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Review

MELATONIN AND THE METABOLIC SYNDROME: A TOOL FOR EFFECTIVE THERAPY IN OBESITY-ASSOCIATED ABNORMALITIES?

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Abstract:

The metabolic syndrome is a cluster of metabolic abnormalities associated with increased risk for cardiovascular diseases. Apart from its powerful antioxidant properties, the pineal gland hormone melatonin has recently attracted the interest of various investigators as a multifunctional molecule. Melatonin has been shown to have beneficial effects in cardiovascular disorders including ischaemic heart disease and hypertension. However its role in cardiovascular risk factors including obesity and other related metabolic abnormalities is not yet established, particularly in humans. New emerging data show that melatonin may play an important role in body weight regulation and energy metabolism. This review will address the role of melatonin in the metabolic syndrome focusing on its effects in obesity, insulin resistance and leptin resistance. The overall findings suggest that melatonin should be exploited as a therapeutic tool to prevent or reverse the harmful effects of obesity and its related metabolic disorders.

Introduction

The metabolic syndrome (MetS), also termed syndrome X or insulin resistance syndrome, represents a cluster of metabolic abnormalities including, amongst others, abdominal obesity, insulin resistance, glucose intolerance, atherogenic dyslipidaemia, raised blood pressure and a pro-inflammatory state (Cornier *et al.* 2008). In addition to an increased risk for cardiovascular diseases and type 2 diabetes, this syndrome is also associated with numerous co-morbidities such as non-alcoholic fatty liver disease, reproductive disorders, obstructive sleep apnoea syndrome, osteoarthritis and some cancers (Pothiwala *et al.* 2009). MetS patients exhibit also sleep/wake disturbances and other circadian abnormalities (Cardinali *et al.* 2011, Reiter *et al.* 2011).

Available evidence indicates that in most developed and developing countries between 20% and 30% of the adult population can be characterized as having MetS (Grundy 2008) with obesity (increased body fat accumulation due to excessive nutrient/energy intake) playing an important role in the development of this condition (Cornier *et al.* 2008). Previous strategies to combat the prevalence of obesity and the MetS have not yet been successful and it is predicted that up to 58% of the global adult population could be either overweight or obese by 2030 (Kelly *et al.* 2008). This alarming prevalence and an increased risk for numerous co-morbidities will have serious socio-economic implications for both government and society in the future (Haslam & James 2005).

The pathophysiological mechanisms involved in the development of obesity-induced MetS, from adipose tissue dysregulation to a chronic inflammatory state, are complex and not well understood. In this regard, several mechanisms in connection with increased body fat accumulation and insulin resistance have been proposed including, amongst others, generation of lipid metabolites, inflammation, and cellular stress (oxidative and endoplasmic reticulum stress) (for review see Boden (2011)). Support for a potential role of oxidative stress in the MetS is rapidly increasing (Roberts & Sindhu 2009, Hopps *et al.* 2010, Otani 2011). A recent USA national survey showed that MetS patients were found to have a low serum antioxidant capacity compared with those without MetS (Beydoun *et al.* 2011). Therefore, along with other substantial interventions (e.g., sustained lifestyle modification with calorie restriction, increased physical activity and adjuvant drugs), antioxidant supplementation in the management of the MetS or prevention of increased oxidative stress associated with obesity-related alterations are currently receiving much attention.

The pineal gland hormone melatonin has potent antioxidant activities (Korkmaz *et al.* 2009a). In addition, it has been shown to play a role in metabolic regulation (Korkmaz *et al.* 2009b, Tan *et al.* 2011). Convincing evidence exists for the association of circadian system derangement (chronodisruption), sleep deprivation, and melatonin suppression in MetS and obesity (Reiter *et*

al. 2011). The present review discusses the effects of melatonin in obesity-associated metabolic alterations focusing on body weight/adiposity and resistance to the actions of insulin and leptin, two important hormones involved in metabolic regulation (Benoit *et al.* 2004). The role of melatonin as a multifunctional molecule and its potential cardiovascular effects are also summarized. Particular attention must be paid to the fact that the overall role of melatonin in obesity-related disorders is due more likely to its combined pleiotropic regulatory effects rather than to its antioxidant activities alone (Hardeland *et al.* 2011). In this regard, the obesity-associated oxidative stress and eventual antioxidant interventions in obesity and insulin resistant states will not be discussed since they have been largely reviewed elsewhere (Houstis *et al.* 2006, Vincent *et al.* 2007, Grattagliano *et al.* 2008, Hopps *et al.* 2010, Otani 2011, Rains & Jain 2011).

Melatonin: a multifunctional molecule more than an antioxidant

Melatonin or N-acetyl-5-methoxytryptamine is the hormone secreted mainly by the pineal gland which is under the control of the central nervous system via the suprachiasmatic nucleus (SCN) of the hypothalamus. Since the pineal gland is active only in darkness, the levels of melatonin in the pineal gland and in blood are high at night and low during the day (Altun *et al.* 2002). The biosynthesis and metabolism of melatonin has recently been extensively reviewed (Pandi-Perumal *et al.* 2006, Hardeland 2008).

Viewed as nature's most versatile biological signaling (Pandi-Perumal *et al.* 2006) and multitasking molecule (Reiter *et al.* 2010), melatonin is a highly conserved molecule found in almost all groups of organisms (Hardeland & Fuhrberg 1996). Beside its classical role as a chronobiotic factor or endogenous synchronizer participating in regulation of seasonal as well as circadian rhythm (Zawilska *et al.* 2009), melatonin is also involved in a wide range of physiological functions in humans and animals having anti-excitatory, antioxidant, anti-inflammatory, immunomodulatory and vasomotor effects (for review see Hardeland *et al.* (2006), Pandi-Perumal *et al.* (2006)). Many of the biological actions of melatonin are elicited through

activation of membrane (Hardeland *et al.* 2006, Pandi-Perumal *et al.* 2008) or nuclear (Wiesenberg *et al.* 1998, Carlberg 2000) receptors while some of its intracellular actions are receptor-independent (for example, free radical scavenging). Two types of membrane receptors have been identified in mammals: melatonin receptor type1 (MT1 in rodents or MTNR1A in humans) and type 2 (MT2 in rodents or MTNR1B in humans); they belong to the family of G-protein-coupled receptors (for review see Hardeland *et al.* (2011)) and are increased in type 2 diabetic patients (Peschke *et al.* 2007).

The antioxidant activity of melatonin is well established (for reviews see Tan *et al.* (2007), Korkmaz *et al.* (2009a)). Most of studies used melatonin at very high concentrations (1 μ M to 100mM) compared to its physiological concentrations (10-60 pM and 43-400pM during the day and the night, respectively) (Barrenetxe *et al.* 2004, Bonnefont-Rousselot & Collin 2010). In both *in vitro* and *in vivo* experiments, melatonin administration was able to neutralize a number of toxic reactants including reactive oxygen species (ROS) and free radicals (Reiter *et al.* 2000, Reiter *et al.* 2008) and no toxicity was found when melatonin was administered to experimental animals or humans at doses varying between 1mg and 300mg per day (Bonnefont-Rousselot & Collin 2010)). It has also been shown to increase the expression and activity of glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (Vural *et al.* 2001, Rodriguez *et al.* 2004) and to increase the efficacy of classic antioxidants such as vitamin E, vitamin C and glutathione (GSH) (Gitto *et al.* 2001). Furthermore, several melatonin metabolites (e.g., N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK)) which are formed when melatonin neutralizes damaging reactants are themselves free radical scavengers (Tan *et al.* 2007, Reiter *et al.* 2008). This would increase the efficacy of melatonin in pathological conditions associated with increased oxidative stress (Korkmaz *et al.* 2009a, Bonnefont-Rousselot & Collin 2010). Importantly, melatonin treatment protects against mitochondrial dysfunction, the major source of reactive oxygen and nitrogen species (ROS/RNS) (Lopez *et al.* 2009, Paradies *et al.* 2010).

Melatonin is a small, highly lipophilic and hydrophilic molecule able to cross all morphological barriers and acts not only in every cell but also within every subcellular compartment (Vural *et al.* 2001, Rodriguez *et al.* 2004). These pleiotropic activities have led to the suggestion that it may be used clinically in disease conditions where its circulating levels are reduced such as in cardiovascular diseases (Reiter *et al.* 2010a) and diabetes (Peschke 2008) as well as in cancer (Srinivasan *et al.* 2008). The description of the role of melatonin in these conditions is beyond the focus of this review and only the cardiovascular effects of melatonin will be summarized.

Cardiovascular effects of melatonin

Endogenous melatonin has been shown to play an important role in the cardiovascular system (CVS) (Dominguez-Rodriguez *et al.* 2010, Reiter *et al.* 2010a). As indicated above, melatonin exerts its physiological functions through its chronobiotic, anti-excitatory, antioxidant, anti-inflammatory, immunomodulatory and vasomotor activities (Pandi-Perumal *et al.* 2006). Indeed, the CVS is connected to the SCN via multisynaptic autonomic neurons, and evidence confirmed that melatonin affects the CVS via these activities (Ruger & Scheer 2009, Dominguez-Rodriguez *et al.* 2010). Moreover, melatonin receptors (MT1/MT2) have been identified in the heart and arteries (Ekmekcioglu *et al.* 2003). Melatonin has been reported to influence blood pressure (Kitajima *et al.* 2001) and heart function (Abete *et al.* 1997) directly and/or indirectly by affecting cardiovascular risk factors including, amongst others, increased visceral fat accumulation and dyslipidaemia (Agil *et al.* 2011a, Kozirog *et al.* 2011, Nduhirabandi *et al.* 2011). The latter will be discussed in the section on obesity and insulin resistance (see figure 1 and table1). Importantly, subjects with coronary heart disease had impaired nocturnal melatonin secretion (Brugger *et al.* 1995, Altun *et al.* 2002) while those with myocardial infarction (Dominguez-Rodriguez *et al.* 2002) and hypertension (Forman *et al.* 2010) were found to have low circulating melatonin levels. Interestingly, a recent case-control study done by Samimi-Fard *et al.* (2011) showed a significant association between single nucleotide

polymorphisms (SNPs) (rs28383653) of melatonin receptor type 1A (MT1A) and coronary artery disease.

Melatonin has potent cardioprotective properties against ischaemia/reperfusion injury (Tengattini *et al.* 2008, Dominguez-Rodriguez *et al.* 2009). The study done by Sahna *et al.* (2002a) reported a bigger post-ischaemic myocardial infarction in pinealectomized rats compared to non-pinealectomized rats, indicating for the first time the cardioprotective effects of endogenous melatonin. The same study and additional investigations in our laboratory (Lochner *et al.* 2006, Genade *et al.* 2008) and elsewhere (Sahna *et al.* 2002b, Sahna *et al.* 2005, Petrosillo *et al.* 2009, Lamont *et al.* 2011) have confirmed that the short- or long-term administration of melatonin at either physiological or pharmacological doses protected the heart against myocardial ischaemia/reperfusion damage. Furthermore, the beneficial effects of exogenous melatonin on the heart in physiological conditions such as ageing (Petrosillo *et al.* 2010) as well as in pathophysiological conditions, for example hyperthyroidism (Ghosh *et al.* 2007), cadmium-induced oxidative damage (Mukherjee *et al.* 2011) and myocardial hypertrophy (Reiter *et al.* 2010b) have been demonstrated. However, the mechanism of the actions of melatonin is still complex and not yet fully explored. Besides its direct free radical scavenger and indirect antioxidant activity (Tengattini *et al.* 2008), the contribution of MT receptors in the cardioprotective properties has also been emphasized (Arvola *et al.* 2006, Sallinen *et al.* 2007, Genade *et al.* 2008, Grossini *et al.* 2011, Lamont *et al.* 2011).

Melatonin supplementation has largely been considered as a potential pharmacological agent in non-dipper and individuals with hypertension (Paulis & Simko 2007, Reiter *et al.* 2009, Grossman *et al.* 2011, Kozirog *et al.* 2011). Melatonin was reported to reduce systolic blood pressure along with aortic pulse wave velocity which is regarded as an important indicator of total cardiovascular risk estimation (Yildiz & Akdemir 2009). A recent meta-analysis of randomized controlled trials by Grossman *et al.* (2011) indicated that melatonin administration (at 2mg: controlled-release preparation) was effective to reduce nocturnal systolic and diastolic

blood pressure in patients with nocturnal hypertension. The regulation and modulation of blood pressure is a complex mechanism with multifactorial aspects (Paulis & Simko 2007). Several reports have indicated a direct effect of melatonin on blood pressure through its anti-adrenergic effects and nitric oxide availability (Kitajima *et al.* 2001, Paulis & Simko 2007). It appears however, as pointed out by Paulis & Simko (2007), that controversial *in vitro* results complicate the explanation of the overall effect on blood pressure *in vivo* while different vascular responses depending on the type of vascular bed (Cook *et al.* 2011) have also been reported. For example melatonin administration caused vasoconstriction in isolated coronary arteries (Tunstall *et al.* 2011) and the renal vascular bed (Cook *et al.* 2011) as opposed to vasodilatation in the aorta, pulmonary and umbilical vascular bed (Thakor *et al.* 2010). In contrast to the vasoconstriction observed in porcine isolated coronary arteries (Tunstall *et al.* 2011), intracoronary infusion of melatonin (70pgmL⁻¹ per minute of coronary blood flow) in anaesthetized pigs, was followed by an increased coronary flow and cardiac function through the beta-adrenoreceptors and nitric oxide (Grossini *et al.* 2011). These inconsistent vasomotor effects could be due to difference in the expression of the type of MT1/MT2 receptor in some vascular regions and involvement of the autonomic nervous system (Grossini *et al.* 2011).

Although more clinical investigations are required, melatonin appears to be an effective cardioprotectant in non-obese animals in addition to its promising antihypertensive effects. Since obesity is strongly associated with the increased prevalence of cardiovascular disorders (Poirier *et al.* 2006) which have been linked to derangement of melatonin's circadian rhythm (Altun *et al.* 2002, Reiter *et al.* 2009, Dominguez-Rodriguez & Abreu-Gonzalez 2011), the role of melatonin in obesity/overweight and other related MetS components (insulin resistance, glucose intolerance, atherogenic dyslipidaemia, elevated blood pressure) is the topic of many investigations.

Melatonin and obesity

Melatonin is involved in energy expenditure and body fat mass regulation (Korkmaz *et al.* 2009b, Tan *et al.* 2011). Previously reported in seasonal animals (Bartness & Wade 1985), the role of melatonin in body weight regulation was clearly demonstrated by the observation that the reduction in circulating melatonin in pinealectomized rats was followed by an increase in body weight and that intraperitoneal (ip) administration of melatonin (30mgkg^{-1} per day for 3 weeks) to these pinealectomized animals reversed the body weight gain (Prunet-Marcassus *et al.* 2003). In non-pathological conditions, melatonin has been shown to directly mediate body weight reduction and loss of adipose tissue: daily oral melatonin supplementation ($0.4\mu\text{gml}^{-1}$ to $4\mu\text{gml}^{-1}$ for 12 weeks) in middle-aged rats increased plasma melatonin and reduced body weight, visceral adiposity, and plasma insulin and leptin levels to youthful levels (Rasmussen *et al.* 1999, Wolden-Hanson *et al.* 2000). Similar effects on body weight and visceral fat were observed in young rats (Bojkova *et al.* 2006, Kassayova *et al.* 2006). Interestingly, these weight loss effects of melatonin are independent of energy intake (for a review see Tan *et al.* (2011)).

The effects of melatonin in obesity have been intensively studied in animal models of diet-induced obesity (Nishida *et al.* 2002, Prunet-Marcassus *et al.* 2003, Puchalski *et al.* 2003, Hussein *et al.* 2007, Sartori *et al.* 2009, She *et al.* 2009, Shieh *et al.* 2009, Rios-Lugo *et al.* 2010, Agil *et al.* 2011a, Cardinali *et al.* 2011, Nduhirabandi *et al.* 2011). It was shown that the amplitude of the nocturnal pineal (Cano *et al.* 2008) and serum (Peschke *et al.* 2006) melatonin peaks decrease significantly in obese animals. Daily melatonin supplementation ($4\text{--}10\text{mg kg}^{-1}$ for 8 to 12 weeks) significantly reduced body weight as well as plasma glucose, leptin, triglyceride (TG) and total cholesterol levels of the rat models of high-fat diet-induced obesity (Prunet-Marcassus *et al.* 2003, She *et al.* 2009, Rios-Lugo *et al.* 2010). Using a rat model of high-calorie diet-induced obesity, our laboratory has demonstrated that long-term oral melatonin consumption (4mg kg^{-1} per day for 16 weeks) starting before the establishment of obesity attenuated weight gain and prevented the development of obesity-induced metabolic

alterations (elevated visceral fat, serum insulin, leptin, TG and reduced high density lipoprotein cholesterol (HDL-C)) (Nduhirabandi *et al.* 2011). This study also reported for the first time the protective effects of melatonin against the increased susceptibility to myocardial ischaemia and reperfusion damage of the hearts from obese rats. We found that melatonin administration reduced post- ischaemic myocardial infarct size and improved myocardial function recovery via activation of reperfusion injury salvage protein kinases (PKB/Atk and ERK1/2) (Nduhirabandi *et al.* 2011). However, how melatonin affects the heart in obesity needs further investigation to determine the underlying mechanisms and the role of its direct or indirect actions.

Beside these metabolic effects, the antioxidant activities of melatonin were also demonstrated in animal models of diet-induced obesity: daily melatonin administration to obese rabbits (1mgkg^{-1} subcutaneously for 4 weeks)(Hussein *et al.* 2007) or rats (4mgkg^{-1} , ip for 8 weeks) (She *et al.* 2009) improved the metabolic profile (reduction in body weight gain, blood glucose, triglycerides, cholesterol, low density lipoprotein cholesterol (LDL-C)) and increased the levels of glutathione peroxidase (GSH-Px) and HDL-C. Additionally, melatonin administration reduced oxidative stress as indicated by plasma malondialdehyde (MDA) levels and increased superoxide dismutase (SOD) activity to control levels (She *et al.* 2009). These changes were also associated with amelioration of blood pressure, heart rate, sympathetic activities and other obesity-related morphological pathologies including disappearance of fatty changes in the liver and kidney as well as atheromatous changes in the blood vessels (Hussein *et al.* 2007).

Despite the studies on the antioxidant activities of melatonin in experimental obese animals, only few have been done in obese humans. In a recent promising study done by Kozirog *et al.* (2011), one month of administration of melatonin (5mg per day) to patients with MetS reduced the body mass index (BMI), systolic blood pressure (SBP) and plasma fibrinogen as well as thiobarbituric acid reactive substrates (TBARS) levels. Interestingly, after two months of treatment, there was a further significant improvement of SBP and antioxidative status as indicated by an elevated catalase activity and a decrease in low density lipoprotein cholesterol

(LDL-C) levels (Kozirog *et al.* 2011). Although no information was given about the levels of circulating melatonin and insulin, this report pointed out, as claimed by other authors, that the levels of melatonin per se are not as important as the melatonin/insulin ratio which correlates negatively with the lipid profile of patients with MetS (Robeva *et al.* 2008).

The impact of obesity on the overall circulating melatonin levels in humans has been marked by divergences. For example, while the mean nocturnal serum melatonin was reported to be lower in patients with type 2 diabetes (Peschke *et al.* 2006) and coronary heart disease (see Cardinali *et al.* (2011)) and higher in severe obesity (Shafii *et al.* 1997), the study done by Rojdmarm *et al.* (Rojdmarm *et al.* 1991) showed that there were no significant modifications of melatonin secretion and excretion in obesity. Additional studies indicated that circulating melatonin levels in pre-diabetic obese male (Robeva *et al.* 2006) and male and female obese diabetic (Robeva *et al.* 2008) patients with MetS did not differ from controls. These discrepancies may be due to various factors including age of patients and severity of obesity (Shafii *et al.* 1997).

MT receptor-mediated pathways may play an important role in melatonin's actions in obesity. This was evidenced by studies using the melatonin agonist NEU-P11 (10mg kg⁻¹ per day for 8 weeks, ip) (She *et al.* 2009) or Ramelteon, a potent selective MT₁/MT₂ receptor agonist (8 mg kg⁻¹ per day for 8 weeks, oral) (Oxenkrug & Summergrad 2010): it was found that melatonin agonist administration exerts similar regulatory effects as melatonin, namely decreasing body weight and blood pressure. Using MT receptor knock out mice, Muhlbauer *et al.* (2009) demonstrated an active role for these receptors in the synchronisation of the major organs involved in blood glucose regulation and that they act negatively on insulin secretion. Since MT receptors are also present in adipose tissue (Brydon *et al.* 2001), it seems that the overall effects of melatonin in obesity are partly mediated through these receptors in addition to activation of the sympathetic nervous system via hypothalamic receptors and subsequent effects on lipolysis and adipose tissue plasticity (Penicaud *et al.* 2000, Song & Bartness 2001, Bartness *et al.* 2002).

In vitro melatonin treatment of adipocytes has been shown to possibly inhibit differentiation and limit adipose tissue hypertrophy (Alonso-Vale *et al.* 2009) by inhibiting fatty acid-induced triglyceride accumulation in cells exposed to physiological levels of oleic acid (Sanchez-Hidalgo *et al.* 2007). This could explain how in vivo melatonin treatment prevents the increase in circulating triglycerides and eventually body fat accumulation and body weight gain in overweight and obesity (Agil *et al.* 2011a, Nduhirabandi *et al.* 2011). The reduction in body weight gain might be due to a significant decrease in fat content as opposed to lean body mass (Wolden-Hanson *et al.* 2000) and could be related to improvements in the compromised insulin and leptin signaling associated with obesity (Sartori *et al.* 2009) (see details in the following sections).

The exact mode of action of melatonin in body weight regulation is however complex and not fully elucidated. The exact mode of action of melatonin in body weight regulation is however complex and not fully elucidated. As previously indicated the divergences in melatonin activities may be explained by differences in experimental protocols. For instance, while body weight reduction following melatonin administration was independent of food intake in middle-aged male rats (Wolden-Hanson *et al.* 2000) and obese rats (She *et al.* 2009, Agil *et al.* 2011a), it was accompanied with a decrease in food consumption in ovariectomized rats (Sanchez-Mateos *et al.* 2007) and obese rabbits (Hussein *et al.* 2007). It appears that melatonin's effects could vary from one study to another depending on the study design: the dose, mode and time of administration as well as the age, sex, species and strain of the animal model. For example, following a prolonged oral melatonin administration to normal rats, serum glucose levels were increased in male and female 48-hours fasted animals (Bojkova *et al.* 2006), decreased in overnight fasted females (Bojkova *et al.* 2006) or in both males and females (Kassayova *et al.* 2006) or unchanged in either sexes of non-fasted animals (Markova *et al.* 2003). Whether the overall effect of melatonin administration in obesity results from its direct or/and indirect actions requires further research.

Melatonin and insulin resistance

Insulin resistance is characterized by a decreased cellular sensitivity to its effects on glucose uptake, metabolism and storage in peripheral tissues (for more details see Benito (2011), Tesouro & Cardillo (2011)). Although not all overweight/ obese persons develop insulin resistance and a normal weight does not equate to insulin sensitivity (McLaughlin *et al.* 2004), obesity is the most important factor in the etiology of insulin resistance (Cornier *et al.* 2008). It is generally accepted that hyperinsulinaemia and insulin resistance are the common links between obesity and its vascular complications (for review see Tesouro & Cardillo (2011)).

Melatonin has been implicated in regulation of insulin secretion and glucose/lipid metabolism (Nishida 2005, Peschke 2008, Peschke & Muhlbauer 2010). Studies on pinealectomized animals also gave more insight into the role of melatonin in insulin resistance: in normal rats, pinealectomy induced insulin resistance and glucose intolerance (Lima *et al.* 1998, Zanutta *et al.* 2003). In type 2 diabetic rats, pinealectomy increased plasma insulin significantly (after 21 weeks) and caused accumulation of triglycerides which was followed later (after 35 weeks) by a net decrease in insulin levels (Nishida *et al.* 2003), reflecting impairment in insulin release from pancreatic β -cells, as seen in patients at an advanced stage of type 2 diabetic mellitus (Kuzuya *et al.* 2002).

Pineal gland melatonin synthesis is decreased in type 2 diabetic Goto-Kakizaki rats (Frese *et al.* 2009); long term melatonin consumption (2.5 mgkg⁻¹ per day for 9 weeks) increased plasma melatonin levels with a concomitant reduction in insulin levels in these animals (Peschke *et al.* 2010). Sartori *et al.* (2009) found that 8 weeks oral melatonin (100mg kg⁻¹ per day) markedly improved insulin sensitivity and glucose tolerance in mice on a high-fat diet. A similar finding was associated with an increase in hepatic glycogen and improvement in liver steatosis following 2 weeks of melatonin administration (10mgkg⁻¹ per day, ip) in high-fat diet-induced diabetic mice (Shieh *et al.* 2009). In high fat/high sucrose-fed rats, 8 weeks treatment with melatonin or its agonist NEU-P11 increased insulin sensitivity (She *et al.* 2009). Besides the

reduction in plasma hyperinsulinaemia, chronic melatonin administration (1.1mgkg^{-1} per day for 30 weeks, subcutaneously via implanted melatonin-releasing pellets) to rats with type 2 diabetes mellitus reduced the hyperlipidaemia, and hyperleptinaemia (Nishida *et al.* 2002). This long term melatonin-induced improvement of insulin sensitivity may therefore be linked to a reduced body weight and improved lipid metabolism as it was recently demonstrated in young Zucker diabetic fatty rats (Agil *et al.* 2011a & b). Although 2 weeks of melatonin administration (1 or 10 mg kg^{-1} per day, ip starting at 4 weeks) did not affect the body weight of rats fed a high-fructose diet for 6 weeks, it ameliorated insulin resistance (Kitagawa *et al.* 2011). This was associated with increase in serum adiponectin levels and reduction in leptin levels (Kitagawa *et al.* 2011). Interestingly, melatonin administration attenuated the levels of circulating free fatty acids (FFA) and serum tumor necrosis factor- α (TNF- α) (Kitagawa *et al.* 2011), two important factors implicated in the development of insulin resistance and vascular dysfunction in obesity (Benito 2011, Tesouro & Cardillo 2011).

On a cellular level, insulin resistance is associated with abnormal or compromised intracellular insulin signaling cascade. This cascade principally includes binding of insulin to insulin receptor (IR), tyrosine phosphorylation of insulin receptor substrate (IRS) proteins and activation of phosphatidylinositol-3-kinase (PI-3K), protein kinase B (PKB/Akt) and protein kinase C (PKC) isoforms (for details see Benito (2011)). Melatonin (1nM) treatment has been shown to stimulate glucose transport in skeletal muscle via the phosphorylation and activation of IRS-1 and PI-3K respectively (Ha *et al.* 2006). It was further demonstrated that melatonin improves glucose homeostasis by restoring the vascular actions of insulin which were characterized by increased phosphorylation of Akt and endothelial nitric oxide synthase (eNOS) in aortic tissue (Sartori *et al.* 2009). In addition to the phosphorylation of Akt and PKC- ζ , Shieh *et al.* (2009) indicated that melatonin (1nM) stimulated glycogen synthesis and increased the phosphorylation of glycogen synthase kinase 3 β (GSK3- β) in hepatic cells. More interestingly, the effects of melatonin could be blocked by using the non-selective MT1/MT2 antagonist, luzindole, or the MT2 selective antagonist, 4-phenyl-2-propionamido tetraline (4P-PDOT) (Ha *et*

al. 2006, Shieh *et al.* 2009), suggesting MT receptor involvement. It is not clear however how activation of the high affinity MT receptors which are G-protein linked leads to stimulation of the IRS-1/PI-3K pathway and the role of PKC- ζ in this regard (see figure 2). In addition, the role of PKB/Akt is not clear in view of the different results that have been reported showing its activation in skeletal muscle cells (Ha *et al.* 2006) as opposed to its inactivation in hepatic cells (Shieh *et al.* 2009).

Using adipose tissue of the female fruit bat, *Cynopterus sphinx* (seasonal animal), Banerjee *et al.* (2011) have shown that melatonin treatment (100ngml^{-1} and 500pgml^{-1}) together with insulin increased the glucose uptake compared to control cells. There was however no correlation between glucose uptake and the protein expression of glucose transporter 4 (GLUT-4) in these cells (Banerjee *et al.* 2011). In this regard, additional exploration of GLUT4-translocation could give more insight in the results obtained. Although a decrease in GLUT-4 gene expression was reported following melatonin treatment ($1\mu\text{M}$ for 14 days) in human brown adipocyte cells lines (PAZ6) (Brydon *et al.* 2001), Zanquetta *et al.* (2003) found that 30 days of calorie restriction or melatonin replacement ($50\mu\text{g}100\text{g}^{-1}$ per day i.p.) to pinealectomised rats was accompanied by increased plasma membrane GLUT-4 protein content in white adipose tissue to values similar to those of control rats. Importantly, Gosh and coworkers (2007) found that melatonin protected against oxidative damage and restored expression of GLUT-4 gene in the hyperthyroid rat heart, establishing the ability of antioxidants to reverse oxidative stress-mediated metabolic derangements. We have recently observed that acute melatonin (100nM) treatment enhances the insulin action on glucose uptake of normal isolated adult cardiomyocytes (Nduhirabandi *et al.* unpublished data). However, further experiments are needed to fully explore the role of melatonin in glucose homeostasis.

Further support for a role of melatonin in the regulation of energy metabolism came from the recent finding that removal of the melatonin receptor type I (MT1) significantly impairs the ability of mice to metabolize glucose and probably induces insulin resistance in these animals

(Contreras-Alcantara *et al.* 2010). Epidemiological studies have also revealed that variants near/in the melatonin receptor type 1B (MTNR1B) are associated with elevated plasma fasting glucose levels (Kan *et al.* 2010) and impaired insulin secretion (Tam *et al.* 2010).

In addition to the above, melatonin receptors MT1 and MT2 are also expressed in pancreatic islets (Peschke *et al.* 2000) and as insulin levels exhibit a nocturnal drop, its production has been suggested to be controlled, at least in part, by melatonin (Mulder *et al.* 2009). Indeed, melatonin administration inhibits insulin secretion in rat pancreatic islets (Picinato *et al.* 2002, Peschke 2008) and could explain why melatonin reduced the fasting insulin levels (Puchalski *et al.* 2003, She *et al.* 2009). Importantly, a recent case study done by (Nieuwenhuis *et al.* 2009) demonstrated a potentially important role of melatonin in diabetes by successfully treating a 40-year-old woman with insulin-dependent diabetes mellitus (IDDM) with phototherapy. Indeed, the exposure to the light during phototherapy could suppress melatonin production as expected and this could lead to an increase in insulin secretion which is low in IDDM and causing a subsequent improvement in glucose metabolism.

However, in the case of type 2 diabetes, as pointed out by Peschke & Muhlbauer (2010), the exploitation of melatonin's inhibitory effect on insulin secretion as a potential therapy to reduce hyperinsulinaemia requires prudence and more large clinical studies. The implication of catecholamines as causal factor controlling the biological relevance of melatonin-insulin interaction has recently been demonstrated in type 1 and 2 diabetes (Peschke *et al.* 2011). It was observed that catecholamines (noradrenaline and adrenaline) and melatonin levels were reduced in type 2 diabetic GK rats (characterized by high insulin levels) and elevated in type 1 diabetic rats (associated with reduced insulin levels) (Peschke *et al.* 2011). The role of catecholamines in these pathological conditions could be explained by their observed (high or low) levels taking into consideration the fact that catecholamines decrease insulin secretion and stimulate melatonin synthesis (Peschke *et al.* 2011).

Melatonin and leptin resistance

Leptin is an adipocyte hormone that has a central role in regulating food intake, body weight and energy expenditure and leptin resistance refers to the inability of elevated circulating leptin levels to reduce common obesity. As a predisposing factor for diet-induced obesity (Scarpace & Zhang 2009), leptin resistance is associated with insulin resistance and an increased pro-inflammatory state (Lago *et al.* 2008). Pinealectomy increases circulating leptin (Baydas *et al.* 2001) while exogenous melatonin decreases serum leptin levels in both pinealectomized (Canpolat *et al.* 2001) and intact rat models of diet-induced obesity (Wolden-Hanson *et al.* 2000) before decreasing plasma insulin levels (Puchalski *et al.* 2003). These observations suggest a secondary modulatory effect of leptin on insulin in body weight reduction (Morrison *et al.* 2009). On the other hand, opposite results (increased leptin levels) have also been reported following melatonin administration to normal and pinealectomized rats (3 mgkg⁻¹ per day, ip, for 6 months) (Baltaci & Mogulkoc 2007) and to male C57BL/6 adult mice (10 µgml⁻¹ in drinking water, for 1 month) (Song & Chen 2009). In this regard, surprisingly, the study done by Baltaci and Mogulkoc (2007) showed that pinealectomy decreased body weight gain and leptin levels. Furthermore, other studies have shown that melatonin had no effect on leptin levels in menopausal women (Cagnacci *et al.* 2002), ovariectomized rats (Sanchez-Mateos *et al.* 2007) and obese horse (Buff *et al.* 2005). However, as expected, in a rat model of high-fructose diet induced MetS (Kitagawa *et al.* 2011) and in young Zucker diabetic fatty rats (Agil *et al.* 2011b) melatonin administration reduced serum leptin levels. Apart from differences in experimental designs and animal models, the causes of these controversial results remain to be clarified.

At a molecular level, the mechanisms of leptin resistance and impaired leptin signaling includes amongst other things increased activity of suppressor of cytokine signaling 3 (SOCS3) (Bjorbaek *et al.* 1999, Emilsson *et al.* 1999) which is a member of a family of proteins which inhibits the JAK-STAT signaling cascade (Myers *et al.* 2008). Melatonin may act initially on hypothalamic leptin and insulin receptor sensitivity (as these hormones do under normal

conditions) and may consequently relay information about peripheral fat stores to central effectors in the hypothalamus to modify food intake and energy expenditure (Song & Bartness 2001). In this regard, melatonin, leptin and insulin have been found to activate the same intracellular signaling pathways namely PI3K and STAT-3 (Carvalho *et al.* 2001, Anhe *et al.* 2004, Picinato *et al.* 2008). As a consequence, melatonin may attenuate or reverse the insulin resistance in obesity by mimicking the actions of insulin and leptin signaling via cross-talk between these pathways. Concerning the effects of leptin administration on melatonin, it was shown that leptin administration (50ngml^{-1}) suppressed melatonin secretion (by pineal explants) during long days and stimulated its secretion during short days in seasonal breeding animals (Zieba *et al.* 2011). While further evidence is required in diet-induced obesity, it appears that an intricate relationship exists between leptin, melatonin and insulin, synchronized in circadian fashion and having profound effects on metabolism.

Conclusion

Although its experimental relevance is still to be validated in the clinical setting, several studies have demonstrated the potential beneficial actions of melatonin in the metabolic syndrome and obesity (see table 1 and figure 1). Apart from its antioxidant actions, the overall metabolic actions of melatonin are the result of its pleiotropic activities associated with multiple signaling in areas of the central nervous system and in peripheral organs (Hardeland *et al.* 2011). In view of the beneficial actions of melatonin on obesity-related metabolic disorders (increased body fat accumulation, glucose intolerance, atherogenic dyslipidaemia, and raised blood pressure), it would seem that melatonin treatment should indeed be exploited in the future as a tool for effective management of obesity-induced complications, including cardiovascular disease. Melatonin is an affordable, cheap and nontoxic molecule with exceptional potential to have a profound effect on public health (Reiter & Korkmaz 2008, Sanchez-Barcelo *et al.* 2010).

Future perspectives

The research on the role of melatonin and its effects on the pathophysiological mechanisms of obesity and metabolic syndrome is a recent, large and growing field. From a circadian system derangement to metabolic disorders, it involves various aspects including epidemiological, physiological and genetic factors. It is clear however, that extensive clinical trials are required to establish the clinical potential of melatonin treatment in a number of pathologies. It appears that the big challenge is the enormous variation of dosage of melatonin administered in experimental animals where low and high doses both seem to be effective. In this regard, the extrapolation of experimental findings to humans will be one of the first obstacles, but this is facilitated by the no-toxicity of melatonin even at high dosage.

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TABLE 1 POTENTIAL MELATONIN'S EFFECTS IN OBESITY- RELATED METABOLIC ALTERATIONS

Parameters		Before treatment	Treatment Effects	References
Body weight		↑	↓	(Rasmussen <i>et al.</i> 1999,Wolden-Hanson <i>et al.</i> 2000,Prunet-Marcassus <i>et al.</i> 2003,Puchalski <i>et al.</i> 2003, Hussein <i>et al.</i> 2007)
Visceral fat		↑	↓	(Rasmussen <i>et al.</i> 1999,Prunet-Marcassus <i>et al.</i> 2003,Puchalski <i>et al.</i> 2003, She <i>et al.</i> 2009)
Blood	Fasting glucose	↑	↓	(Prunet-Marcassus <i>et al.</i> 2003,Shieh <i>et al.</i> 2009, Peschke <i>et al.</i> 2010,Rios-Lugo <i>et al.</i> 2010)
	Insulin	↑	↓	(Nishida <i>et al.</i> 2002,Puchalski <i>et al.</i> 2003, Sartori <i>et al.</i> 2009,Shieh <i>et al.</i> 2009,Peschke <i>et al.</i> 2010)
	HDL-C	↓	↑	(Hussain 2007,Hussein <i>et al.</i> 2007, She <i>et al.</i> 2009, Agil <i>et al.</i> 2011a)
	LDL-C	↑	↓	(Hussein <i>et al.</i> 2007, Agil <i>et al.</i> 2011a, Kozirog <i>et al.</i> 2011)
	TG	↑	↓	(Nishida <i>et al.</i> 2002,Hussain 2007,Rios-Lugo <i>et al.</i> 2010,Agil <i>et al.</i> 2011a,Kozirog <i>et al.</i> 2011)
	VLDL	↑	↓	(Hoyos <i>et al.</i> 2000)
	Leptin	↑	↓ or ↑	↓ (Wolden-Hanson <i>et al.</i> 2000,Nishida <i>et al.</i> 2002,Prunet-Marcassus <i>et al.</i> 2003,Puchalski <i>et al.</i> 2003) or ↑ (Baltaci & Mogulkoc2007, Song & Chen2009)
	Adiponectin	↓ or ↑ (?)	↑ or ↓ (?)	↑ (Agil <i>et al.</i> 2011b, Kitagawa <i>et al.</i> 2011) or ↓ (Rios-Lugo <i>et al.</i> 2010) (?)
	TNF-α	↑	↓	(Nishida 2005,Oztekin <i>et al.</i> 2006, Kitagawa <i>et al.</i> 2011)
Liver	Fibrinogen secretion	↑	↓	(Bekyarova <i>et al.</i> 2010)
	TG & VLDL release	↑	↓	(Hussain 2007)
	Glucose release	↑	↓	(Kaya <i>et al.</i> 2010)
	C-reactive protein	↑	↓	(Bekyarova <i>et al.</i> 2010)
	Glycogen content	↓	↑	(Shieh <i>et al.</i> 2009)
	Liver weight	↑	↓	(Pan <i>et al.</i> 2006)
Muscle	Insulin sensitivity (glucose uptake)	↓	↑	(Sartori <i>et al.</i> 2009,Srivastava & Krishna2010)
	FFA /TG uptake	↑	↓	(Dauchy <i>et al.</i> 2003)
	Glycogen content	↓	↑	(Mazepa <i>et al.</i> 2000)
Heart & Vessels	Blood pressure	↑	↓	(Paulis & Simko2007, Kozirog <i>et al.</i> 2011)
	Heart rate	↑	↓	(Hussein <i>et al.</i> 2007)
	Endothelial dysfunction	↑	↓	(Sartori <i>et al.</i> 2009)
	Cardiomyopathy /Hypertrophy	↑	↓	(Bertuglia & Reiter2007, Ghosh <i>et al.</i> 2007)

Table 1 Only some references have been indicated in this table as evidence of the potential effects of melatonin in metabolic syndrome. ↓: decreases or attenuates; ↑: increases or elevates; (?): needs more studies/unusual model of obesity; FFA: free fatty acids; TNF-α: tumor necrosis factor-alpha; VLDL: very low density lipoprotein; HDL-C: high density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; TG: triglyceride.

LEGEND FOR FIGURES

Figure 1 Melatonin improves obesity-induced metabolic alterations by reducing circulating free fatty acids (FFA) and hyperglycaemia and dyslipidaemia as well as hyperinsulinaemia with a concomitant increased in high density lipoprotein-cholesterol (HDL-C) and adiponectin. In addition, melatonin improves leptin and insulin resistance and hypertension. These effects are still complex and interconnected and may lead to improvement of coronary heart disease (CHD), heart failure and arrhythmias. As evidence, we showed that melatonin administration reduced myocardial ischaemia reperfusion (I/R) damage by reducing infarct size, improving post-ischaemic myocardial function recovery via activation of reperfusion injury salvage protein kinases (PKB/Akt and ERK1/2). ↓: reduction, ↑: increase,?: no information available, FFA: free fatty acids; LDL-C: Low density lipoprotein-cholesterol; TG: triglyceride, GLUT: glucose transport, SOD: superoxide dismutase, BW: body weight, Visc fat: visceral fat, HW: heart weight, TBARS: thiobarbituric acid reactive substrates, GSH-Px: glutathione peroxidase (References see in the text).

Figure 2 Melatonin administration was associated with a significant increase in glycogen synthesis in hepatic cells and improved glucose homeostasis in skeletal muscle by activation of eNOs (endothelial nitric oxide synthase). How melatonin stimulated phosphorylation of IRS remains unknown. The effect of melatonin in glucose uptake remains unclear. The mitogen-activated protein kinase (MAPK) pathway was not included in the figure. ?: no available data, IR: insulin receptor, IRS-1: insulin receptor substrate 1, PI-3K: phosphatidylinositol-3-kinase, PKC-ζ: Protein kinase C -zeta, GSK-3β: Glycogen synthase kinase -3 beta, GLUT-4: glucose transporter -4, Mel: melatonin, MT1/2: melatonin receptor 1, 2, Ins: Insulin. (References see in the text).

Figure 1 Hypothetical representation of the beneficial actions of melatonin in obesity and its related cardiovascular complications.

Figure 2 Simplified representation of the effect of melatonin on insulin signaling pathway in peripheral tissues