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REVIEW ARTICLE

Melatonin, energy metabolism, and obesity: a review

Abstract: Melatonin is an old and ubiquitous molecule in nature showing multiple mechanisms of action and functions in practically every living organism. In mammals, pineal melatonin functions as a hormone and a chronobiotic, playing a major role in the regulation of the circadian temporal internal order. The anti-obesogen and the weight-reducing effects of melatonin depend on several mechanisms and actions. Experimental evidence demonstrates that melatonin is necessary for the proper synthesis, secretion, and action of insulin. Melatonin acts by regulating GLUT4 expression and/or triggering, via its G-protein-coupled membrane receptors, the phosphorylation of the insulin receptor and its intracellular substrates mobilizing the insulin-signaling pathway. Melatonin is a powerful chronobiotic being responsible, in part, by the daily distribution of metabolic processes so that the activity/feeding phase of the day is associated with high insulin sensitivity, and the rest/fasting is synchronized to the insulin-resistant metabolic phase of the day. Furthermore, melatonin is responsible for the establishment of an adequate energy balance mainly by regulating energy flow to and from the stores and directly regulating the energy expenditure through the activation of brown adipose tissue and participating in the browning process of white adipose tissue. The reduction in melatonin production, as during aging, shift-work or illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization characterizing a state of chronodisruption leading to obesity. The available evidence supports the suggestion that melatonin replacement therapy might contribute to restore a more healthy state of the organism.

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Introduction

Melatonin (N-acetyl-5-methoxytryptamine or, according to IUPAC, N-[2-(5-methoxy-1H-indol-3-yl) ethyl] acetamide) is an ancient molecule ubiquitously present in nature including both plant and animals [1–5]. It is well known that in mammals, melatonin is synthesized in several cells, tissues, and organs mainly for local utilization (autocrine and paracrine actions) and that circulating melatonin is largely provided by the pineal gland where it is produced and directly released to the blood and cerebrospinal fluid [6–9].

While pineal melatonin has all the characteristics of a hormone, it also has features, which distinguish it from classical hormones. It is centrally produced in an endocrine gland, circulates in a free and albumin-linked form [10–12], and can act through specific G-protein-coupled membrane receptors (MT1 or MTRN1a, MT2 or MTRN1b and MT3) [13, 14] as well as on putative nuclear RZR/ROR retinoid receptors [15–17]. Melatonin's membrane receptor-mediated mechanisms of action and its physiological effects via those receptors have been defined [18–20]. Conversely, its mechanisms of action at the nuclear level are less well defined [21, 22]. Melatonin's direct free radical scavenging actions account for its receptor-independent effects [23–25].

Pineal melatonin production is under control of the paraventricular nucleus of the hypothalamus, which project, eventually, to the intermediolateral column of the upper thoracic segments of the spinal cord where the sympathetic preganglionic neurons are located. The axons of these neurons exit the cord and pass to the rostral third of the superior cervical ganglia, which in turn send postganglionic sympathetic projections through the conarii nerves to the pineal gland [26, 27]. Norepinephrine is released from these nerve endings where it interacts with β_1 and α_1 postsynaptic adrenoreceptors to trigger several intracellular transduction mechanisms that activate melatonin synthesis in the pinealocytes [1].

The activation/deactivation of this complex neural pathway controlling pineal melatonin synthesis is under the precise control of the master circadian clock, the suprachiasmatic nucleus of the hypothalamus (SCN). Via this pathway, melatonin production expresses a circadian rhythm that is tightly synchronized to the light/dark cycle. The circadian control is such that melatonin production is always circumscribed to the night, regardless the behavioral distribution of activity and rest of the considered mammalian species (diurnal, nocturnal, or crepuscular species), that is, it is considered the chemical expression of darkness [28]. Moreover, high production is maintained

during the dark phase of the light/dark cycle provided there is no light in the environment, as light during the night (related to the irradiance, wavelength, and duration) blocks melatonin production [29–33]. These functional particularities of the mammalian system that control pineal melatonin production guarantee that the circadian clock triggers melatonin production daily at night and that environmental light and the clock determine the duration of the daily episode of melatonin synthesis [34–36]. In this way, given the adequate ecological and social habitat conditions, the physiological system that controls melatonin synthesis allows the nocturnal profile of circulating melatonin to vary according to the duration of the daily scotoperiod reflecting therefore the season of the year and acting as a neuroendocrine mediator of the photoperiod [27, 37]. Because of this, the circadian melatonin rhythm drives annual reproductive and metabolic cycles in photoperiod-sensitive mammals [38–40]. In part due to the above chronobiological characteristics of production, melatonin is one of the main mediators used by the central master clock to time central and peripheral tissues, acting as an internal synchronizer or 'internal zeitgeber' [41]. Moreover, melatonin is able to act on peripheral oscillators regulating their phase and period, mainly by controlling the transcription/translation circadian cycle of the peripheral clock genes [42, 43]. This functional aspect makes melatonin one of the most important chronobiotic [41, 44] that directly participates in the organization of the circadian temporal coordination of physiological and behavioral phenomena.

Melatonin and energy metabolism

All physiological and behavioral processes of the body are organized to balance energy intake, storage, and expenditure. The energy balance guarantees the individual's survival, growth and reproduction, and, consequently, species perpetuation. Through the adequate circadian distribution and organization of the metabolic processes, most animals optimize energy balance by concentrating energy harvesting and intake during the active phase of the day and mobilizing body energy stores during the resting phase in order to produce the energy necessary to sustain the living processes. Melatonin is the key mediator molecule for the integration between the cyclic environment and the circadian distribution of physiological and behavioral processes and for the optimization of energy balance and body weight regulation, events that are crucial for a healthy metabolism [45]. In this scenario, to fully understand the role played by melatonin in the control of energy metabolism, it is necessary to address the subject from following the perspectives: i), from the perspective of the classical endocrinology, examining the role played by melatonin in the regulation of metabolic processes; ii), from the perspective of the chronobiology, considering the role played by melatonin in the regulation of the circadian internal temporal order of the physiological processes involved in energy metabolism; iii), and finally, understanding the role played by melatonin in the regulation of energy balance and its final outcome, that is, body weight, as a way to sum up its regulatory role on energy metabolism.

Melatonin and the regulation of metabolic processes

The relation between pineal gland, melatonin, and energy metabolism was initially hinted at in both humans [46] and rodents [47] many years ago. The very first experiments [48–52] demonstrated that infusion of pineal extracts led to hypoglycemia, increased glucose tolerance, and hepatic and muscular glycogenesis after glucose loading, while pinealectomy induced a diminished glucose tolerance and a reduced hepatic and muscular glycogenesis. More recently, the metabolic disruption caused by the absence of melatonin in the pinealectomized animal was characterized as a diabetogenic syndrome that includes glucose intolerance and peripheral (hepatic, adipose, and skeletal muscle) and central (hypothalamus) insulin resistance [53–55]. This dramatic pathological picture can be reverted by melatonin replacement therapy or restricted feeding [54, 56, 57], but not by physical training [58–60]. Moreover, insulin resistance, glucose intolerance, and several alterations in other metabolic parameters can be seen in some physiological or pathophysiological states associated with reductions in blood melatonin levels, as aging, diabetes, shift work, and environmental high level of illumination during the night [61–68]. It is emphasized that adequate melatonin replacement therapy alleviates most of the mentioned metabolic alterations in these situations. Furthermore, a similar metabolic syndrome is seen in MT1-knockout animals [69].

The genesis of the pinealectomy-induced insulin resistance and glucose intolerance is related to the cellular consequences of the absence of melatonin, such as a deficiency in the insulin-signaling pathway and reduction in GLUT4 gene expression and protein content. The insulin-sensitive tissues (white and brown adipose tissue and skeletal and cardiac muscles) of the pinealectomized animal exhibit a greater reduction in GLUT4 mRNA and microsomal and membrane protein contents that reverts to the level of the intact animal following adequate melatonin replacement therapy [53, 56, 70–73]. Moreover and emphasizing the functional synergism between melatonin and insulin, it was shown that melatonin by itself, acting through MT1 membrane receptors, induces rapid tyrosine phosphorylation and activation of the tyrosine kinase β-subunit of the insulin receptor, and mobilizing several intracellular transduction steps of the insulin-signaling pathway (tyrosine phosphorylation of IRS-1; IRS-1/PI(3)-kinase and IRS-1/SHP-2 associations; and downstream AKT serine, MAP-kinase, and STAT3 phosphorylation) [74–76].

One of the first direct pieces of evidence of the functional synergism between melatonin and insulin was published by Lima and coworkers two decades ago [77]. This group showed that in vitro incubation of isolated visceral white adipocytes with melatonin shifted the dose x response curve for C^{14}-2-deoxy-D-glucose uptake stimulated by insulin to the left. This was the first demonstration that the peripheral function of insulin was potentiated by the action of melatonin, and, in addition, it was the first evidence of a direct action of melatonin on adipocytes. This indicated that the adipose tissue is a peripheral target of melatonin for the regulation of the overall

metabolism. Similarly, Brydon et al. [78] demonstrated that melatonin activation of MT2 receptors in human adipocytes modulates glucose uptake by these cells.

In reference to adipose tissue physiology, it was possible to document the synergistic effect of melatonin on several other insulin actions in addition to glucose uptake. In a series of reports, Alonso-Vale et al. [42, 79, 80] demonstrated that insulin-induced leptin synthesis and release in isolated adipocytes is potentiated by the MT1-mediated melatonin action. This potentiating effect is enhanced by 100% if the in vitro incubation with melatonin mimics its usual 24-hr cycle; this was achieved by alternating melatonin-added medium for 12 hr (in vitro induced night) with melatonin-free medium for the following 12 hr (in vitro induced day) for 3–5 cycles. There are data confirming that melatonin regulates other aspects of adipocyte biology that influence energy metabolism, lipidemia, and body weight, as lipolysis, lipogenesis, adipocyte differentiation, and fatty acids uptake among others [42, 78, 81–83].

Another major site of melatonin's action in reference to the regulation of energy metabolism is the pancreatic islets where it influences insulin and glucagon synthesis and release. MT1- and/or MT2-mediated melatonin action decreases glucose-stimulated insulin secretion in isolated rat pancreatic islets and rat insulinoma beta-cells [84–90]. The activation of these receptors inhibits glucose- and forskolin-induced insulin secretion showing that melatonin acts by inhibiting the adenylate cyclase/cAMP system and reducing the content of PKA with no alteration in the content of PKCα-subunit, in parallel to a reduction in cGMP. In addition, through MT1 activation, melatonin induces insulin receptor, IRS-1, AKT, ERK1/2, and STAT3 phosphorylation, controlling insulin synthesis and release by islets B cells [76, 91–93].

Additionally, this indolamine induces IGF-1 receptor phosphorylation, which participates in the integrity and trophism of islet cells [94], [76]. Moreover, it has been demonstrated, as well, that melatonin stimulated glucagon synthesis and secretion either in vivo or in a particular glucagon-producing alpha-cell line [95, 96]. Most importantly, however, is that these actions of melatonin are required to build the circadian profile of insulin secretion, keeping the daily peak allocated to the first half of the active phase of the day and contributing to the synchronization of the pancreas metabolic rhythms with the circadian rhythm of activity-feeding/rest-fasting [97].

Finally, considering the physiological and pathophysiological importance of the regulatory action of melatonin on the pancreatic islet function, it has been suggested, using genome-wide association studies, that common non-coding variants in MTNR1B (encoding melatonin receptor 1B, also known as MT2) increase type 2 diabetes risk [98, 99]. This is a result of a putative inadequate pancreatic beta-cell response to the action of melatonin on insulin secretion, resulting in morning hyperglycemia. It should be noted that insulin is able to regulate pineal melatonin synthesis by potentiating norepinephrine-stimulated melatonin production at two sensitive time points during the night, one immediately after lights off and another just before lights on [100, 101].

As an addition to the importance of melatonin on the regulatory processes in energy metabolism, it was recently demonstrated that the intrauterine metabolic programming is modified if there is deficiency of melatonin in the pregnant mother [102]. The adult offspring of melatonin-deficient dams show glucose intolerance, insulin resistance, and a serious impairment in the glucose-induced insulin secretion by isolated pancreatic islets. These programming effects disappear with the appropriate schedule of melatonin replacement therapy to the mothers during gestation.

Melatonin and the regulation of daily rhythms in energy metabolism

The mammalian circadian master clock (SCN) times all peripheral clocks and, consequently, all the physiological and behavioral processes. This regulatory effect is accomplished using direct or indirect neural connections and/or humoral/hormonal mediators. As mentioned above, melatonin is one of these mediators, being one of the most important internal synchronizing agents. As a consequence, melatonin is fundamental for the maintenance of the internal circadian temporal organization, timing many physiological processes, including energy metabolism and their synchronization, which is crucial for health maintenance [103, 104].

The energy balance and energy metabolism are under control of the circadian system and exhibits a clear differential 24-hr distribution [105–108] (Fig. 1). The active/wakefulness phase of the day is, typically, associated with energy harvesting and eating that results in energy intake, utilization, and storage. It is a period associated with high central and peripheral sensitivity to insulin and high glucose tolerance, elevated insulin secretion, high glucose uptake by the insulin-sensitive tissues, glycogen synthesis and glycolysis (hepatic and muscular), blockade of hepatic gluconeogenesis, and increased adipose tissue lipogenesis and adiponectin production. By comparison, the rest/sleep phase of the day is characterized by the usual fasting period that requires the use of stored energy for the maintenance of cellular processes. This phase of the daily cycle exhibits insulin resistance, accentuated hepatic gluconeogenesis and glycogenolysis, adipose tissue lipolysis, and leptin secretion.

Several metabolic parameters exhibit a pronounced diurnal rhythm [109–111], including blood glucose and insulin levels. Although blood insulin and glucose levels being correlated to the feeding schedule, their diurnal variation in fasted animals was clearly demonstrated. These data and free-running experiments point to the possible role of endogenous factors, in addition to environmental ones, such as food availability, on the regulation of the 24-hr rhythmic fluctuations of energy metabolism [112, 113]. There is experimental evidence that melatonin and the autonomic nervous system output are among the mediators of the circadian master clock in the regulation of circadian glucose and insulin blood levels [114, 115].

It is well known that both humans [116–120] and rats [121] exhibit a diurnal fluctuation in response to an oral and intravenous glucose tolerance test as well as in the insulin tolerance test. In humans, during the first hours

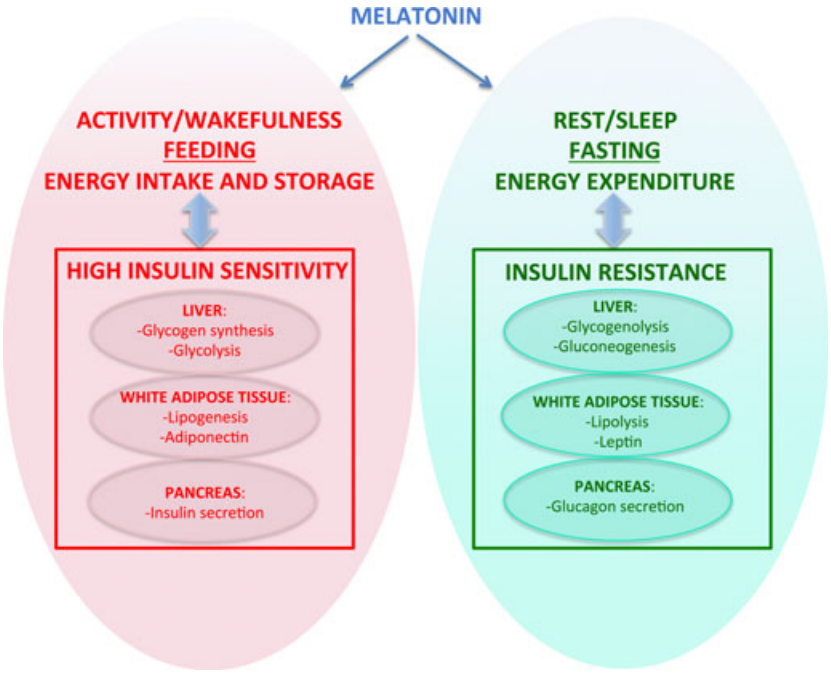

Fig. 1. Melatonin and the circadian control of energy metabolism. An adequate diurnal profile of plasma melatonin is important for the maintenance of the circadian synchronization between the activity-feeding/rest-fasting rhythm and the necessary metabolic physiological processes that subsides the proper intake, storage, and expenditure of energy.

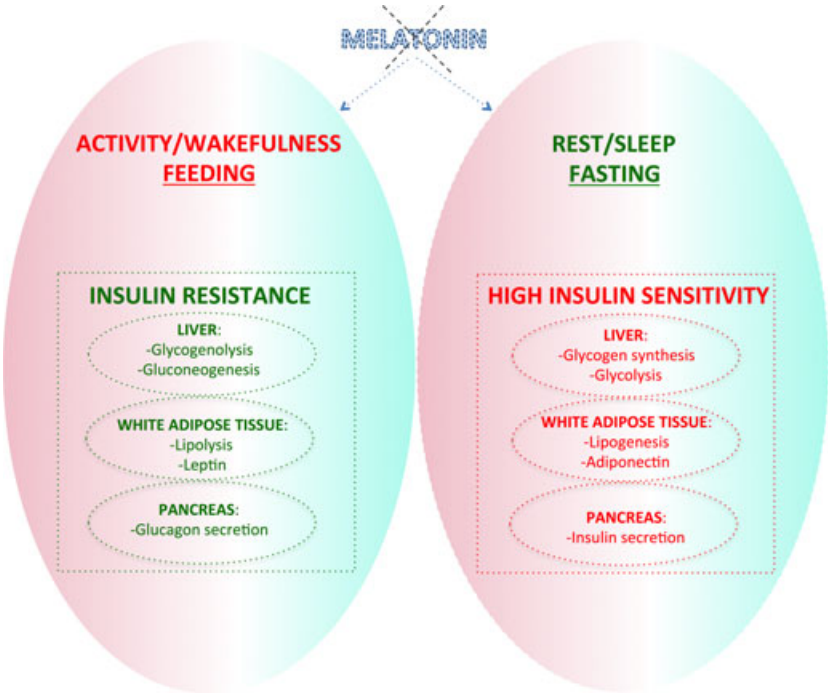

Fig. 2. Deficiency in melatonin production leads to a state of internal circadian desynchronization between the circadian activity-feeding/rest-fasting rhythm and the metabolic periods of high insulin sensitivity and insulin resistance.

after awaking, the glucose tolerance and insulin sensitivity were reported as the highest of the day, and both diminished as the day progresses reaching their nadir at the time of sleep onset. In rodents, a similar phenomenon is observed, but as these animals have nocturnal habits, the pattern of variation in glucose tolerance and insulin sensitivity is in phase opposition in comparison with humans.

There are consistent experimental data showing that the absence of melatonin cycle in the blood of pinealectomized animals impairs the temporal organization and circadian distribution of several metabolic functions associated with energy metabolism, such as daily insulin secretion [97, 122], glucose tolerance and insulin sensitivity [53, 54], metabolic adaptations to activity/feeding and rest/fasting [54, 58, 59, 80, 123], and daily distribution of glycogen synthesis and lipogenesis as opposite to those of glycogenolysis and lipolysis [123] (Fig. 2). The picture of circadian metabolic chronodisruption [113, 124] in pinealectomized animals is reversed by the appropriate melatonin replacement therapy.

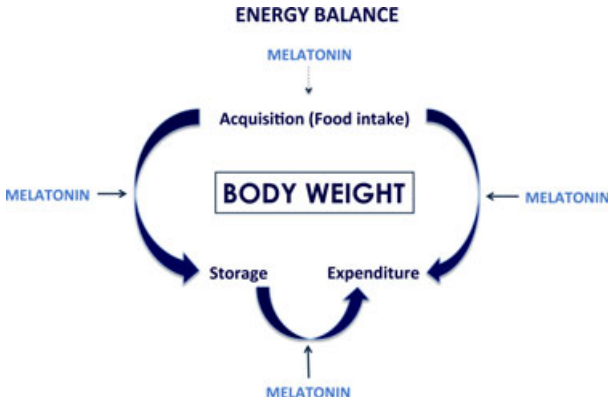

Fig. 3. Melatonin and the regulation of energy balance. Melatonin regulates the flow of energy to and from the energy stores and, in particular, regulates energy expenditure controlling the size and activity of the brown adipose tissue as well the browning process of the white adipose tissue.

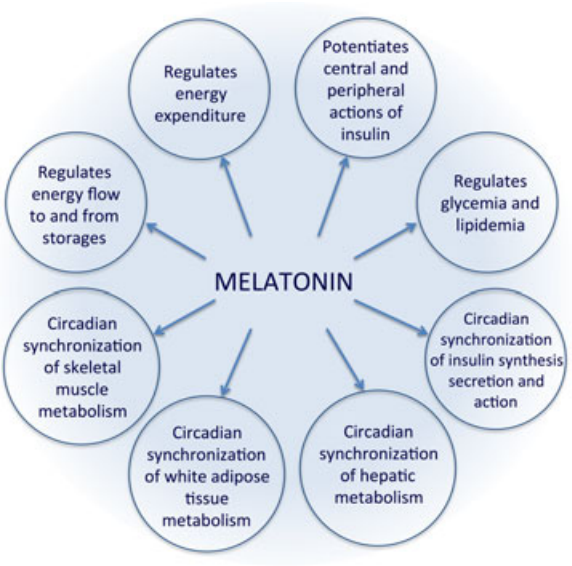

Fig. 4. Summary of metabolic and chronobiological actions of melatonin resulting in the regulation of energy metabolism, energy balance, and ultimately body weight.

To emphasize this critical role of melatonin, it is documented that the adult offspring of pinealectomized dams experience a misalignment of their circadian rhythms of energy metabolism by misplacing gluconeogenesis predominance to the active/feeding daily phase. Rhythmic melatonin replacement therapy to the pregnant mothers completely eliminates this dyssynchrony [102].

Other hormones that exert powerful influences on cellular metabolism, for example, glucocorticoids, growth hormone, and catecholamines, also show circadian rhythmic fluctuations in their secretion and action. One of the putative roles of melatonin in the circadian organization of the metabolic processes is to prepare and modify the central and peripheral metabolic tissues to respond to several of those hormones [79, 125].

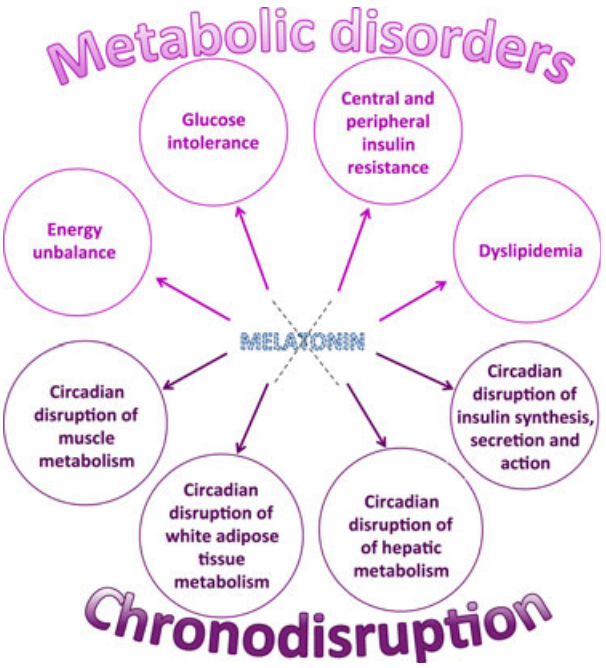

Fig. 5. Consequences of the absence or reduction in melatonin production. The consequences are of two types: those related to the metabolism leading to insulin resistance, glucose intolerance, and dyslipidemia; and those related to circadian synchronization of metabolic processes leading to chronodisruption.

The importance of melatonin in the timing of circadian metabolic processes was confirmed in an in vitro adipocyte preparation subjected to 24-hr rhythmic melatonin exposure [42]. In this experimental setup, melatonin was added to the preparation media in a rhythmic fashion so that the cells were exposed to alternating periods of 12 hr with melatonin followed by 12 hr of an absence of melatonin; this was repeated for four cycles. Under these conditions, melatonin synchronized the expression of clock genes, particularly *Bmal1, Clock,* and *Per1*. More interesting, however, was that important metabolic functions of the adipocytes were synchronized by the rhythmic addition of melatonin so that during the in vitro induced night (melatonin present for 12 hr) high lipogenesis, incorporation of glucose into lipids, high fatty acid incorporation, and low lipolysis were observed. During the in vitro induced subjective day (12 hr of absence of melatonin), the opposite was observed.

Melatonin and the regulation of energy balance and obesity

Figure 3 shows the classical energy balance cycle and the putative points of action of melatonin. A precondition of life is being able to balance energy intake, storage, and expenditure, and it is the net result of this balance that determines the final body weight. When energy intake exceeds energy expenditure, overweight and obesity are the consequence. The postulated anti-obesogenic effect of melatonin is, in part, a result of its regulatory role on the balance of energy, acting mainly on the regulation of the energy flux to and from the stores and in energy expendi-

Fig. 6. The deficiency in melatonin production, as in aging, shift-work and illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization characterizing a state of chronodisruption and metabolic disorders that constitute a vicious cycle, aggravating the health condition and leading to obesity.

ture. Moreover, its association with all the physiological processes typical of the daily activity-wakefulness/rest-sleep rhythm may impact body weight.

In spite of the well-defined regulatory action of melatonin on the seasonal variation in food intake and body weight [126–130], herein we concentrate the discussion on the role of melatonin on the day-by-day control of body weight.

Unpublished observations from our group show that, in rats, long-term pinealectomy leads to overweight and that daily rhythmic melatonin replacement therapy completely reverses this effect (Castro, C. L., Ferreira, S. G., Scialfa, J. H., and Cipolla-Neto, J.).

Additionally, however, it was demonstrated that even with an intact pineal production of melatonin, melatonin supplementation therapy in young animals reduces long-term body weight gain (roughly by 25%) and the size of the visceral fat deposits (by 50%) [131]. These effects were not dependent on a reduction in food intake. The same anti-obesity protective effect of melatonin was seen in experiments of diet-induced obesity [132, 133].

The anti-obesogen and the weight-reducing effects of melatonin supplementation therapy are clearly seen in another experimental model as well, that is, the aging animal. When middle aged (10 months), already fat animals, monitored to old age (22 months), were supplemented with melatonin in the drinking water [61, 134–137], they showed a significant reduction in body mass and intra-abdominal visceral fat. The reduced body weight, already apparent within 2 wk, persisted throughout the study period (14 wk) and disappeared with the interruption of melatonin administration. It is important to stress that the body weight and abdominal visceral fat reductions were not dependent on either the decreased food intake or on alteration (compared with the age-matched control group) of any other hormones that could influence energy metabolism, for example, testosterone, total thyroxine (T4), total triiodothyronine (T3), or insulin-like growth factor I (IGF-I). The exceptions were nonfasted plasma insulin and plasma leptin levels, which dropped in melatonin-treated animals.

This study also demonstrated that, in addition to an increase in the nocturnal locomotor activity by 19% (see also, [138]), the treated rats showed an increase in the core body temperature, indicating a putative rise in energy expenditure rather than a reduction in the energy intake. This elevation in core body temperature is consistent with a rise in the energy expenditure dependent on the trophic and metabolism-activating effect of melatonin in the brown adipose tissue (BAT) and in the browning of the white adipose tissue [139–143]. Recently, Tan et al. [131] suggested the potential involvement of brown adipose tissue as a factor whereby animals lose weight in response to melatonin administration (and gain weight when there is a deficiency of melatonin). BAT has high metabolic activity and is responsible for non-shivering thermogenesis; as a result, BAT burns large numbers of calories for the purpose of heat production, thereby consuming glucose and fatty acids and limiting fat deposition [144]. Moreover, BAT seems to be of crucial importance in the regulation of glycemia, lipidemia, and insulin sensitivity [145, 146]. As BAT is present in adult humans [147, 148], the observed effect of melatonin as a weight-reducing agent in rodents may be applicable to humans as recently suggested [131].

It should be noted that during the aging process, the insulin-signaling pathway is impaired, which accounts for the appearance of insulin resistance and glucose intolerance that might be partially responsible for the observed age-associated weight gain. Related to this, we recently demonstrated [149] that the rhythmic melatonin supplementation treatment of aged rats provoked a full recovery of central (hypothalamus) and peripheral (liver, adipose, and skeletal muscle tissues) insulin signaling well before any detectable concurrent weight loss. In addition, melatonin supplementation of aging rats improves considerably the metabolic and body weight reduction beneficial effects of physical training [57].

In summary, it seems that the adequate supplementation of melatonin lowers body weight and body weight gain as well as the intra-abdominal visceral fat deposition. This might be the result of the re-establishment of the circadian distribution of energy metabolism, the recovery of insulin signaling, the consequent disappearance of insulin resistance and glucose intolerance and, most importantly, the accentuation of the energy expenditure over the energy intake, resulting in weight loss and stabilization of weight gain.

Concluding Remarks

Melatonin is the key mediator molecule in the integration between the cyclic environment and the circadian distribution of physiological and behavioral processes necessary for a healthy metabolism and for the optimization of energy balance and body weight regulation (Fig. 4). Melatonin acts by potentiating central and peripheral insulin action either due to regulation of GLUT4 expression or triggering the insulin-signaling pathway. Thus, it induces, via its G-protein-coupled membrane receptors, the phosphorylation of the insulin receptor and its intracellular substrates. Melatonin is a powerful chronobiotic influencing, among others, the circadian distribution of metabolic processes synchronizing them to the activity-feeding/rest-fasting cycle. Melatonin is responsible for the establishment of an adequate energy balance mainly by regulating energy flow to and from the stores and directly regulating the energy expenditure through the activation of brown adipose tissue. Additionally, melatonin causes the browning of the white adipose tissue, thereby aiding in regulating

body weight. The absence or reduction in melatonin production (Fig. 5), as during aging, shift-work or illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization characterizing a state of chronodisruption and metabolic diseases that constitute a vicious cycle (Fig. 6), aggravating overall health and leading to obesity. The available evidence supports the suggestion that melatonin replacement therapy, if adequately carried out (in terms of dose, formulation, and time of the day of administration), might prevent and/or contribute to the elimination of the above pathologies and restore a more healthy state to the organism.

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