Chapter 5

Melatonin: A Silent Regulator of the Glucose Homeostasis

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Additional information is available at the end of the chapter

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Abstract

In the human organism, the circadian regulation of carbohydrates metabolism is essential for the glucose homeostasis and energy balance. Unbalances in glucose and insulin tissue and blood levels have been linked to a variety of metabolic disorders such as obesity, metabolic syndrome, cardiovascular diseases and type 2 diabetes. Melatonin, the pineal hormone, 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 organism. This chapter reviews the interplay between melatonin modulatory physiological effects, glucose homeostasis and metabolic balance, from the endocrinology perspective. The tremendous effect of melatonin in the regulation of metabolic processes is observed from the chronobiology perspective, considering melatonin as a major synchronizer of the circadian internal order of the physiological processes involved in energy metabolism.

Keywords: melatonin, pineal gland, chronobiology, glucose homeostasis, metabolic syndrome

1. Introduction

Chronobiology depicts the temporal structure of biology. It integrates the rhythmic development and existence of the utmost majority of cells, comprising also cellular functions, as a

fundamental property of the living matter, detectable at all levels of its organization, from the molecular level to rhythms in the integrity of the complex organisms. It regulates the species' biological clock, the circadian and seasonal biorhythms, synchronizing the existence of a cell within an organ, the functioning rationale of an organ within a system and the epigenetic temporal regulation of the whole living entity.

Synchronicity between external and internal circadian rhythms and harmony among molecular fluctuations within cells are essential for normal organ biology. Circadian clocks exist within multiple components of the metabolic, cardiovascular and immune systems, having the potential of affecting multiple cellular processes and, therefore, holding the promise of modulating various physiopathological aspects over the course of the 24 h cycle.

2. The pineal gland, a neuroendocrine transducer

Metabolic physiology undergoes diurnal variations, and serious pathologic events appear to be conditioned by the time of day. The suprachiasmatic nucleus imprints the control of circadian rhythms in peripheral tissues, by different neural and humoral signals, such as melatonin.

The molecular clock mechanism in mammals is currently understood as a transcriptional feedback loop involving several genes. The genes Clock and Bmal1 encode bHLH-PAS (basic helix-loop-helix) proteins that form the positive limb of the feedback circuit. The CLOCK:BMAL1 heterodimer initiates the transcription by binding to specific DNA elements, E-boxes (5′-CACGTG-3′) and E′-boxes (5′-CACGTT-3′) in the promoters of target genes. This set of activated genes includes members of the negative limb of the feedback loop including the PER (PER1 and PER2) and CRY (CRY1 and CRY2) genes. The resulting PER and CRY proteins dimerize and inhibit further CLOCK:BMAL1 transcriptional activity allowing the cycle to repeat from a level of low transcriptional activity. Thus, cellular metabolism may prove to play an important role in regulating the transcriptional state and therefore the phase of the clock. Degradation of the negative limb proteins PER and CRY is required to terminate the repression phase and restart a new cycle of transcription. The transcriptional feedback loop described above can be observed not only in the SCN, but also in nearly every mammalian cell. If viewed at the single-cell level, the molecular clockwork of transcription and translation can be observed as autonomous single-cell oscillators [1].

Melatonin (*N*-acetyl-5-methoxytryptamine) is synthesized by multiple tissues in the body, but the pineal gland is the major contributor to circulating melatonin concentration, as pinealectomy abolishes detectable melatonin in the blood.

In young- and middle-aged people, pineal melatonin is secreted based on a circadian pattern, with a high rhythm amplitude and a considerable nocturnal maximum.

Melatonin from extrapineal sites often oscillates with considerably lower amplitudes. According to current knowledge, some of the extrapineal sources are of particular importance, either

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in quantitative terms, such as the gastrointestinal tract or, with regard to functional aspects, some areas of the central nervous system (CNS) and several leukocytes. The physiological significance of other sites of melatonin biosynthesis is, at the moment, uncertain. Melatonin is secreted in small amounts from most of the extrapineal sites or only under specific conditions, for example, the postprandial release from the gastrointestinal tract, during which relatively high quantities can enter the circulation, being chronobiologically rather irrelevant. Thus, melatonin is not only a pineal hormone but also has additional functions as a local tissue factor and leukocyte-derived cell hormone with paracrine and autocrine actions [2].

The pineal gland or the epiphysis weighs about 150 mg, and it is located in the posterior part of the third cerebral ventricle. The pineal gland of mammals is a homogeneous tissue containing pinealocytes, glial cells, phagocytic cells and neurons. The pineal gland is innervated by nervous fibers of different origins. The gland was considered a vestigial organ until 1950s. Its position in the center of the brain and its presence in other species of vertebrates indicate its evolution in the evolutionary cerebral system of the humans, based on its absolute necessity on the overall organism development and important particular functions.

In the current scientific frame, it is generally acknowledged that the pineal organ is a neuroendocrine transducer. The pinealocytes, the main secretory pineal parenchymal cells, are fotoneuroendocrine cells, phylogenetically derived from primary sensory cells, having neural embryological origin. They primary respond to nervous-photic modulated stimulation and secondary to hormones in target organs. The endocrine secretory function is directly dependent on sympathetic innervation, the pinealocytes translating the nervous information in endocrine information.

In terms of phylogenetic evolution, the pinealocyte functions as a fotoneuroendocrine neuron. On some species of amphibians, reptiles and birds, the epiphysis is also called "parietal eye" or third eye because it has the form of a rudimentary eye fitted with a lens and a retina. Therefore, it is considered to be a vestigial of a sensory organ, functional in primitive vertebrates. Being directly affected by the light absorbed by the eye, the pineal gland regulates the sleep-wake states, the menstruation and the reproduction, the hibernation and the seasonal migration and other "instinctive" behaviors.

The role of the pineal gland, as an integral component of the brain, evolved on the phylogenetic scale from photoreceptor organ (fish, amphibians, reptiles), to neuroendocrine modulator of brain functions, in mammals and humans, thus having a role in the adaptation of reproductive conditions environment in some mammals (particularly rodents) and to a major role in the modulation of brain excitability in relation to the external environmental conditions in humans.

Nowadays, melatonin, the major pineal hormone, is considered the master hormone, regulating all other hormones within the human organism.

The main regulatory pathway is a complex one called the retinoic-hypothalamic-pineal axis that ends with the sympathetic transmission of the pineal parenchymal. The pineal gland receives neuronal transmissions of central and parasympathetic origin. These pineal nervous endings contain a great variety of neurotransmitters. The rhythm of melatonin synthesis depends on

three interrelated factors: the endogenous circadian oscillator, located in the suprachiasmatic nucleus (SCN), the light/dark and day/night cycles that synchronize the endogenous oscillator and the light that dramatically inhibits the synthesis of melatonin [3].

In conclusion, the pineal gland is a connection point between various neural transmissions, its activity being under the high-fidelity control of the hypothalamic clock, the temporal message being delivered to the pineal gland via a polysynaptic path. However, new neuroanatomic and immunocytochemical proofs changed the concept according to which the pineal gland is innervated only by the sympathetic nervous system, presently, being unanimously accepted to be the target of several neurotransmitters of different origins.

3. Melatonin, the universal synchronizer

Melatonin biosynthesis at the level of pinealocytes occurs and is initiated by the absorption of tryptophan from the blood. Increased daytime tryptophan concentration at the pineal level precedes increased serum free and total tryptophan, suggesting that the essential amino acid is captured by the pineal against a concentration gradient. Once arrived in the pinealocyte, the major part of tryptophan is used for the synthesis of indole derivatives and the rest for protein synthesis (**Figure 1**).

The transformation of tryptophan into serotonin occurs in two stages: first, the hydroxylation into 5-hydroxytryptophan under the enzymatic action of tryptophan hydroxylase, this being a limiting step of the synthesis. The enzyme activity requires the presence of oxygen, tetrahydrobiopterin, $NADPH^+$ and a metal, iron or copper. Second, the decarboxylation of 5-hydroxytryptophan into serotonin by the action of L-aromatic amino acid decarboxylase, in the presence of pyridoxal phosphate (PLP).

The transformation of serotonin into melatonin also includes two stages: the acetylation of $–NH_2$ group by the *N*-acetyltransferase (NAT) enzyme to form *N*-acetyl-serotonin, and thereafter, the methylation of –OH group in position 5 by hydroxyl-indole-*O*-methyltransferase (HIOMT), an enzyme that catalyzes the transfer of methyl group from *S*-adenosyl methionine. This final step results in acetyl-5-methoxytryptamine or melatonin synthesis. The two enzymes, NAT and HIOMT, specific for this synthesis pathway, have different profiles of activity. The NAT enzyme is a limiting enzyme of reaction: it is subject to many mechanisms of transcriptional and/or posttranscriptional regulation depending on the species, which allows it to be active only during darkness. The NAT activity is strongly regulated by circadian alternation light/dark, contrary to HIOMT enzyme showing a constitutive activity along the nictemeral cycle. For example, in rats and humans, a short exposure to bright light during the dark period causes an inhibition of the NAT activity for the next 15 min [3].

The enzymes responsible for the melatonin production can be modulated in a circadian manner, in order to imprint its nictemeral synthesis cycle.

Extrapineal melatonin synthesis in mammals has been reported in the retina, Harderian glands, gastrointestinal tract and pancreas. In humans, melatonin has been reported outside

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the pineal gland in the follicles, the lining of the intestinal appendix, platelets and red blood cells. Melatonin is also produced by numerous nonendocrine cells, as is the case of the immune cells. In conclusion, while the pineal gland quantitatively accounts for most of the circulating melatonin, substantial local synthesis also occurs in retinal and peripheral tissues such as the gastrointestinal tract [4].

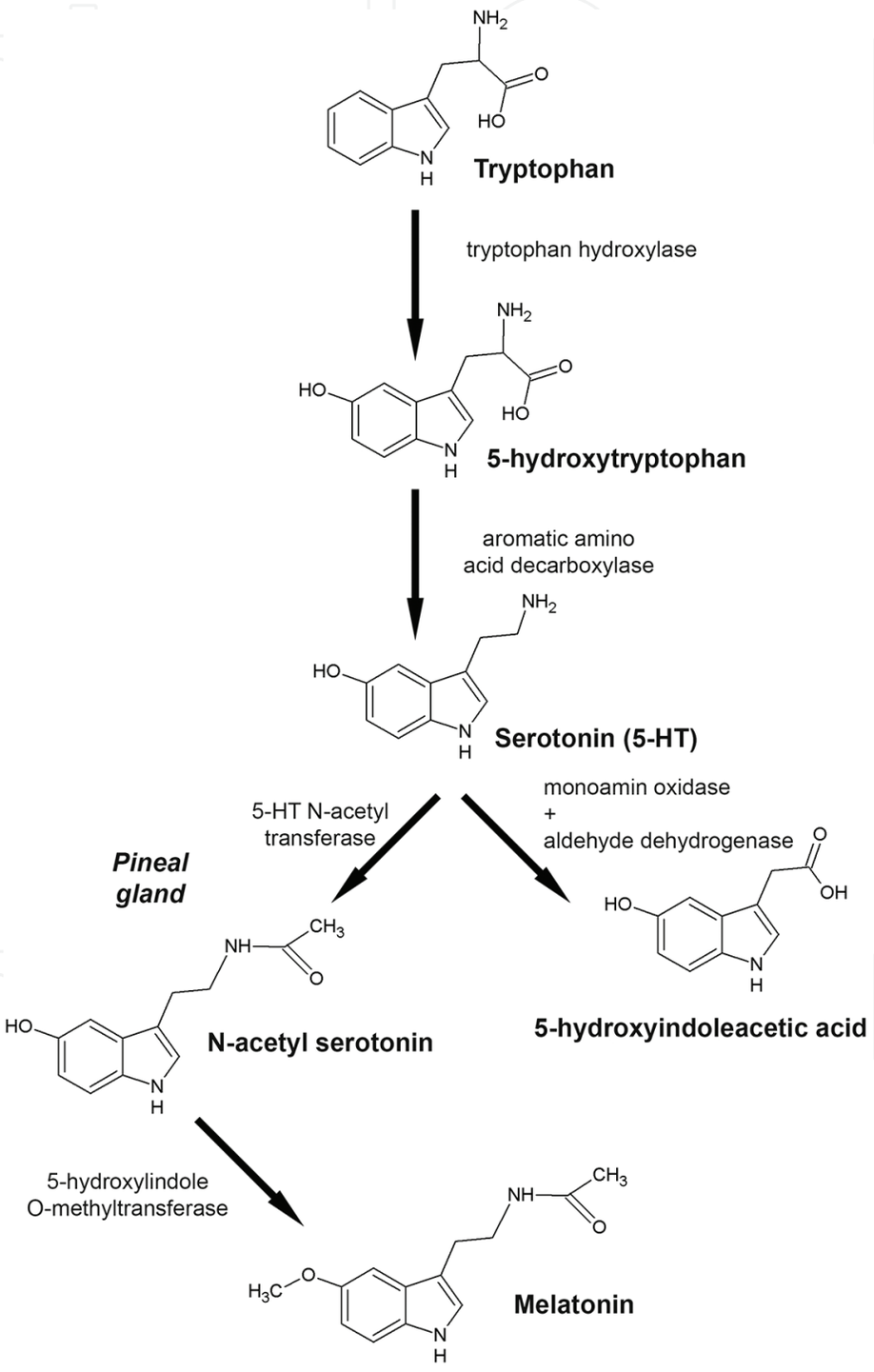

Figure 1. Melatonin biosynthesis pathway.

Melatonin appears to be secreted by the pineal gland in circulation by simple diffusion, because it is highly soluble in the cell membrane lipoproteins. Furthermore, melatonin may have effects on the pineal gland itself, as there are specific receptors for it, at this level. The cells of the suprachiasmatic nucleus also possess receptors for melatonin. In conclusion, melatonin has an inhibitory effect on the activity of the suprachiasmatic nucleus. So, melatonin is self-regulating its own synthesis. However, melatonin secreted into the bloodstream will send to all central and peripheral structures that possess receptors or melatonergic sites this information regarding the photoperiodicity, allowing the organism a physiological adaptation to alternations day/night or to the seasonal ones.

The circadian pacemaker within the suprachiasmatic nucleus triggers the pineal gland to produce high melatonin concentrations at night. There is a photic synchronized endogenous circadian biorhythm, allowing the maximum human melatonin production at night, between midnight and 3 a.m., and the serotonin during the day (**Figure 2a**). Initiating the melatonin synthesis in humans occurs between 9 and 11 p.m. and lasts for about 8–9 h in adults, these parameters being fairly constant from day to day. The daily and seasonal melatonin rhythms are involved in time of day and time of year signaling, and it is for this reason that they are considered to serve as a bioclock and biocalendar.

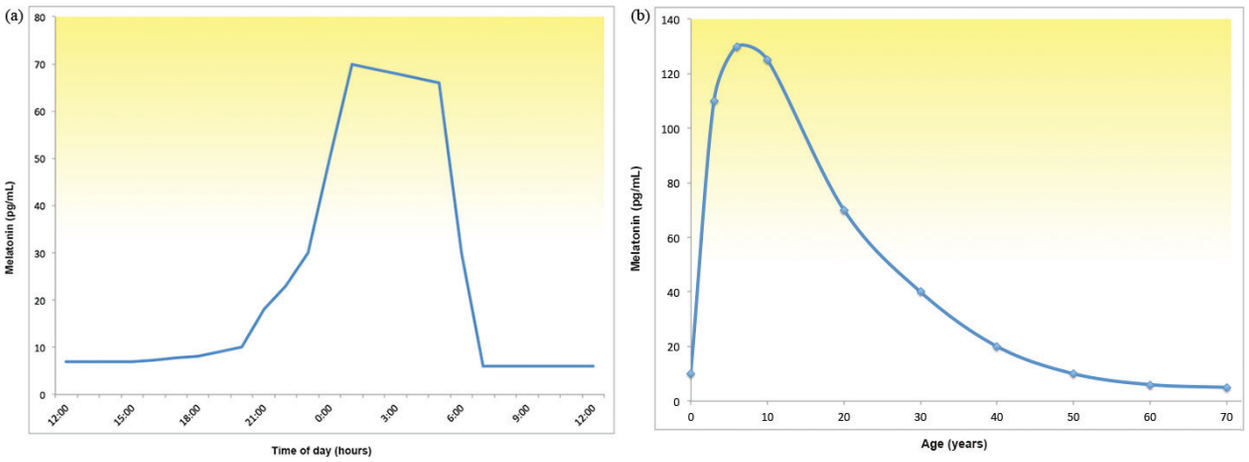

Figure 2. The daily (a) and lifetime (b) melatonin biosynthesis fluctuations.

In humans, it is required an intensity of light greater than in other mammals, over 1500 lux, for disrupting this synthesis biorhythm by external light. In all studied mammals, those with activity at day and at night, the nocturnal melatonin production is maximal and prevailing overnight.

In humans, blood levels of melatonin have a particular dynamics from birth (**Figure 2b**). The pineal synthesis begins in infants over 3 months old, to older age, and the time of puberty is very controversial whether it represents or not a particular step on the downward slope. It is of real interest the fact that melatonin synthesis decreases with the age of humans and has abnormal low levels in a series of age-related pathological disorders, as it is the case of cardiovascular and metabolic disease. Melatonin rhythmic profile has many implications in pathophysiological processes as inflammation, oxidative stress, hypertension and metabolic syndrome.

The half-life of blood melatonin is under 30 min, and the metabolic clearance is 630 mL/min in healthy men. Melatonin is a lipophilic substance metabolized in several compounds both in the liver (**Figure 3a**) and in the central nervous system (**Figure 3b**) [3, 5].

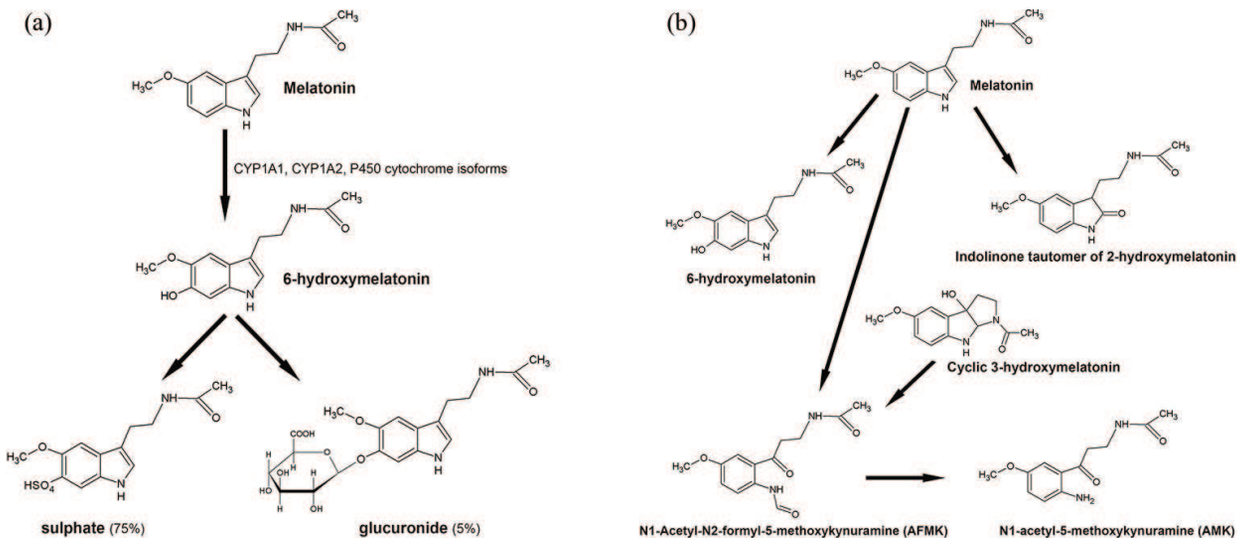

Figure 3. Melatonin hepatic (a) and cerebral (b) metabolism.

Circulating melatonin is catabolized in humans, under the action of hepatic microsomal hydroxylases in *N*-acetylserotonin, which is biologically inactive, and 6-hydroxymelatonin, which is urinary eliminated, as a sulfate (75%) or glucuronide (5%) conjugate. The rest of melatonin is eliminated under three forms: the native form (below 1%), as 5-metoxy indolacetic acid (0.5%) or catabolized as *N*-acetyl-5-metoxy kynurenamine via *N*-formyl-5-metoxy kynurenamine in the central nervous system (15%).

In the brain, melatonin is metabolized in several compounds of which 5-metoxytriptamine is involved in the dreaming process and it will subsequently metabolize N, *N*-dimethyl-5-methoxytryptamine and other tryptamines.

Approximately 60–70% of the circulating melatonin in the bloodstream is bound to albumin, and about 30% is found in free state, this fraction being the one, that crosses the blood brain barrier [6, 7].

4. Melatonin's pleiotropic effects and the metabolic epigenetic regulation

Considered as nature's most versatile biological signaling and multitasking molecule, melatonin is a highly conserved molecule found in almost all types of organisms. Melatonin has several functions ranging from coordination of circadian activity, which is generally considered as a sleep-promoting effect, and melatonin administration induces hypothermic effects and heat loss via the distal skin regions, and stabilizes sleep-wake cycles [8].

Melatonin demonstrates properties of a powerful antioxidant, at sufficiently high concentrations as a direct radical scavenger, but, at lower, near-physiological levels, as a regulator of redox-relevant enzymes, suppressor of prooxidant excitatory and inflammatory processes and as a mitochondrial modulator [2]. Melatonin also acts on bone metabolism, activating its MT1 and MT2 specific receptors in an autocrine or paracrine fashion, near the target tissues. Melatonin may exert vasodilatatory (MT2) or vasoconstriction (MT1) effects, depending on the receptor type or the target cell, and it can also down-regulate the cortisol secretion [9].

Melatonin has a great influence on diabetes and associated metabolic unbalances by regulating insulin secretion, and also by scavenging reactive oxygen species, the pancreatic β-cells being highly susceptible to oxidative stress, and possessing only low-antioxidative potential. On the other hand, in several genetic studies, human MT2 receptor polymorphisms have been described as being causally linked to an elevated risk of developing type 2 diabetes [4].

5. Chronobiology, metabolic control and disease modulation by melatonin

It is universally accepted that social and industrial pressures, such as shift work, which opposes the physiological temporal circadian order, may be factors determining the occurrence or the development of chronic illnesses, such as metabolic disorders. In many disease states as diabetes mellitus and hypertension, neurohumoral circadian rhythms are chronically impaired and result in dyssynchrony of cellular order in different tissues and between the organism and the environment.

Diabetes mellitus is associated with a phase shift in the cardiac circadian clock. Shift workers have an increased incidence of cardiovascular disease, which might be related to alterations in cardiovascular and metabolic intracellular circadian clock function [5, 10].

The cardiovascular system actually exhibits significant daily variation regarding physiological, pathophysiological and molecular processes. Diurnal variations also affect gene and protein expression. Circadian clocks exist in cardiomyocytes, vascular smooth muscle cells and endothelial cells.

At molecular level, a complex interplay occurs between environmental influences and intrinsic mechanisms, which contributes to change in metabolic functions over the 24 h period.

Loss of synchronization occurs when there are changes in feeding or sleep patterns and during exposure to light at abnormal times, at night, considering this phenomenon as "light-at-night pollution." Such dyssynchronization is seen in patients with hypertension, diabetes mellitus, obesity and shift workers, in whom there is an elevated risk of cardiovascular disease [5, 11].

Melatonin is the key mediator molecule in the in vivo scenario, mediating the integration between the cyclic environment and the circadian distribution of physiological and behavioral processes.

The relation between pineal gland, melatonin and energy metabolism was initially studied in both humans and rodents. Over 70 years ago, one of the first references to the functional

connection between the pineal gland and carbohydrates metabolism was made by the Romanian researcher Constantin I. Parhon, followed by his coworkers, endocrinologists Milcu and Nanu. They conducted animal experiments on "pinealin," a pineal peptide, described as having metabolic effects similar to insulin, displaying hypoglycemic, anabolic, anticholesterolemic and glomerulotrophic characteristics. In the following years, a controversial discussion was carried out in many publications on the importance of pineal extracts on glucose metabolism. Even after the isolation and identification of the molecular structure of melatonin, by Aron Lerner and colleagues, this discussion continued [12].

6. The functional synergism between melatonin and insulin

The scientific literature states that first experimental injections with pineal extracts led to hypoglycemia, increased glucose tolerance, and hepatic and muscular glycogenesis. The metabolic disruption caused by the absence of melatonin in the pinealectomized animals was characterized as a diabetogenic syndrome depicted by glucose intolerance and insulin resistance, both expressed peripherally: hepatic, adipose, and skeletal muscle, and centrally, at the level of the hypothalamus. This pathological picture can be reverted by melatonin replacement therapy or restricted feeding.

In addition to this dramatic finding, insulin resistance, glucose intolerance, and several other metabolic disorders can be seen in some physiological or pathological states associated with reductions in blood melatonin levels, as aging, diabetes, shift work, and environmental illumination during the night and the so-called phenomenon of light pollution. An adequate melatonin replacement therapy alleviates most of these alterations.

Emphasizing the functional synergism between melatonin and insulin, it is considered that the pinealectomy-induced insulin resistance and glucose intolerance are related to the mechanistic consequences of the depletion of melatonin, perceived at the molecular level as a deficiency in the insulin-signaling pathway and reduction in GLUT4 gene expression and protein content. It was shown that melatonin, acting through MT1 membrane receptors, induces rapid tyrosine phosphorylation and activation of the tyrosine kinase beta-subunit of the insulin receptor, succeeding to overcome several intracellular transduction steps of the insulin-signaling pathway [6, 7].

7. Melatonin effects on adipocytes

The melatonin-insulin synergism was described in an in vitro experiment which supposed the incubation of isolated visceral white adipocytes with melatonin, the peripheral function of insulin being potentiated by the action of melatonin, and, in addition, this was the first evidence of a direct action of melatonin on adipocytes [6].

All in all, this was a proof that the adipose tissue is a peripheral target of melatonin for the regulation of the overall metabolism. Similarly, it was demonstrated that melatonin activation

of MT2 receptors in human adipocytes modulates glucose uptake by these cells. Considering the adipose tissue physiology, it was possible to document synergistic effect of melatonin on several other insulin actions in addition to glucose uptake: insulin-induced leptin synthesis and release in isolated adipocytes is potentiated by the MT1-mediated melatonin action, and melatonin regulates other aspects of adipocyte biology that influence energy metabolism, lipidemia and body weight, as lipolysis, lipogenesis, adipocyte differentiation and fatty acids uptake [6].

Melatonin also exerts different effects on the carbohydrates metabolism, considering various targets: it stimulates glucose uptake in muscle cells by phosphorylation of insulin receptor substrate-1 through MT2 signaling, MT2 receptors are expressed in hepatocytes, and melatonin therapy elevates glucose release from the liver [9].

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.

Molecular and immunocytochemical studies confirmed the presence of melatonin receptors MT1 and MT2 in the islets of Langerhans and also in human pancreatic tissue [13]. MT1 and/or MT2-mediated melatonin action decreases glucose-stimulated insulin secretion in isolated rat pancreatic islets and rat insulinoma beta-cells.

Melatonin influences exocytosis of insulin by β-cells as concluded from experiments via nonhydrolyzable guanosine-5′-trisphosphate (GTP) analog and luzindole, a melatonin antagonist, both of which inhibit the melatonin action on secretion of insulin from neonatal rat islets.

The intracellular signal transduction pathways of the pancreatic β-cell influenced by melatonin via MT1 and MT2 membrane receptors include cAMP, cGMP and IP3 signaling pathways. 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.

The pineal indolamine induces IGF-1 receptor phosphorylation, which participates in the integrity of islet cells. Moreover, it has been demonstrated, as well, that melatonin stimulated glucagon synthesis and secretion.

Above all considerations, these actions of melatonin are required to build the circadian profile of insulin secretion, synchronizing the pancreatic metabolic rhythms with the circadian rhythm of the activity/rest profile. And it should be also noted that insulin is able to regulate pineal melatonin synthesis by potentiating norepinephrine-stimulated melatonin production.

Interestingly, the association between melatonin and type 2 diabetes could be based on the observation that insulin secretion is inversely proportional to plasma melatonin concentration. These two hormones, melatonin and insulin, exhibit a circadian rhythm, but there is negative correlation between their synthesis dynamics.

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Decreased abnormally regulated melatonin levels have been related to diabetes, which suggests that the melatonin signal is critical for glucose homeostasis. In patients with type 2 diabetes, gluconeogenesis and endogenous glucose production exhibit circadian rhythms that impose fasting high blood glucose and do not exist in healthy humans.

Melatonin inhibits glucose-mediated release of insulin from pancreatic cells emphasizing its activity in the function of insulin. Suppression of melatonin secretion by nocturnal light exposure could be a trigger for type 2 diabetes development (**Figure 4**) [9].

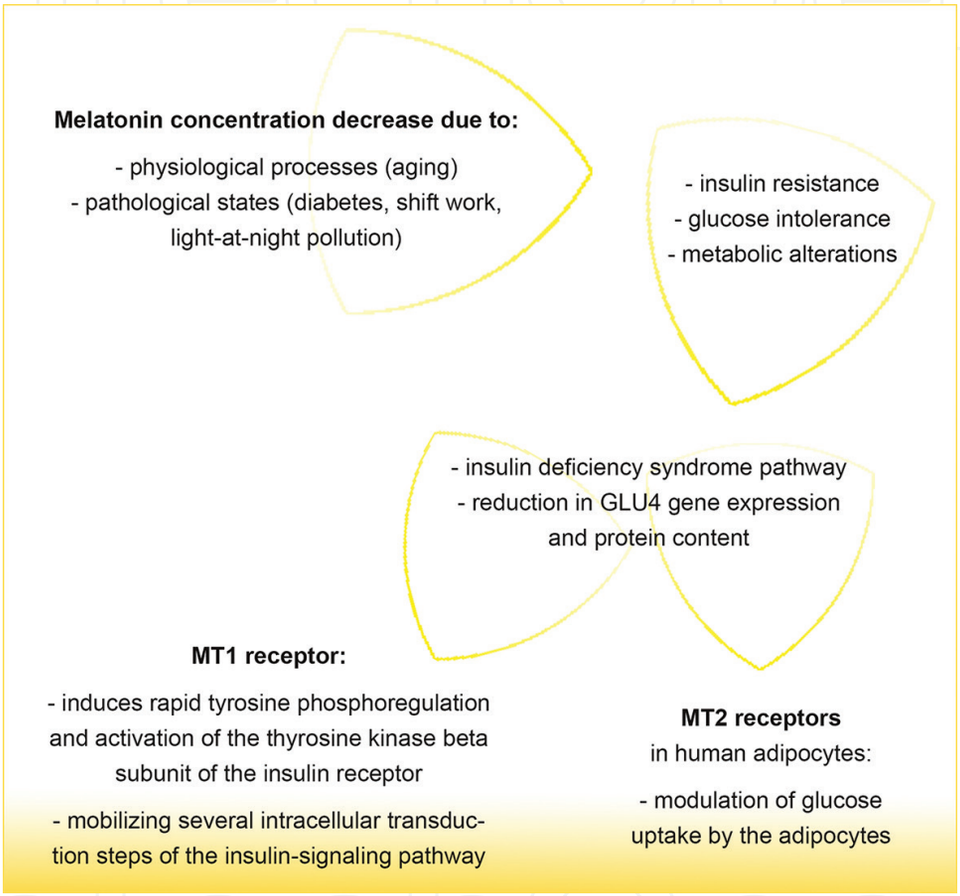

Figure 4. Melatonin depletion induced pathological consequences.

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 completely disturbed by the deficiency of melatonin in the pregnant mother. The adult child of a melatonin unpaired mother presents glucose intolerance, insulin resistance and a serious delay in the glucose-induced insulin secretion by isolated pancreatic islets [6, 13, 14].

This in once more a clear evidence that melatonin has a crucial role in the metabolic epigenetic regulation of a healthy organism that undergoes vicious trials and environmental demands that are, to a certain extent, meant to test the physiological robustness.

Robustness is one of the fundamental organizational principles of biological systems, this being the major characteristic involved in their adaptation, survival and reproduction. Metabolic diseases are considered a breakdown in the robustness in biological systems, the continuous maintenance of physiological functions being of extreme importance, despite external and internal disturbances [4].

Melatonin is a powerful chronobiotic, regulating the daily metabolic processes so that the activity/feeding phase of the day is assimilated with high insulin sensitivity, and the rest/fasting is synchronized to the insulin-resistant metabolic phase of the day. Melatonin is the key mediator molecule for the nictemeral integration of physiological and behavioral processes and for the modulation of energy balance and body weight regulation, all crucial for a healthy life [6].

The hypothalamus controls a great variety of physiological processes, including sleep/wake cycles, sexual behavior and reproduction, and metabolic control such as thermoregulation, glucose metabolism, lipid metabolism, energy intake/expenditure, and food and water intake, all these functions following circadian rhythms.

The hypothalamus identifies nutrients such as glucose and lipids, and via a specialized area of the blood brain barrier in the arcuate nucleus it also detects circulating metabolic hormones such as leptin, insulin, thyroid hormone, adiponectin and ghrelin. Researchers showed that SCN lesions abolished the daily rhythms in plasma concentrations of glucose and insulin and revealed the existence of a pronounced day/night difference in the response to 2-deoxy glucose, a glucose-utilization inhibitor, proving that the SCN is involved in the daily rhythm of glucose metabolism. SCN-lesioned rats do not have a rhythm in food intake either, so it should not be excluded an indirect effect of the lack of a feeding rhythm on glucose metabolism [11].

The chronobiotic nature of energy balance and energy metabolism is depicted by the two separated phases that exist during a 24 h period. The first one is characterized by energy harvesting and eating that results in energy intake, utilization, and storage, 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 hepatic and muscular glycolysis, blockade of hepatic gluconeogenesis, and increased adipose tissue lipogenesis and adiponectin production.

In opposition, the second one, the rest/sleep phase of the day, is characterized by fasting periods that require the use of stored energy for maintaining the cellular homeostasis, exhibiting insulin resistance, accentuated hepatic gluconeogenesis and glycogenolysis, adipose tissue lipolysis, and leptin secretion [6].

Other hormones exerting modulatory effects on cellular metabolism, as glucocorticoids, growth hormone and catecholamines, present circadian rhythmic fluctuations in their secretion and activity. Melatonin, as an orchestrating factor in the circadian organization of the metabolic processes, prepares and modifies the central and peripheral metabolic tissues in order to respond to these hormones.

The antiobesogenic 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 mobilization from the stores and in energy expenditure. It was demonstrated that in healthy young animals, melatonin supplementation therapy reduces long-term body weight gain and the size of the visceral fat deposits, effects independent on the reduction in food intake. The same antiobesity protective effect of melatonin was seen in experiments of diet-induced obesity [6, 15, 16].

The adequate supplementation of melatonin lowers body weight and regulates body weight gain as well as the intra-abdominal visceral fat accumulation, as a result of the reestablishment of the circadian distribution of energy metabolism, the insulin signaling pathway reinstatement, the consequent disappearance of insulin resistance and glucose intolerance and, most importantly, the accentuation of the energy expenditure over the energy intake.

8. Conclusions

Melatonin is the key modulatory molecule responsible for the integration between the cyclic environment and the circadian distribution of physiological and behavioral processes, assuring a healthy metabolism and the optimization of energy balance and body weight regulation.

The circadian system may be a tractable target for decreasing the prevalence of metabolic disturbances. Melatonin acts by potentiating central and peripheral insulin action either due to regulation of GLUT4 expression or triggering the insulin-signaling pathway. Melatonin is responsible for maintaining an adequate energy balance mainly by regulating energy flow and the energy expenditure through the activation of brown adipose tissue. It also assures the metabolic processes respect the nictemeral physiology of the two major phases existent during 24 h, the activity/wakefulness/feeding state versus the rest/sleep/fasting phase.

The decline in melatonin synthesis, during physiological processes as aging, or pathology associated events as shift-work or illuminated environments during the night, induces insulin resistance, glucose intolerance, sleep disturbances and metabolic circadian disorganization, depicting a state of chronodisruption and metabolic imbalances, aggravating the general health state.

The present evidence that melatonin induces insulin secretion and can improve β-cell function certify melatonin supplementation as an accurate therapeutic approach for glucose homeostasis reestablishment. The available scientific proofs support the suggestion that melatonin replacement therapy, if adequately carried out, in terms of dose, formulation and time of the day of administration, might contribute to maintaining optimal blood glucose levels in diabetic patients and restore the chronobiotic order for achieving a more robust healthy state of the organism.

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References

[1] Johnston J.D., Skene D.J. Regulation of mammalian neuroendocrine physiology and rhy thms by melatonin. Journal of Endocrinology. 2015;JOE-15-0119. doi:10.1530/JOE-15-0119

[2] Hardeland R. Neurobiology, pathophysiology, and treatment of melatonin deficiency and dysfunction. The Scientific World Journal. 2012;640389. doi:10.1100/2012/640389

[3] Drăgoi C.M. Tryptophan, serotonin, melatonin-the spectacular triad: physiological, pathological and therapeutic implications of some bio-compounds with indolic structure. LAP Lambert Academic Publishing, Germany; 2013.

[4] Espino J., Pariente A.J., Rodríguez A.B. Role of melatonin on diabetes-related metabolic disorders. World Journal of Diabetes. 2011 June 15;2(6):82–91. doi:10.4239/wjd.v2.i6.82

[5] Dominguez-Rodriguez A., Abreu-Gonzalez P., Sanchez-Sanchez J.J., Kaski J.C., Reiter R.J. Melatonin and circadian biology in human cardiovascular disease. Journal of Pineal Research. 2010;49:14–22. doi:10.1111/j.1600-079X.2010.00773.x

[6] Cipolla-Neto J., Amaral F.G., Afeche S.C., Tan D.X., Reiter R.J. Melatonin, energy metabolism, and obesity: a review. Journal of Pineal Research. 2014;56:371–381. doi:10.1111/jpi.12137

[7] Drăgoi C.M. Biochemical mechanisms of action of some bio-compounds with indolic structure [thesis]. Bucharest; 2012.

[8] Nduhirabandi F., du Toit E., Lochner A. Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? Acta Physiologica. Forthcoming. doi:10.1111/j.1748-1716.2012.02410.x

[9] Cardinali D.P., Hardeland R. Inflammaging, metabolic syndrome and melatonin: a call for treatment studies. Neuroendocrinology. Forthcoming. doi:10.1159/000446543

[10] Kalsbeek A., la Fleur S., Fliers E. Circadian control of glucose metabolism. Molecular Metabolism. 2014;3(4):372–383.

[11] Peschke E., Bähr I., Mühlbauer E. Melatonin and pancreatic islets: interrelationships between melatonin, insulin and glucagon. International Journal of Molecular Sciences. 2013;14(4):6981–7015. doi:10.3390/ijms14046981

[12] Owino S., Contreras-Alcantara S., Baba K., Tosini G. Melatonin signaling controls the daily rhythm in blood glucose levels independent of peripheral clocks. PLos One. 2016;11(1). doi:10.1371/journal.pone.0148214

[13] Sharma S., Singh H., Ahmad N., Mishra P., Tiwari A. The role of melatonin in diabetes: therapeutic implications. Archives of Endocrinology and Metabolism. 2015;59(5). doi:10.1590/2359-3997000000098

[14] Nicolae A.C., Drăgoi C.M., Ceaușu I., Poalelungi C., Iliescu D., Arsene A.L. Clinical implications of the indolergic system and oxidative stress in physiological gestational homeostasis. Farmacia. 2015;63(1):46–51.

[15] Drăgoi C.M., Nicolae A.C., Grigore C., Dinu-Pîrvu C., Arsene A.L. Characteristics of glucose homeostasis and lipidic profile in a hamster metabolic syndrome model, after the co-administration of melatonin and irbesartan in a multiparticulate pharmaceutical formation. In: March; Bucharest. Book of abstracts: ASRMN; 2016. p. 25.

[16] Suzana E.V., Diana L.D., Adrian E.R., Vlad Z., Diana M.C., Andreea L.A., Cristina M.D., Alina C.N., Leon Z., Torsten S., Ana-Maria Z. Behavioral and molecular effects of prenatal continuous light exposure in the adult rat. Brain Research. 2016;1650:51–59.

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