zücker lean

Zn/Cu-dependent SOD Cytoplasmic Zn/Cu-SOD

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**Figures legends**

**Fig. 1** Effect of chronic melatonin administration on metabolic regulation of Zücker diabetic fatty (ZDF) rats.