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Inflammaging, Metabolic Syndrome and Melatonin: A Call for Treatment Studies

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Abstract

The metabolic syndrome (MS) is a collection of risk factors for cardiovascular disease, including obesity, hypertension, hyperinsulinemia, glucose intolerance and dyslipidemia. MS is associated with low-grade inflammation of the white adipose tissue, which can subsequently lead to insulin resistance, impaired glucose tolerance and diabetes. Adipocytes secrete proinflammatory cytokines as well as leptin and trigger a vicious circle which leads to additional weight gain largely as fat. The imbalance between inflammatory and anti-inflammatory signals is crucial to aging. Healthy aging can benefit from melatonin, a compound known to possess direct and indirect antioxidant properties, to have a significant protective effect on mitochondrial function, to enhance circadian rhythm amplitudes, to modulate the immune system and to exhibit neuroprotective actions. Melatonin levels decrease in the course of senescence and are more strongly reduced in diseases related to insulin resistance. This short review article analyzes the multiple protective actions of melatonin that are relevant to the attenuation of inflammatory responses and progression of inflammaging and how melatonin is effective to curtail MS in animal models of hyperadiposity. The clinical data supporting the possible therapeutical use of melatonin in human MS are also reviewed. Since attention has been focused on the development of potent melatonin analogs with prolonged effects (ramelteon, agomelatine, tasimelteon, piromelatine) and in clinical trials these analogs were administered in doses considerably higher than those usually employed for melatonin, clinical trials on melatonin in the range of 50-100 mg/day are needed to further assess its therapeutic value in MS.

Inflammaging and the Metabolic Syndrome

The metabolic syndrome (MS) is a collection of risk factors for cardiovascular disease, including obesity, hypertension, hyperinsulinemia, glucose intolerance and dyslipidemia. MS is a major clinical challenge with a prevalence of 15-30%, depending on the world region considered [1-3]. MS increases overall cardiovascular mortality by 1.5 to 2.5 times and, together with neurodegenerative disorders like Alzheimer's disease, it represents one of the two major public health problems nowadays[4].

There is impressive information indicating that the obesity in MS is associated with low-grade inflammation of the white adipose tissue, which can subsequently lead to insulin resistance, impaired glucose tolerance and diabetes [5;6]. Adipocytes actively secrete proinflammatory cytokines such as tumor necrosis factor (TNF) -α, interleukin (IL) -1β and IL-6 as well as leptin and trigger a vicious circle which leads to additional weight gain largely as fat. Increased circulating levels of C-reactive protein and other inflammatory biomarkers support also the occurrence of inflammation in obesity [7;8].

Several studies have shown that altered production of proinflammatory cytokines modulate adipocyte size and number through paracrine mechanisms that exert an important role in the regulation of fat mass [9-11]. The amounts of proinflammatory molecules derived from adipose tissue in obese patients diminishes after weight loss [12]. Therefore, the fat cells are both a source as well as a target for TNF-α, IL-1β and IL-6.

The imbalance between inflammatory and anti-inflammatory signals is also a hallmark of aging and contributes to its progression. The term "inflammaging" was introduced to underscore the importance of inflammation in senescence and its role in the development of age-related diseases as MS [13-15]. The levels of inflammatory mediators typically increase with age, even

in the absence of acute infection or physiological stress. Such stress leads to inflammatory damage of cellular components, including proteins, lipids and DNA, and contributes to the age-related decline in physiological functions particularly in neural, immune and endocrine cells that regulate homeostasis. Therefore, the functional losses observed during aging include a slowly progressing, persistent type of oxidative stress resulting from the increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which is enhanced by damage to the mitochondria [16;17].

An age-related pro-inflammatory tendency is mostly unavoidable because of thymic involution and extended germ exposure, which both lead to the exhaustion of various subforms and developmental stages of leukocytes (details in[17]). However, considerable interindividual differences exist in the velocity of these changes and the balance between proinflammatory and antiinflammatory cytokines [17].This may in part be due to genetic predispositions[18] as well as to histories of viral load [19], which contribute an immune risk profile (IRP) [20].In some centenarians, either an “inverted IRP” has been found or a combination of elevated pro- and anti-inflammatory cytokines, two conditions which are believed to represent protective phenotypes[21;22]. On this background, it has been concluded that an increased tendency to inflammatory responses may place limits on lifespan [22]and that a well-functioning immune system is the strongest predictor of human longevity and healthy aging[23-25]. Therefore, inflammaging is associated with a state of oxidative stress, defined as an excessive production of ROS and RNS compared to the level of antioxidants that act in the natural defense systems. Among antioxidants, melatonin has a special place on the one hand for its antioxidant and anti-inflammatory properties, and partly for its role as a metabolic regulator [26;27]. As melatonin

modulates many processes involved in obesity and related metabolic disorders, it could have a therapeutic benefit in the treatment of obesity.

Melatonin and Inflammaging

A role of melatonin in attenuating inflammaging and its progression has been especially discussed with regard to options of treatment under conditions of reduced endogenous melatonin levels. Melatonin is one the hormones known to decline during aging and, even more, in a number of age-related diseases, changes that have been particularly documented in humans[26-28].Interindividual variations observed among elderly persons may be explained, to a certain extent, by differences in the acquisition of melatonin-depressing diseases and disorders. Among these pathological causes of melatonin reduction, neurodegenerative processes have been identified as well as MS-related changes. For instance, decreases in melatonin were observed in coronary heart disease/cardiac syndrome X [28-34]and in diabetes type 2[35;36]. In either case, the pathophysiological nexus to inflammation and obesity is well established. Additional evidence from polymorphisms of human melatonin receptor genes indicates that deviations in melatonergic signaling favor the development of prediabetic states, diabetes type 2, elevated cholesterol and coronary heart disease (see[28]). Moreover, insulin resistance was induced in mice by knocking out the melatonin receptor MT_1[37] and also by pinealectomy [38;39].

Counteractions of inflammaging by melatonin seems to occur at different levels. One of them concerns the correction of metabolic dysregulation (Table 1), including the prevention of insulin resistance, an inflammation-promoting change and hallmark of MS [40-43]. Notably, melatonin was effective in suppressing insulin resistance in different models, tissues and methods of induction (Table 1).

INSERT TABLE 1

Although in these studies several regulatory pathways have been found to be modulated by melatonin treatment, the decisive effect at which the relevant routes converge is the reduced serine phosphorylation of IRS-1 (insulin receptor substrate 1), which has sometimes been accompanied by an upregulation IRS-1 expression. The activated, tyrosine-phosphorylated insulin receptor is known to activate IRS subforms, in particular, IRS-1, by tyrosine phosphorylation, a process that is inhibited by serine 307 phosphorylation which causes interruption of insulin signaling[69].Melatonin and the melatonergic agonist piromelatine have been shown to reverse the blockade of this key step of insulin signal transduction[41;43;52].Persistent insulin sensitivity has gained in recent years a particular relevance to inflammaging of the brain, because insulin resistance was shown to represent an early sign of low-grade neuroinflammation in dementias, such as Alzheimer's disease, and to aggravate their progression (see[70]).

A further level of action concerns the avoidance of processes that favor or lead to inflammation. This comprises calcium overload, excessive nitric oxide (NO) release that results in the formation of peroxynitrite, peroxynitrite-derived free radicals ($^{\bullet}OH$, $CO_3^{\bullet-}$, $^{\bullet}NO_2$), and, finally, tyrosine nitration as well as mitochondrial dysfunction with its consequence of oxidative stress (summarized in[17;27]). All these changes are known to initiate low-grade inflammation in various organs, which is relevant to aging progression and comprises, in the central nervous system, microglia activation and vicious cycles via overexcitation and damage by oxidants that ultimately cause impaired neuronal and astrocytic functions. In various animal models, melatonin has been shown to counteract these detrimental processes to a substantial extent, by multiple antiexcitatory actions[17;71], mitochondrial protection[17;27;42;72-74], reduction of

peroxynitrite-related damage [75] and attenuation of microglia activation[27;76;77]. These effects go far beyond the frequently discussed direct antioxidant properties of melatonin based on scavenging of free oxygen radicals. In fact, antioxidative protection by melatonin comprises various mechanisms that reduce the formation of free radicals rather than eliminating those already formed, as outlined in the concept of radical avoidance [78].

Immunological effects of melatonin represent a third area relevant to inflammaging. In this field, one of the major problems consists of melatonin's multiple roles as an immune modulatory agent, which comprise both proinflammatory and antiinflammatory actions, which, consequently, also lead to an either prooxidant or antioxidant balance[17;27;79]. At first glance, these observations appear to be contradictory, but they may only reflect the conditionality of melatonin's actions. However, the precise reasons for when melatonin behaves in a pro- or antiinflammatory way remain to be identified, although the strength of inflammation and the temporal sequence of initiation and healing processes may play a role. Moreover, changes due to immune remodeling in the course of senescence have to be taken into account. With regard to aging and age-associated diseases, proinflammatory/prooxidant effects are mainly observed under rheumatic conditions, especially rheumatoid arthritis [80;81]. However, under other conditions concerning senescence, melatonin's antiinflammatory side seems to prevail. In the liver of aged, ovariectomized female rats, melatonin downregulated proinflammatory cytokines, such as TNF-α, IL-1β and IL-6, and upregulated the antiinflammatory IL-10 [82]. Corresponding findings were obtained in the dentate gyrus, in conjunction with an upregulation of sirtuin 1[83], which is assumed to also possess antiinflammatory properties. Reductions of TNF-α and IL-1β and increased levels of IL-10 were also observed in liver [84], pancreas [85]and heart [86]of the senescence-accelerated mouse strain SAMP8. Numerous other reports on antiinflammatory

actions of melatonin that were not obtained under conditions of aging, but in brain trauma, ischemia/reperfusion, hemorrhagic shock, and various forms of high-grade inflammation including endotoxinemia and sepsis, have been summarized elsewhere [17]. The applicability of these results to inflammaging and MS remains uncertain, but the data certainly underline melatonin's antiinflammatory potential.

Melatonin-induced changes in gene expression require detailed analyses beyond the primary signaling pathways transduced by MT_1 and MT_2 receptors via decreases of cAMP and ERK1/2 activation and modulations by protein-protein interactions [87]. However, from a mechanistic point of view, it is not always easily possible to discriminate between direct actions and indirect effects via changes in phase and amplitude of circadian oscillators. While the changes induced in the circadian master clock, the suprachiasmatic nucleus (SCN), are relatively well understood, this is less the case in the numerous peripheral oscillators, which strongly differ in their dependence on the SCN [88]. Since circadian oscillators are cellular machineries, in which the core oscillators are modulated by accessory oscillator components in an often cell type-specific way [89;90], tissue-dependent differences can be expected. With regard to the cellular generation of circadian rhythms, oscillators may be assumed to be present in any nucleated non-resting cell. Notably, peripheral oscillators exist in cells of particular relevance to MS, such as pancreatic beta cells[91], hepatocytes, adipocytes, cardiomyocytes[92]and leukocytes [93;94]. Moreover, effects of melatonin are known in all these cell types and factors involved in metabolic sensing are modulated by this hormone, such as peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), peroxisome proliferator-activated receptor-γ (PPARγ), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), including the accessory oscillator components AMP kinase (AMPK), nicotinamide phosphoribosyl transferase (NAMPT)

and sirtuin 1[17;90]. However, the effects of melatonin on all these factors are by far not uniform, but rather often contradictory or, at least, conditional[17]. Therefore, it is of utmost importance to remain in the context of inflammaging and to discriminate between direct effects and indirect actions via circadian central or peripheral oscillators, demands that have frequently not been considered in respective studies. It would be also important to be aware of the fundamental rules of phase dependency of any action on circadian oscillators, which can lead to either up- or downregulations at different circadian times. Cases of direct effects not mediated by oscillators may be present in the induction of antioxidant enzymes in rat liver and pancreas under inflammatory conditions, where melatonin promotes the expression and nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) that mediates the upregulation of the protective enzymes [95-97]. Correspondingly, melatonin reduced proinflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and inducible nitric oxide synthase (iNOS) by suppressing the expression of nuclear factor-κB (NF-κB) via recruitment of a histone deacetylase (HDAC) to its promoter [95;96]. However, it is important to remain aware of the conditionality of melatonin effects on pro- and anti-inflammatory cytokines, which may be either up- or downregulated by this hormone [79]. Importantly, pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 have been shown to be reduced in various models of aging, whereas the anti-inflammatory IL-10 was typically stimulated [27]. Whether this would be also the case under conditions of beginning MS at younger age deserves future attention and thorough analysis, especially as the pro-inflammatory cytokines are usually upregulated by melatonin under basal conditions [79]. Various other effects of melatonin on gene expression seem to be mediated by the circadian system. In particular, the role of SIRT1 should be considered, which is not only believed to be an aging suppressor, but acts as a protein deacetylase and, moreover, as a

component of circadian oscillators that interacts with the BMAL1/CLOCK dimer and is required for high rhythm amplitudes [89;98]. In various models of aging including senescence-accelerated mice, SIRT1 was upregulated by melatonin and caused enhanced deacetylation of various of its substrates, such as PGC-1α, FoxO1, NFκB, and p53 [27;86]. Notably, these effects strongly contrast with opposite effects in epigenetically dysregulated oscillators of cancer cells. Other aspects of epigenetic modulation including possible indirect effects by melatonin via circadian oscillators have been recently summarized [99].

Evidence of Melatonin Therapeutic Value in MS. Animal Studies

Treatment with melatonin in rats has the ability to reduce obesity, type 2 diabetes and hepatic steatosis [100;101]. In several animal models of hyperadiposity melatonin injection is able to normalize most observed alterations and corrects the altered biochemical pro-inflammatory profile (Fig. 1, Table 1).

INSERT FIGURE 1

Moreover, melatonin treatment of streptozotocin-induced type 1 diabetic rats induces the regeneration and proliferation of beta cells in the pancreas leading to a decrease in blood glucose [102]. Loss of melatonin in circulation after pinealectomy of rats results in hyperinsulinemia and accumulation of triglycerides in the liver [103]. The long term administration of melatonin improves lipid metabolism in type 2 diabetic rats via restoring insulin sensitivity[104].Melatonin treatment increases glycogen content in the liver of rats[105]and in high fat diet-induced diabetic mice the intraperitoneal injection of 10 mg kg melatonin improved glucose utilization and insulin sensitivity and ameliorated hepatic steatosis[106].

Table 1 summarizes the effect of melatonin in animal models of obesity. Melatonin was usually very effective in reversing hyperadiposity. The reasons for the decrease in body weight

after melatonin in the absence of significant differences in food intake is worth to be explored. A key piece of evidence in this regard is the observation that melatonin plays a role in seasonal changes in adiposity by increasing the activity of the sympathetic nervous system innervating white fat which leads to lipolysis [107].

Melatonin not only affects white adipose tissue, but also increases the recruitment of brown adipocytes and increases their metabolic activity in mammals (see[108]). It was speculated that the hypertrophic effect and functional activation of brown adipose tissue induced by melatonin can likely be applied to treatment of human obesity. Collectively, the results indicate that the administration of melatonin effectively counteracts some of disrupting effects seen in diet-induced obesity in animals, in particular, insulin resistance, dyslipidemia and obesity.

INSERT TABLE 2

Evidence on Melatonin Therapeutic Value in MS. Clinical Studies

Table 2 summarizes the results of clinical studies on melatonin activity relevant to human MS. Medical literature was identified by searching databases including (MEDLINE, EMBASE), bibliographies from published literature and clinical trial registries/databases. Searches were last updated on March 23, 2016.

Type 2 diabetic patients have low circulating levels of melatonin [36]with a concurrently and expected upregulation of mRNA expression of melatonin membrane receptor [109]. Furthermore, allelic variants for melatonin receptors were associated with level of fasting blood glucose and / or increased risk of type 2 diabetes [110-112] and with polycystic ovary syndrome [113]. These findings strongly bind melatonin to glucose homeostasis in blood.

Patients with coronary artery disease show decreased melatonin secretion [31-34] and among elderly hypertensive individuals, nocturnal urinary melatonin excretion was inversely associated with the non-dipper pattern[114].In turn, administered melatonin proved capable of reducing nocturnal blood pressure in hypertensives [117-120] and attenuated age-dependent disturbances of cardiovascular rhythms[121]. A meta-analysis of randomized controlled trials suggest that melatonin controlled release is effective and safe in improving nocturnal hypertension [136]. As a pleiotropic molecule, melatonin may exert its antihypertensive and anti-remodeling effects through its antioxidant and scavenging properties, preserving the availability of nitric oxide and having sympathoplegic effects that provide cardiovascular protection in MS.

As well as in animal models, clinical studies have shown that melatonin improves lipid profiles in MS patients. Melatonin treatment (1 mg / kg for 30 days) increased levels of HDL cholesterol in peri- and postmenopausal women [137]. Several mechanisms may explain the hypolipidemic effects of melatonin, such as reduced intestinal absorption of cholesterol [138]or inhibiting cholesterol biosynthesis [139].

Catecholamine-induced hypercoagulability in acute stress that contributes to the growth of thrombus after rupture of coronary plaque was prevented by the administration of melatonin [122]. This was probably mediated by the reported inhibitory effects of melatonin on platelet aggregation [123-125]. In light of these results melatonin may have a protective effect in reducing atherothrombotic risk in MS.

Several studies support the beneficial role of melatonin in patients with MS. Melatonin treatment ameliorates MS in obese patients [126;127]as well as in bipolar and schizophrenic patients after treatment with second generation antipsychotics [128-130]. Melatonin administration normalizes MS in elder hypertensive patients[140] and improves enzymatic

profile in patients with on alcoholic liver steatosis[131;132]. The combination of melatonin and zinc acetate, when used alone or in combination with metformin improved glycemic control in type 2 diabetic patients [133] and an inverse relationship between urinary 6-sulfatoxy melatonin excretion and insulin levels and insulin resistance was reported in healthy women in the Nurses' Health Study cohort [141]. However, a recent a placebo-controlled, single-blind study including 21 healthy women, reported that melatonin (5 mg) decreased glucose tolerance [135]. Further studies are needed to clarify this controversy.

Overall, the results discussed above suggest that melatonin therapy may be beneficial for patients with MS. Undoubtedly, more studies are needed to evaluate an appropriate time / duration of treatment / dose relationship administration of melatonin in patients with MS.

As with many diseases, particularly those related to MS, hypertension, cardiovascular disease, obesity, diabetes, etc., evidence supports the hypothesis that metabolic rhythms attenuation and / or disruption contribute to the etiology of the disease. Diabetes mellitus, a significant risk factor for developing heart disease and / or MS in humans, is associated with a phase change in the cardiac circadian clock [142]. Actually, metformin, a diabetes medication commonly used under CCG guidelines, increases the circadian amplitude of the metabolic sensor AMP kinase (AMPK) and modulates liver casein kinase 1α (CK1α) and muscle CK1ε, two regulators of the respective circadian core oscillators, effects that influence the expression and temporal patterns of several clock components and key genes of energy metabolism [143].

Conclusions

Melatonin can provide an innovative strategy in MS by combining their effects on the circadian rhythm with their cytoprotective properties. Melatonin protects against several MS

comorbidities, such as diabetes and concomitant oxyradical mediated damage, inflammation, microvascular disease and atherothrombotic risk. At an early stage of the treatment of MS, a non-drug approach as changing lifestyle, low-fat diet and exercise is commonly recommended. Patients who are refractory to these changes are treated with antihypertensive drugs (antidiabetic, lipid-lowering drugs) that can have significant side effects.

Melatonin may have thus a place since the initial phases of MS treatment. It has a high safety profile and shows a reduced toxicity, thus differing from most many pharmaceutical agents used in MS patients. Moreover, melatonin is usually remarkably well tolerated at very high doses[144]. As melatonin is a short-lived molecule that has a limited duration of action (half-life from 0.54 to 0.67 h) analogs with a high affinity for melatonin receptors and a longer duration of action have synthesized to treat circadian disorders[145]. To what extent the new melatonergic agents approved by the US Food and Drug Administration or the European Medicines Agency (ramelteon, agomelatine, tasimelteon) share the protective activity of melatonin in MS remains to be defined. There is evidence that one of these analogs, ramelteon, given daily in drinking water (8 mg/ kg) for 8 weeks to spontaneously hypertensive male Wistar-Kyoto rats significantly attenuated systolic blood pressure and body weight gain associated with age [146]. In addition, an investigational melatonergic agonist, piromelatine (NEU-P11) has been reported to be similarly effective as or even superior to melatonin in improving some MS-associated parameters[52;60;147].

Given higher binding affinities, longer half-life and high relative potencies of the various melatonin agonists, studies using 2 or 3 mg / day of melatonin are probably inadequate to provide adequate comparison with the effects of the natural compound. Doses that considerably exceed those usually applied have been found to be safe, e.g., in the treatment of ALS patients

who received either 60 mg / day orally for up to 13 months[148] or enteral doses of 300 mg / day for up to 2 years [144]. In a phase I dose escalation study in healthy volunteers to assess the tolerability and pharmacokinetics of 20, 30, 50, and 100 mg oral doses of melatonin, no adverse effects after oral melatonin, other than mild transient drowsiness with no effects on sleeping patterns, were seen [149].Therefore, further clinical trials using dosages of melatonin in the range of 50 to 100 mg / day appear to be reasonable and are warranted. The priorities for populations, outcomes, and durations of these studies must be defined.

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Figure Legend

In several animal models of MS, hyperadiposity occurs together with an augmented systolic blood pressure (BP), increased circulating low-density lipoprotein-cholesterol, total cholesterol and triglyceride (TG) concentration and pro-inflammatory cytokine levels. Melatonin injection is able to normalize most observed alterations and corrects the altered biochemical pro-inflammatory profile (see Table 1 for references). BAT: brown adipose tissue.

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Table 1. Effects of melatonin in animal models of hyperadiposity

Observation	Reference(s)
In rats fed from weaning with a high-fat diet melatonin decreased body weight gain, feed efficiency and plasma glucose, leptin and triglyceride levels	[44]
In middle-aged rats receiving a high caloric liquid diet, melatonin reduced weight gain and plasma insulin and leptin levels	[45]
In high-fat diet-fed mice, melatonin improved insulin sensitivity and glucose tolerance	[46]
In ovariectomized rats, melatonin was effective to reduce obesity	[47-49]
In olanzapine-treated rats, melatonin was effective to reduce obesity	[50]
In gold fish body weight gain and specific growth rate were reduced by melatonin treatment	[51]
Melatonin and its analog piromelatonin inhibited weight gain and improves insulin sensitivity in high-fat fed rats	[52]
In high-fat fed rats, melatonin attenuated body weight increase, the increase in plasma glucose, insulin, adiponectin, leptin, triglycerides and cholesterol levels, and counteracted disrupted 24 h patterns	[53]
Melatonin reduced body weight gain, visceral adiposity, blood triglyceride and insulin levels and TBARS under a high calorie diet in rats.	[54]
In young male Zucker diabetic fatty rats melatonin treatment reduced mean weight gain without affecting food intake, decreased in a non-significant way blood pressure, and improved dyslipidemia	[55]
Melatonin improves MS induced by high fructose intake in rats without affecting food intake	[56-59]
Melatonin and its analog piromelatonin reduced blood pressure in spontaneously hypertensive rats	[60]
Melatonin prevents the development of the MS in male rats exposed to different light/dark regimens	[61]
Melatonin attenuates high fat diet-induced fatty liver disease in rats	[62]

Melatonin, given at the time of reperfusion, prevents ventricular arrhythmias in isolated hearts from fructose-fed rats and spontaneously hypertensive rats	[63]
Melatonin ameliorates low-grade inflammation and oxidative stress in young Zucker diabetic fatty rats	[64]
Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats	[65]
Melatonin normalizes clinical and biochemical parameters of mild inflammation in diet-induced MS syndrome in rats	[66]
Melatonin counteracts changes in hypothalamic gene expression of signals regulating feeding behavior in high-fat fed rats	[67]
Melatonin reduces obesity and restores adipokine patterns and metabolism in obese (ob/ob) mice	[68]

Table 2. Clinical observations on melatonin relevant to MS.

Finding	Subjects	Design	Study´s duration	Treatment	Measured	Results	Ref.
Low plasma melatonin levels in type 2 diabetic patients	36 type 2 diabetic patients and 13 age-matched healthy subjects	Obser-vational study	Unquoted	None	Serum melatonin levels measured by RIA between 02:00-04:00 and 16:00-18:00 h. Cardio-vascular reflex tests, HRV, and 24-hBP monitoring	Nocturnal melatonin levels and the nocturnal melatonin surge were significantly lower in the diabetic group. A negative correlation occurred between nocturnal melatonin levels and the degree of systolic BP decrease at night. Patients with autonomic neuropathy showed decreased melatonin levels both at night and during day when compared to healthy controls. In patients with autonomic neuropathy nocturnal melatonin levels were positively correlated with nocturnal high and low frequency components of HRV and systolic and diastolic BP at night	[36]
Increased number of melatonin receptors in type 2 diabetic patients	Surgical specimens of pancreata obtained from 25 patients who underwent partial or total pancrea-tectomy because of cancer or severe chronic pancreatitis	Obser-vational study	Unquoted	None	Real time PCR and immune-cytochemistry of MT_1 and MT_2 receptors	The existence of the melatonin MT_1 and MT_2 receptors in human pancreatic tissue and in islets of Langerhans was assessed. mRNA transcript levels of melatonin receptors and their immunocytochemical expression were significantly higher in type 2 diabetic patients. Transcripts of the nuclear orphan receptors were also higher in human pancreatic tissue and islets of type 2 diabetic patients.	[109]
Melatonin receptor gene polymorphism associated with	36 610 individuals of European descent	Obser-vational study	Unquoted	None	Leading association signals in ten genome-wide association scans	The strongest signal was observed at rs10830963, where each G allele (frequency 0.30 in HapMap CEU) was associated with an increase of 0.07 mmol/l in fasting glucose levels and reduced beta-cell function as measured by homeostasis model assessment. The	[110]

high risk of type 2 diabetes						same allele was associated with an increased risk of type 2 diabetes	
Genetics of MT_2receptor associated with left ventricular function in hypertensive patients	605 patients with arterial hypertension and cardiac ejection fraction ≤40%	Obser-vational study	Unquoted	None	SNPs of MT_2. Cardiac parameters assessed by echocardiography	Analysis of SNPs rs10830962, rs4753426, rs12804291, rs10830963, and rs3781638 revealed two haplotypes 1 and 2 with frequencies of 0.402 and 0.277, respectively. Carriers with haplotype 1 showed compared to a higher mean 24-h systolic BP. Haplotype 2 was significantly related to cardiac ejection fraction with an absolute increase of 1.8% in carriers versus non-carriers	[111]
Genetics of MT_2 receptor associated with increased risk of impaired fasting glucose in youth with obesity	346 Caucasians, 218 African-Americans, and 217 Hispanics obese children and adolescents	Obser-vational study	Variable	None	Oral glucose tolerance test. Evaluation of insulin secretion by the oral minimal model	The MTNR1B rs10830963 variant was associated with higher fasting glucose levels and lower dynamic beta-cell response in Caucasians and Hispanics and conferred an increased risk of showing impaired fasting glucose to Caucasians, African-Americans and Hispanics	[112]
Melatonin receptor gene polymorphisms in polycystic ovary syndrome	789 participants (Han Chinese)	Obser-vational study	Unquoted	Unquoted	Genotypes were obtained by sequencing	An association was detected between MTNR1B rs2119882 and polycystic ovary syndrome, suggesting that the MTNR gene may indicate increased susceptibility to polycystic ovary syndrome in Chinese. No significant association was found for rs10830963. CC genotype carriers had higher levels of clinical and metabolic features of polycystic ovary syndrome than the TC and TT genotypes. A significant difference in transmission of allele C of rs2119882 was found between obese and non-obese women with polycystic ovary syndrome	[113]
Low melatonin production in coronary disease independent of	48 male patients with angio-graphically documented severe	Obser-vational cross-sectional study	Unquoted	24 patients took beta-blockers daily in therapeutic dosages	aMT6s was measured by RIA from overnight urine	Urinary aMT6s concentration was significantly decreased in patients, and beta-blocker treatment did not further suppress melatonin production	[31]

β-adrenoceptor blockade	coronary artery disease. 18 age-matched men, with no evidence of coronary sclerosis, served as controls						
Low melatonin production in coronary disease independent of β-adrenoceptor blockade	Three groups of individuals were studied: a) 24 healthy subjects; b) 32 patients with chronic, stable, coronary disease); c) 27 patients with unstable angina	Obser-vational cross-sectional study	Unquoted	24 patients with chronic coronary disease and 14 patients with unstable angina received beta-blockers daily in therapeutic dosages	aMT6s was measured by RIA from overnight urine	Urinary aMT6s excretion was significantly lower in unstable angina patients than in healthy subjects or in patients with stable angina. aMT6s correlated negatively with age in healthy subjects, but not in coronary patients. aMT6s excretion in patients treated with beta-adrenoceptor blockers did not differ significantly from coronary patients not receiving beta-blockers	[32]
Low melatonin production in myocardial infarction	25 patients diagnosed with acute myocardial infarction and 25 patients with no evidence of coronary artery disease were studied	Obser-vational cross-sectional study	Unquoted	Unquoted	Levels of melatonin, glutathione peroxidase and lipid peroxidation in serum samples collected at 10:00 h (light period) and 03:00 h (dark period)	A reduced nocturnal elevation of melatonin was found in the acute myocardial infarction group. Glutathione peroxidase levels were lower after acute myocardial infarction and did not show diurnal variations. In the control group, lipid peroxidation levels presented a light/dark pattern but in the acute myocardial infarction group diurnal variations of this parameter were lost	[33]

Low melatonin production in coronary disease	16 patients with angiographically documented coronary disease and 9 healthy controls	Observational cross-sectional study	Unquoted	Unquoted	Melatonin levels measured by RIA in serum samples collected every 2 h between 22:00 and 08:00 h	A large interindividual variation in the pattern of melatonin secretion was seen in both groups. Patients with coronary disease secreted less nocturnal melatonin at 02:00, 04:00 and 08:00 h than control subjects. Peak time of melatonin secretion was observed earlier in patients with coronary disease (02:00 h vs. 03:45 h)	[34]
Low melatonin production in in elderly hypertensives	141 elderly hypertensives	Observational cross-sectional study	Unquoted	Unquoted	Overnight urinary melatonin excretion, ambulatory blood pressure and actigraphic physical activity	When participants were divided into two groups (high and low melatonin groups) by the cutoff value for identifying the top tertile, the characteristics, except for age, did not significantly differ between the two groups. In a multivariate analysis after adjustment for age, diabetes and daytime activity, the odds ratio for the non-dipper pattern in the high melatonin group was significantly lower than that in the low melatonin group. The mean percentage systolic blood pressure nocturnal fall, adjusted for the former covariates, was significantly higher in the high melatonin group than the low melatonin group. Among elderly hypertensive individuals, nocturnal urinary melatonin excretion was significantly and inversely associated with the non-dipper pattern	[114]
Melatonin treatment decreases nocturnal BP in type 1 adolescent diabetics	11 normotensive adolescents with type 1 diabetes and 10 healthy controls	Randomized placebo-controlled double-blind cross-over study	2 weeks	5 mg melatonin or placebo taken at bedtime p.o.	BP every 20 min for 24 h by an ambulatory device on the day before and on the last day of each treatment. Sleep measures were recorded by a diary and a wrist activity meter.	Exogenous melatonin given to healthy normotensive adults reduces BP. In the patients with type 1 diabetes, the decline in diastolic BP during sleep was significantly greater on melatonin than on placebo. No significant drug effect was present in the controls. No significant side effects were noted	[115]
Melatonin treatment decreases	9 normotensive adolescents	Open-label trial	1 week	10 mg melatonin	BP was measured every 20 min by ambulatory	In patients with diabetes the mean BP during sleep was lower on melatonin than before treatment. In controls there was no significant effect of melatonin	[116]

nocturnal BP in type 1 adolescent diabetics	with type 1 diabetes and 8 healthy controls			taken at bedtime p.o.	monitoring device for 24 h before treatment onset and on the last treatment day; sleep was monitored by diary and wrist actigraphy	on BP. There was no significant effect of sleep duration or number of awakenings on the BP responses	
Melatonin treatment decreases high nocturnal BP in hypertensives	16 men with untreated essential hypertension	Ran-domized placebo-controlled double-blind cross-over study	3 weeks	acute (single) and repeated (daily for 3 weeks) oral melatonin (2.5 mg) intake 1 h before sleep	BP was measured every 20 min by ambulatory monitoring device for 24 h before treatment onset and on the last treatment day	Repeated melatonin intake reduced systolic and diastolic BP during sleep by 6 and 4 mm Hg, respectively. The treatment did not affect heart rate. The day-night amplitudes of the rhythms in systolic and diastolic BP were increased by 15% and 25%, respectively. A single dose of melatonin had no effect on BP. Repeated (but not acute) melatonin also improved sleep	[117]
Melatonin treatment decreases high nocturnal BP in hypertensives	18 women, 47 to 63 years of age with normal BP (N = 9) or treated essential hypertension (N = 9)	Ran-domized double-blind study	6 weeks	Slow-release melatonin pill (3 mg) or placebo 1 h before going to bed.	Ambulatory BP was recorded for 41 hat baseline at the end of each treatment period	In comparison with placebo, melatonin administration did not influence diurnal BP but did significantly decrease nocturnal systolic, diastolic and mean BP without modifying heart rate. The effect was inversely related to the day-night difference in BP	[118]
Melatonin treatment decreases high nocturnal BP in hypertensives	38 treated hypertensive patients with confirmed nocturnal hypertension according to repeated 24-hour ambulatory	Ran-domized double-blind study	4 weeks	controlled release melatonin 2 mg or placebo 2 hours before bedtime	Ambulatory BP was recorded for 24 h	Melatonin treatment reduced nocturnal systolic BP significantly from 136 to 130 mm Hg, and diastolic BP from 72 to 69 mm Hg, whereas placebo had no effect on nocturnal BP. The reduction in nocturnal systolic BP was significantly greater with melatonin than with placebo and was most prominent between 0200 and 0500 h. Nocturnal BP control in treated patients with nocturnal hypertension	[119]

	BP monitoring						
Melatonin treatment decreases high nocturnal BP in type 2 diabetic hypertensives	60 dipper and 64 non-dipper patients	Open-label trial	8 weeks	3 mg melatonin p.o. at bedtime was administered to 32 dipper and 34 non-dipper patients for 4 weeks. Then the same patients received 5 mg of melatonin for the next 4 weeks. 28 dippers and 30 non-dippers did not receive melatonin	Ambulatory BP was recorded for 24 h	29.5% of non-dippers treated with 3 mg/day melatonin achieved features of dippers compared to control group. Five mg of melatonin per day restored normal diurnal BP rhythm in 32.4% non-dippers. In non-dippers treated with melatonin significant decreases of diastolic, systolic and mean night BP values were observed	[120]
Melatonin treatment attenuates age-dependent disturbances of cardiovascular rhythms	97 normo-tensive and hypertensive volunteers (63 to 91 years old)	Placebo con-trolled trial	3 weeks	1.5 mg melatonin or placebo p.o. each day at 22:30 h for two weeks	Systolic and diastolic BP and HR) were measured using semi-automated devices at 03:00, 08:00, 11:00, 14:00, 17:00, 23:00 h each day of the first and the third week	The 24-h HR rhythm was monophasic with a steeper increase in the morning. The daily systolic and diastolic BP rhythms were bimodal. In reference to previously reported data of younger subjects, mean BP was elevated, particularly the nocturnal fall was less pronounced. Also, the overall systolic BP variability was higher as was the percentage of the 12-h component. Both values and also the systolic and diastolic BP were reduced during melatonin treatment. The hypotensive effect of melatonin was most pronounced between 03:00 and 08:00 in the morning. Melatonin not only has a direct hypotensive effect. Also, it stabilizes the internal temporal order enhancing the circadian component	[121]

						and the synchronization between rhythms of different physiological functions	
Melatonin treatment prevents catecholamine-induced hyper-coagulability	45 healthy young men	Placebo con-trolled trial	1 h	A single oral dose of either 3 mg melatonin (n = 24) or placebo (n = 21). One hour thereafter, they underwent a standardized short-term psychosocial stressor	Plasma levels of clotting factor VII activity (FVII:C), FVIII:C, fibrinogen, D-dimer, and catecholamines were measured at rest, immediately after stress, and 20 min and 60 min post-stress	Compared with the melatonin group, the placebo group showed a greater increase in absolute D-dimer levels from rest to immediately post-stress and significant recovery of D-dimer levels from immediately post-stress to 60 min thereafter. Stress-induced changes in FVII:C, FVIII:C, fibrinogen, and catecholamines did not significantly differ between groups. Oral melatonin attenuated the stress-induced elevation in the sensitive coagulation activation marker D-dimer without affecting catecholamine activity	[122]
Melatonin inhibits human platelet aggregation	22healthy young men	In vitro study	Unquoted	10^{-9} – 10^{-5} M melatonin	Platelet aggregation and TxB2 production in PRP	Melatonin inhibited in a dose-dependent way ADP-induced platelet aggregation with individual inhibitions 40% or more at 10^{-6} – 10^{-5} M concentrations and a higher global inhibitory at 1800 h. TxB2 production elicited by AA in the evening was inhibited significantly in a concentration-related manner by 10^{-9} – 10^{-5} M melatonin, while during the morning hours the inhibition was significant only at 10^{-6} M or higher melatonin concentrations. Melatonin depression of TxB2 generation was about 2-fold greater at 1800 h than at 0830 h	[123]
Melatonin inhibits human platelet aggregation	10 healthy young men and 5 women in early follicular phase	In vitro study	Unquoted	10^{-9} – 10^{-5} M melatonin	Platelet aggregation and ATP and serotonin release in PRP	ADP-induced ATP and serotonin release, indexes of platelet secretory processes, showed a generally greater, dose-dependent inhibition after adding melatonin (10^{-9} M – 10^{-5} M concentrations) at 2030 h as compared to 0830 h	[124]

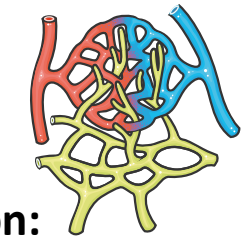
Melatonin inhibits human platelet aggregation	5 healthy young men	Obser-vational study	Unquoted	For in vitro studies 10^{-9} – 10^{-5} M melatonin were used	Plasma melatonin concentration, platelet aggregation and TxB2 production in PRPsampled at 2 h intervals from 2130 to 0930 h.	Inhibition by 10^{-6} M melatonin of AA-induced PRP aggregation and TxB2 production was observed mainly in samples taken at 0130 h. Assessed as a global effect, the inhibitory activity of melatonin on PRP TxB2 showed a maximum at 0130 h and minimal effects at 0330 h, at the time when plasma concentrations of melatonin were highest	[125]
Melatonin treatment ameliorates MS in obese patients	30 patients with MS who did not respond to 3-month lifestyle modification, and 33 healthy volunteers	Open-label trial	2 months	Melatonin (5 mg/day, 2 h before bedtime) for 2 months. Controls did not receive melatonin	Systolic and diastolic BP, levels of glucose, serum lipids, C-reactive protein, fibrinogen, activities of antioxidative enzymes	Melatonin treatment decreased significantly systolic BP, diastolic BP, low-density lipoprotein cholesterol and TBARS and augmented catalase activity	[126]
Melatonin treatment ameliorates MS in obese patients	39 SM patients	Double-blind, placebo-con-trolled, cross-over, ran-domized trial	26 weeks	8.0 mg p.o. melatonin or placebo nightly for 10 weeks. After a 6-week washout, subjects received the other treatment for 10 more weeks	Waist circumference, triglycerides, HDL cholesterol, fasting glucose, and BP at the beginning and end of both 10-week treatment periods	The mean 10-week change for most MS components favored melatonin over placebo (except fasting glucose). Freedom from MS tended to be more common following melatonin versus placebo treatment	[127]
Melatonin treatment ameliorates the MS caused by second generation antipsychotics	44 patients treated with second-generation antipsychotic s (20 with bipolar	Double-blind, random-ized, placebo-con-trolled,	8 weeks	Patients randomly received melatonin 5 mg p.o. at bedtime (n = 20) or	Body weight, BP, lipid, glucose, body composition, and anthropometric measures.	The melatonin group showed a decrease in diastolic BP and attenuated weight gain. The strong beneficial metabolic effects of melatonin in comparison to placebo on fat mass and diastolic BP were observed in the bipolar disorder and not in the schizophrenia group	[128]

in bipolar and schizophrenic patients	disorder and 24 with schizo-phrenia),	parallel-group trial		placebo (n = 24)			
Melatonin treatment ameliorates the MS caused by olanzapine in schizophrenic patients	48 patients with first-episode schizo-phrenia	Ran-domized double-blind placebo-controlled study	8 weeks	Patients randomly received melatonin 3 mg p.o. at bedtime or placebo	Anthropometric and metabolic parameters as well as psychiatric symptoms were assessed at baseline, week 4, and 8. Primary outcome measure was the change from baseline in weight at week 8.	At week eight, melatonin was associated with significantly less weight gain, increase in waist circumference and triglyceride concentration than the placebo. Patients in the melatonin group experienced significantly more reduction in their psychiatric symptomatology than the placebo group	[129]
Melatonin treatment ameliorates the MS caused by olanzapine in adolescents with bipolar disorder	48 adolescent outpatients with bipolar mood disorder	Ran-domized placebo-con-trolled study	12 weeks	24 patients were allocated to olanzapine, lithium carbonate, and 3 mg / day melatonin p.o. and 24 patients were allocated to olanzapine, lithium carbonate, and placebo	Young mania rating scale was performed at baseline. Before treatment initiation and at 6th and 12th weeks after treatment, lipid profile, fasting blood sugar, systolic BP and diastolic BP were measured	Fasting glycemia and serum triglyceride demonstrated a trend to a greater increase in the placebo group compared to the melatonin group. Melatonin significantly inhibited the rise in total cholesterol levels. Mean systolic BP rose more slowly in the melatonin group compared to placebo	[130]
Melatonin treatment improves enzymatic	42 patients with histological evidence	Ran-domized placebo-con-	12 weeks	30 patients were allocated to 2 x 5 mg /	BMI, plasma alanine amino-transferase, aspartate amino-	Aspartate aminotransferase and gamma-glutamyl transpeptidase decreased significantly in melatonin-treated patients only. Plasma levels of triglycerides and glucose as well as BMI in controls and	[131]

profile in patients with non-alcoholic liver esteatosis	(liver biopsy) of nonalcoholic steato-hepatitis	trolled study		day melatonin p.o. and 12 patients were allocated to placebo	transferase, gamma-glutamyl-transpeptidase, alkaline phosphatase, cholesterol, triglycerides, glucose and melatonin	melatonin-treated patients were not significantly different from baseline	
Melatonin treatment improves enzymatic profile in patients with non-alcoholic liver esteatosis	42 patients with histological evidence (liver biopsy) of non alcoholic steato-hepatitis (follow-up of the previous study)	Ran-domized placebo-con-trolled study	24 weeks	30 patients were allocated to 2 x 5 mg / day melatonin p.o. and 12 patients were allocated to placebo	BMI, plasma alanine amino-transferase, aspartate amino-transferase, gamma-glutamyl-transpeptidase, alkaline phosphatase, cholesterol, triglycerides, glucose and melatonin	Aspartate aminotransferase and gamma-glutamyl transpeptidase decreased significantly in melatonin-treated patients only. Plasma levels of triglycerides and glucose as well as BMI in controls and melatonin-treated patients were not significantly different from baseline	[132]
Melatonin alone or in combination with metformin improves glycemic control in type 2 diabetic patients	46 type 2 diabetic patients	Placebo con-trolled, double-blind trial	90 days	Patients were allocated into 3 groups: a. single daily oral doses of both 10 mg melatonin and 50 mg zinc acetate alone; b. 10 mg melatonin and 50 mg zinc acetate	Fasting plasma glucose, glycated hemoglobin (HbA1C) and serum C-peptide before starting the treatment and after 30 and 90 days of treatment	Daily administration of melatonin and zinc improved the impaired fasting and post-prandial glycemic control and decreased the level of glycated hemoglobin; addition of this treatment regimen in combination with metformin improved the tissue responses to this oral hypoglycemic agent	[133]

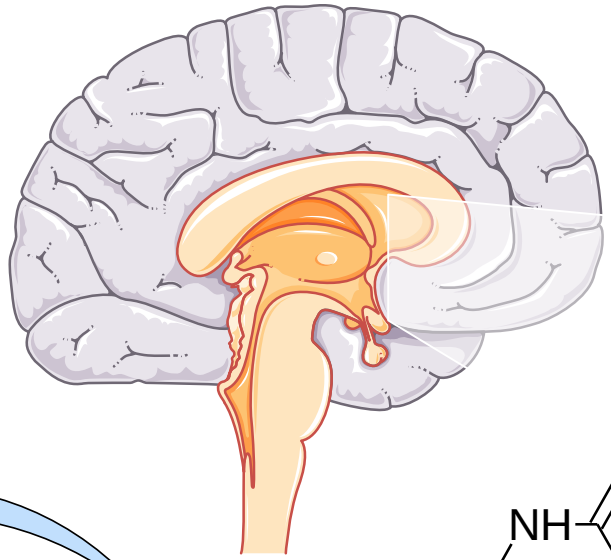
				in addition to the regularly used metformin; c. placebo, all given at bed time			
Melatonin treatment ameliorated oxidative stress and inflammatory parameters of obese women	44 obese women	Ran-domized double-blind, placebo-con-trolled trial	40 days	6 mg melatonin p.o. at bedtime	Serum TNF-α, IL-6, hsCRP, TAC, and MDA levels	In the melatonin group, mean serum TNF-α, IL-6, hsCRP, and MDA levels decreased significantly whilst in the placebo group the decrease in values were not statistically significant. Mean TAC level increased in the melatonin group whereas it decreased slightly in the placebo group. Melatonin decreased significantly TNF-α and IL-6 levels.	[134]
Acute melatonin administration in healthy women impairs glucose tolerance	21 healthy young women	Ran-domized double-blind, placebo-con-trolled trial	4 non-con-secutive days	5 mg melatonin p.o	Glucose tolerance was assessed by oral glucose tolerance tests 15 minutes after melatonin or placebo administration on 4 occasions: in the morning (0900 h), and evening (2100 h)	Melatonin administration significantly impaired glucose tolerance. The effect of melatonin on the insulin response depended on the time of day. In the morning, melatonin decreased glucose tolerance primarily by decreasing insulin release, while in the evening, by decreasing insulin sensitivity.	[135]

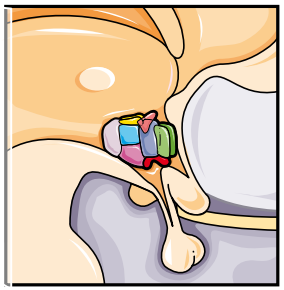
AA: arachidonic acid; aMT6s: 6-sulfatoxymelatonin; BP: blood pressure; hsCRP: human serum C-reactive protein; HR: heart rate; HRV: heart rate variability; MDA: malondialdehyde; p.o.: per os; PRP: platelet-rich plasma;RIA: radioimmunoassay; SNP: single nucleotide polymorphism; TAC: total antioxidante capacity; TBARS: thiobarbituric acid reactive substances; TNF: tumor necrosis factor; TxB2: thromboxane B2



Circulation:

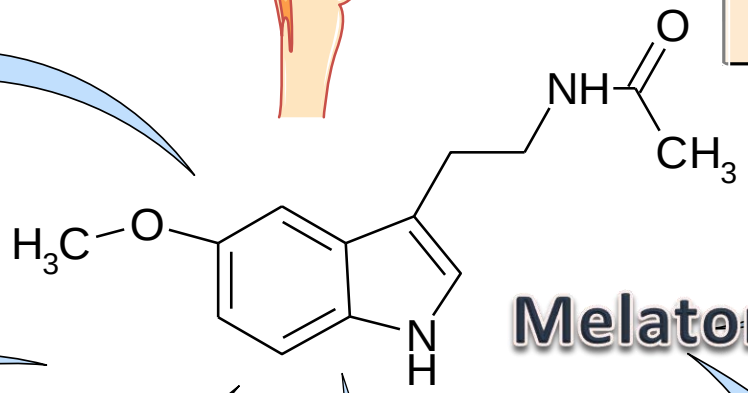
↓ Leptin
↓ Insulin
↓ Glycemia
↑ Adiponectin
↓ IL-6, TNFα
↓ IL-1β, IFNγ
↓ C Reactive Protein
↓ LDL-c, TG
↑ HDL-c, IL-4, IL-10



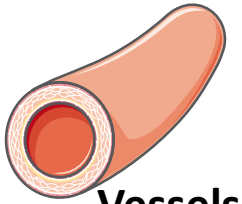


MBH Gene Expression

↓ NPY
↓ PrRP
↓ Leptin-R
↓ Insulin-R
↓ IRS-1
↓ IRS-2

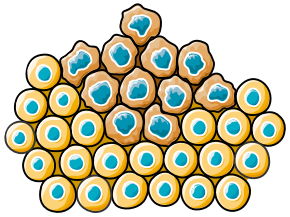


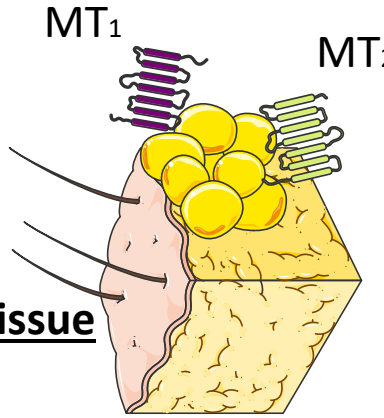
Melatonin



Vessels

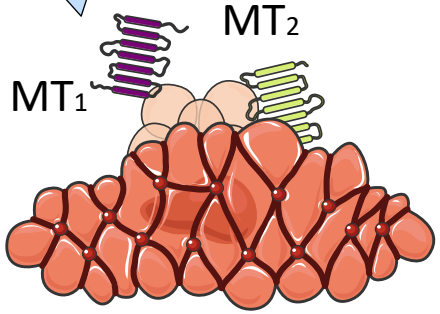
↓ BP





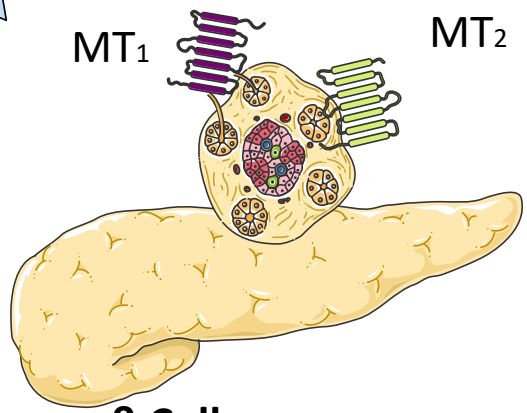
↓ **White Adipose Tissue**

↑ lipolysis



↑ **Brown Fat**

↑ energetic expenditure



β Cells

↓ Insulin secretion