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Мелатонин при сахарном диабете: от патофизиологии к перспективам лечения

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Гормон эпифиза мелатонин обеспечивает синхронизацию секреции инсулина и гомеостаза глюкозы с чередованием светлого и темного времени суток. Нарушение альянса между опосредованными мелатонином циркадными ритмами и секрецией инсулина наблюдается при сахарном диабете (СД) 1 и 2 типа (СД1 и СД2). Дефицит инсулина при СД1 сопровождается повышением продукции мелатонина в эпифизе. СД2, напротив, характеризуется снижением секреции мелатонина. В полногеномных исследованиях варианты гена рецептора мелатонина MT2 (rs1387153 и rs10830963) ассоциированы с уровнем гликемии натощак, функцией β-клеток и СД2. Мелатонин увеличивает пролиферацию и неогенез β-клеток, улучшает чувствительность к инсулину и уменьшает окислительный стресс в сетчатке и почках в экспериментальных моделях СД. Для оценки терапевтической ценности данного гормона у больных СД необходимы дальнейшие исследования.
Ключевые слова: *сахарный диабет, мелатонин, циркадные ритмы, инсулин, эпифиз*

Melatonin and diabetes: from pathophysiology to the treatment perspectives

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Pineal hormone melatonin synchronizes insulin secretion and glucose homeostasis with solar periods. Misalliance between melatonin-mediated circadian rhythms and insulin secretion characterizes diabetes mellitus type 1 (T1DM) and type 2 (T2DM). Insulin deficiency in T1DM is accompanied by increased melatonin production. Conversely, T2DM is characterized by diminished melatonin secretion. In genome-wide association studies the variants of melatonin receptor MT2 gene (rs1387153 and rs10830963) were associated with fasting glucose, beta-cell function and T2DM. In experimental models of diabetes melatonin enhanced beta-cell proliferation and neogenesis, improved insulin resistance and alleviated oxidative stress in retina and kidneys. However, further investigation is required to assess the therapeutic value of melatonin in diabetic patients.
Keywords: *diabetes, melatonin, circadian rhythms, insulin, epiphysis*

Biorhythms of the endocrine system, as well as their changes during pathological conditions, have attracted the attention of researchers for several decades. Of special interest in the study of diabetes mellitus from the chronomedical point of view is the hormone melatonin, which is synthesised by the pineal gland. This hormone plays a pivotal role in the timing of hormonal stimuli and metabolic processes in relation to the light and dark cycle [1]. In recent years, new data have been obtained concerning the role of melatonin in the regulation of insulin secretion and carbohydrate metabolism. As the potential for melatonin to be used in the treatment of diabetes has been widely discussed, we summarised recent data from this field in the current review.

Secretion and principal physiological effects of melatonin

Melatonin was first isolated from bovine pineal glands in 1958. This hormone is synthesised from L-tryptophan through serotonin under the activity of arylalkylamine-N-acetyltransferase (AA-NAT; key regulatory enzyme) and hydroxyindole-O-methyltransferase. In adults, approximately 30 μg of melatonin per day is produced, and the concentration of melatonin in the blood serum at night is 20 times higher than that in the daytime. The circadian rhythm of melatonin synthesis is controlled by the suprachiasmatic nucleus (SCN) of the hypothalamus. After receiving information about changes in light from the retina, the SCN sends signals through the superior cervical sympathetic ganglion and noradrenergic fibres to the pineal gland. Then, activation of the pineal β1-adrenoceptor inhibits the cleavage of AA-NAT and increases melatonin synthesis [2].

In addition to production in the pineal gland, melatonin production has been observed in neuroendocrine cells of the retina; enterochromaffin cells of the gastrointestinal tract (EC cells); respiratory cells; cells of the thymus, adrenal gland, paraganglia and pancreas; and other cells that form the diffuse neuroendocrine system. In addition, leukocytes, platelets, endothelial cells, renal cortex cells, and other non-endocrine cells are also capable of producing melatonin. However, the pineal gland is the main source of circulating melatonin, whereas the rhythms of melatonin secretion coinciding with the light and dark cycle are an intrinsic feature of the epiphysis and retina only [3].

The physiological effects of melatonin are produced in response to signals from membrane and nuclear receptors. There are two types of receptors for melatonin in humans: MT1 (MTNR1A) and MT2 (MTNR1B) receptors. MT2 receptors

are found in the retina and in different parts of the brain, and it is accepted that circadian rhythms are mediated through these receptors [4]. The primary function of melatonin is the synchronisation of physiological and metabolic processes with circadian and seasonal cycles [5, 6]. In particular, melatonin affects the rhythms of the cardiovascular, immune and endocrine systems [7].

Effects of melatonin on insulin secretion and glucose homeostasis

The apparent discrepancy between the circadian rhythms of melatonin and insulin secretion may be explained by the different biological functions of these hormones. In contrast to melatonin, the lowest level of insulin occurs in humans during the night hours, as the main function of insulin, i.e., to control metabolism in the postprandial state, should not be realised at night. In volunteers, one study observed a disruption in the normal alliance between food taking and the day/night period when meals were shifted by 12 h, followed by an increase in insulin production [8]. Melatonin provides synchronisation of metabolic processes, with the night-time programmed for starvation in humans, which can cause an inhibitory effect on insulin secretion [9].

The expression of the MT-1 and MT-2 receptors has been demonstrated in the pancreatic islets of both rats [10] and mice [11]. In human islets, MT2 is expressed at a lower level than MT-1 [12, 13]. In addition, the MT1 receptors are expressed mainly by α-cells [11, 12], whereas MT2 receptors are expressed mainly by β-cells [11, 13, 14]. Experiments in vitro have also demonstrated the inhibitory effect of melatonin on insulin secretion in β-cells [13], as well as in mouse and rat insulinoma cells (MIN-6, INS-1) [12, 15]. However, the whole-body effect of melatonin may not be so straightforward. For example, it was shown that melatonin stimulates both insulin and glucagon secretion in perfused human islets [12], although the absence of an effect of melatonin on insulin secretion was demonstrated in the islets of ob/ob mice, an animal model of obesity and type 2 diabetes (T2D) [16]. This ambiguity in the action of melatonin is likely explained by the numerous signalling pathways that mediate its effect; the inhibitory effect of melatonin on insulin production has been associated with the inhibition of cAMP- and cGMP-dependent pathways, whereas the stimulatory effect of melatonin is mediated by G (q)-proteins and phospholipase C and IP [17].

Changes in insulin secretion and glucose homeostasis have been observed in animals with a surgically removed epiphysis. Furthermore, it was shown that pinealectomy in rats induces hepatic insulin resistance, activation of gluconeogenesis [18] and elevated blood glucose at night-time [19]. Additionally, an increase in glucose-stimulated insulin secretion and the disturbance of its amplitude rhythm were observed in cultured β-cells from pinealectomised rats [20], and removal of the pineal gland in OLETF rats (T2D model) was shown to produce hyperinsulinaemia and the accumulation of triglycerides in the liver [21]. Furthermore, it was suggested that maternal melatonin can program the circadian rhythms of energy metabolism in the foetus, and the offspring of pinealectomised rats display diminished glucose-stimulated insulin secretion, hepatic insulin resistance, and consequently impaired glucose tolerance at the end of the light phase of the light/dark cycle [22].

In patients with arterial hypertension diminished night melatonin secretion is associated with elevated levels of fasting insulin and increased homeostatic model assessment of insulin resistance (HOMA-IR) [23].

These data support the notion that melatonin contributes to the adjustment of energy metabolism during conditions of low insulin secretion and high insulin sensitivity at night-time hours.

Melatonin receptor gene polymorphisms and risk of type 2 diabetes

The results of molecular genetic studies have shown an association between polymorphic variants of the melatonin receptor genes and the development of T2D. For example, it was found that two MT2 (MTNR1B) single nucleotide polymorphisms, namely rs1387153 and rs10830963, are associated with fasting plasma glucose, insulin secretion and T2D in European populations. The presence of the T-allele at the rs1387153 locus is also associated with fasting plasma glucose elevation (β=0.06 mmol/l) and the risk of hyperglycaemia or T2D (OR=1.2) [14]. Furthermore, data from 10 genome-wide association studies have indicated that the presence of each G-allele at the MTNR1B rs10830963 locus was associated with an elevated fasting glucose level of 0.07 mmol/l and with a decline in β-cell function, as evaluated by the HOMA-B index. A meta-analysis of 13 case-control studies also found that the presence of the G-allele at this locus increases the risk of T2D (OR=1.09) [24].

These findings indicate that the MTNR1B gene can be considered a new T2D locus. Although the influence of MTNR1B on disease risk is rather modest, it is comparable to the effect of other "diabetogenic" genes. Furthermore, combinations of genetic traits including MTNR1B and other genes related to fasting glucose level (GCK, GCKR and G6PC2) may demonstrate more close associations with diabetes [25, 26].

Changes in melatonin secretion in diabetes

Disturbances in melatonin secretion have been found in aging individuals and in a number of human diseases, including seasonal affective and bipolar disorder, dementia, sleep disorders, pain syndromes and cancer [3]. Diabetes is also characterised by changes in melatonin secretion, as an elevated level of melatonin in the blood and increased expression of AA-NAT in the pineal gland have been demonstrated in models of type 1 diabetes (T1D) [17, 27, 28]. It was also shown that severe hypoinsulinaemia is accompanied by increased pineal expression of the insulin receptor, β1-adrenoceptor and clock genes PER1 and BMAL1 [17]. Insulin substitution also normalises the plasma melatonin level and pineal gene expression in this model [27].

Other changes in melatonin production have been observed in T2D. For example, a reduction in insulin receptor expression and a diminution of AA-NAT activity in the pineal gland were observed in Goto Kakizaki rats (genetic model of

T2D), and patients with T2D have reduced blood melatonin levels [29]. Furthermore, a study that assessed hourly blood sampling revealed a severe decline in nocturnal melatonin secretion among men with T2D [30]. Alterations in melatonin secretion, as revealed by blunted night-time increases in 6-hydroxymelatonin sulphate (6-COMT) urinary excretion, were found in subjects with metabolic syndrome [31]; however, in contrast to those results, enhanced excretion of 6-COMT in patients with metabolic syndrome was also reported [32]. Patients with metabolic syndrome had reduced melatonin/insulin ratio in plasma, collected at 3 a.m. The difference between day and night melatonin concentrations inversely correlated with the level of fasting blood glucose [33].

Little is known about extrapineal melatonin production in diabetes. However, it was shown that in rats with streptozotocin-induced diabetes, the melatonin level and AA-NAT activity in the retina were reduced, although these changes could be ameliorated by insulin [34]. Features of retinal melatonin production in diabetic retinopathy have not yet been studied. Interestingly, melatonin plasma levels in T2D patients with proliferative diabetic retinopathy are significantly lower compared to patients without the complication [35].

Thus, T1D and T2D are characterised by alternative changes in pineal melatonin secretion and plasma melatonin concentration. In both types of diabetes, there is inverse relation between insulin and melatonin production, which suggests a reciprocal relationships between these hormones.

Melatonin perspectives in diabetes treatment

The effects of melatonin on the development of T1D have been studied in numerous experiments. It was shown that melatonin enhances the proliferation of β-cells and increases the plasma level of insulin in rats with streptozotocin-induced diabetes [36]. In addition to its proliferative effects on β-cells, melatonin suppresses β-cell apoptosis and stimulates the formation of new islets from the pancreatic ductal epithelium [27]. In a model of neonatal streptozotocin-induced diabetes in rats, melatonin demonstrated no effect on insulin secretion; however, it enhanced insulin sensitivity and decreased the blood glucose level [37]. The protective effect of melatonin on β-cells may be explained, at least partially, by its antioxidant and immunomodulatory properties. For example, it was shown that melatonin has marked antioxidant ability and helps to restore the imbalance of antioxidants in animals with diabetes [38]. Moreover, the inhibitory effect of melatonin on Th1-lymphocytes doubled the life expectancy of transplanted islets in NOD diabetic mice [39].

The use of melatonin in models of metabolic syndrome and T2D (Zucker rats) was shown to result in reductions in fasting glucose, HbA1c, free fatty acids, insulin, HOMA-IR and the concentration of inflammatory cytokines in the plasma; in addition, melatonin reduced the level of leptin and increased the adiponectin level. These data suggest that melatonin has beneficial effects on adipose tissue, chronic inflammation, insulin sensitivity, and carbohydrate and fat metabolism [40, 41]. Melatonin promotes weight loss in animal models of obesity [42]. According to results of the non-randomized studies, intake of melatonin in patients with the metabolic syndrome is accompanied by decrease in blood pressure, oxidative stress markers [43], HOMA-IR and cholesterol levels [23]. The use of long-acting melatonin for the treatment of insomnia in T2D patients produced no effect on the levels of insulin and C-peptide but was accompanied by a significant reduction in HbA1c after 5 months of therapy [44].

Data have also been published concerning the effect of melatonin on diabetic vascular complications. For example, melatonin was shown to prevent the accumulation of lipid peroxides in the retina [45, 46], as well as to improve electrophysiological properties and alleviate the retinal production of vascular endothelial growth factor during hyperglycaemia [47]. Melatonin administration to rats with streptozotocin-induced diabetes also prevented the increase in urinary albumin excretion [47, 48]. In the kidneys of diabetic animals, melatonin reduces oxidative stress [48] and prevents the hyperexpression of fibrogenic factors, including TGF-β and fibronectin [47]. Under conditions of oxidative stress and inflammation, hormones can have a protective effect on the endothelium [49], and melatonin was shown to restore endothelium-dependent dilatation of the aorta, which is impaired in hyperglycaemia [50]. Moreover, the antioxidant effect of melatonin in the bone marrow was accompanied by an increase in endothelial progenitor cells in the circulation of streptozotocin-induced diabetes rats [51]; these data are of great interest because impaired mobilisation of these cells from the bone marrow is a characteristic feature of diabetes [52].

In patients with T1D, melatonin enhances the nocturnal reduction in diastolic blood pressure [53], and this effect could be valuable for the treatment of diabetic autonomic neuropathy associated with blunted physiological blood pressure reduction at night [54].

Conclusion

The findings presented here demonstrate the pivotal role of melatonin in the regulation of the circadian rhythms of insulin secretion and glucose homeostasis. Diabetes is characterised by impaired circadian melatonin production in the pineal gland and altered melatonin concentrations in the blood. Experimental data support the notion that melatonin may mitigate the dysfunction of β-cells and delay the development of diabetes and its complications. Further investigations are required to clarify the role of melatonin in the pathophysiology of diabetes and to estimate the therapeutic value of this hormone in diabetic patients.

The authors declare no conflicts of interest related to this manuscript.

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