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The role of melatonin in the development of gestational diabetes

Abstract

This review summarizes the literature on melatonin production and its role in the regulation of carbohydrate metabolism, mechanisms of functional relationships between melatonin, insulin, glucagon and circadian organization of the pancreas. The results of experimental and clinical studies have shown that the basis for the development of gestational diabetes is low production of melatonin and the lack of its circadian rhythm in women with abnormal neuroimmunoendocrino system that determines the possibility of prediction and prevention of this complication of pregnancy.

This review summarizes many of the published reports about the production of melatonin and its role in regulation of carbohydrate metabolism, interrelationships between melatonin, insulin, glucagon and diurnal signaling the blood-glucose-regulating of the islet. The results of experimental and clinical investigations support that low melatonin levels and absence of its circadian rhythm, play the role in the development of gestational diabetes mellitus in women with pathology of neuroimmunoendocrinology system and suggest the possibility of prognosis and Prophylaxis for this complication of pregnancy.

Keywords: melatonin, gestational diabetes mellitus, insulin, circadian rhythm

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Introduction

Increase in the frequency of gestational diabetes mellitus (GDM) and its adverse consequences for mother and child dictates the need to study the mechanisms underlying the development of pregnancy complications.[1–5] It is known that, in the course of physiological pregnancy there are moderate hyperinsulinemia and insulin resistance associated with an increased need for insulin as a result of the restructuring of metabolic processes in the female body, designed to ensure optimal delivery of nutrients to the developing fetus is thus observed to increase insulin biosynthesis, increased stimulated glucose secretion and increase in mass of pancreatic β-cells.[6] However, the question arises: why the number of pregnant pancreatic function is not sufficient to accommodate the metabolic needs during pregnancy, blood glucose levels rise to pathological variables and diagnosed with diabetes? Since the frequency of GDM varies considerably among ethnic populations, and its growth is in direct proportion to the increase of type 2 diabetes, which develops later in life in survivors of HSD (Health Search Database), the attention of researchers in recent years, attracted to the study of genetic factors predisposing to this complication of pregnancy.[7] A number of genetic variants that may explain some of the individual features of the predisposition to HSD,[8,9] include different genes (PPARG, KICNJ11, TCF2 / HNF1B, WFS1, HNF4A), dysfunction associated with insulin secretion of pancreatic β-cells with gestational diabetes and type 2 diabetes.[10] In addition, it discusses the role of epigenetic modifications activity of genes involved in the regulation of glucose metabolism and insulin secretion occurring during sleep disorders, in a pregnant woman, the night shift, low physical activity, etc.[7,11] At the same time, numerous studies have shown that GDM risk is present in obese women,[12,13] the metabolic syndrome,[14,15] PCOS, endometriosis[16] as well as in having a history of miscarriage due to hormonal causes[17] HSD previous pregnancy complications.[7,10,18] The results of our investigations have revealed the disease three or more functional systems (endocrine, cardiovascular, immune, gastrointestinal tract) in 85% of mothers whose pregnancy was complicated by gestational diabetes. This suggests that they have a diffuse pathology neuroimmunoendocrinosystem, which is a leading hormone melatonin - homeostasis regulator providing a functional relationship between mechanisms.[19,20] It should be emphasized that for all the above forms of disease, determining the risk of developing GDM, researchers have noted a low level of melatonin in the body, and its violation of the circadian changes.[21–28] Melatonin is synthesized from pinealocytes in pineal gland, the endocrine function of which is controlled by the suprachiasmatic nuclei of the hypothalamus and has a diurnal rhythm. Light information from the retinal ganglion cells through retino-hypothalamic tract enters the suprachiasmatic nuclei (SCN) of the hypothalamus, where the signals are in the upper cervical ganglia and then sympathetic noradrenergic pathways reach epiphysis, where melatonin is synthesized. Light inhibits the production and secretion of melatonin, so its maximum level in the epiphysis and human blood is observed during night, and the minimum, in the afternoon.[29,30] Availability circadian rhythm of melatonin production is a marker of normal operation endogenous circadian biorhythm regulation and synchronization with the external circadian rhythm of alternation between day and night.[19,31–33]

Melatonin is produced not only in the epiphysis. Ekstrapinealny melatonin was found in all organs: the gastrointestinal tract, liver, kidneys, adrenal glands, heart, thymus, gonads, placenta, uterus, platelets, eosinophils, leukocytes, and other cells of the immune system.[34,35] Thus, its synthesis in mitochondria of eukaryotic cells indicates unique protection of melatonin cellular organelles from oxidative damage and maintaining their physiological functions.[36–38] Melatonin is synthesized from the amino acid tryptophan by hydroxylation of which (an enzyme tryptophan hydroxylase) and decarboxylation (the enzyme 5-ksitriptofandekarboksilaza) is

converted into serotonin. Using enzymes N-acetyltransferase (NAT) and oxindole-O-methyltransferase (HIOMT) formed of serotonin, melatonin. From pinealocytes, pineal melatonin is released into the blood and cerebrospinal fluid, whereas melatonin secreted by other cells in the body, enters the blood in small amounts, giving a field of its synthesis paracrine and autocrine effect.[39] With a hydrophilic molecule of melatonin at the same time, it is highly lipophilic and therefore easily penetrates the blood-brain and the placental barrier, takes place in the capillaries, where 70% of melatonin binds to albumin. The half-life of melatonin ranges from 30 to 45 minutes.[40] Melatonin is metabolized in the liver and kidneys. The end products of metabolism are 6-sulfatoksi-melatonin and acetylsalicylic acid.[29,39] Melatonin provides regulating effect through specific G-protein linked membrane receptors (MT1, MT2, MT3) and nuclear receptors (RORα),[38,41] which are found in the suprachiasmatic nuclei of the hypothalamus, the cerebellum, retina, spleen, pancreas, liver, mammary gland, uterus, thymus, gastrointestinal tract, platelets, lymphocytes.[39,42–44] More than 75 years ago, the role of the pineal gland peptide, called "pinealinom" in the regulation of carbohydrate metabolism was first reported.[45] It was identified with insulin-like hypoglycemic, anabolic and anti-cholesterol effects.[40] In the following decades, numerous experimental studies were performed at the molecular level, the mechanisms established functional connections between melatonin, insulin and glucagon.[40,45] The pancreas tissue revealed membrane MT1, MT2 and G-protein associated (GPR50) receptors, as well as mRNA nuclear receptors through which melatonin performs a modulating effect on the insulin and glucagon secretion.[46–48] Furthermore, in the pancreas as well as in other tissues, there are autonomous circadian genes (Bmal, Clock, Per1, Cry1), through which is realized the impact synchronizing circadian rhythm of melatonin on epiphyseal β- and α-cells.[49] At night there is a high production of melatonin, but lower insulin secretion, and at day on the contrary.[31,50] Melatonin stimulates the secretion of glucagon pancreatic α-cells, which defines the circadian rhythm of production and glucose metabolism.[49,51] The effect of melatonin on pancreatic α- and β-cells and insulin secretion is provided through a complex type of intercellular and intracellular signalling pathways.[52] Furthermore, melatonin protects pancreatic cells from free radical damage by the elimination of free radicals and activates antioxidant enzymes.[31,37,53] The circadian amplitude of the melatonin level decreases with age, especially when working and active lifestyle at night, and sleep disorders, resulting in hyper insulinemia, insulin resistance, and hyperglycemia, i.e. symptoms characteristic of type 2 diabetes.[54–57] The development of these pathological conditions with low production of melatonin and absence of its circadian rhythm are associated with impaired regulation of synthesis and secretion of insulin from β-cells of the pancreas and its binding to the receptor membranes of the target cells, suppression of expression GLYUT4 gene and decrease of the protein content.[58,59] The experiment demonstrated that the removal of the epiphysis in insulin-sensitive tissues (white and brown adipose tissue, skeletal and cardiac muscle) sharply decreases GLYUT4 mRNA (GLUT4 mRNA), and the content of microsomal membrane protein. Furthermore, in the absence of melatonin disrupted insulin receptor function, in particular, MT2 adipocytes in adipose tissue, dramatically reduces glucose uptake by these cells.[60,61] Identified pinealectomy effects disappeared as a result of treatment with melatonin.[62,63] Thus, melatonin epiphyseal is required for the synthesis, secretion and insulin implementation functions. Reducing its production leads to disruption of circadian rhythms of metabolic processes in the body and the development of the pathological condition of the energy balance, obesity, insulin resistance and impaired glucose tolerance.[58] The level of melatonin in the blood plasma as well as its synthesis, play the key enzyme activity (AA-NAT) in the pineal gland which is significantly reduced in type 2 diabetes, that underlies excess of pancreatic β-cells,[49] insulin resistance and impaired glucose tolerance.[58]

Melatonin and its circadian rhythm of secretion is determined for a successful pregnancy and birth of a healthy child. First, the melatonin and its metabolites function as direct absorbers produced during pregnancy of free radicals stimulate antioxidant enzymes, thereby providing a stable protection against free radical damage at the cellular and tissue levels in a single system mother-placenta – fetus.[64–66] In individuals with abnormal neuroimmunoendocrinosystem and initially low production of melatonin, when the body's adaptation to pregnancy, significant activation of free radical oxidation leads to the depletion of antioxidant reserves and primarily melatonin.[67,68] Not only low levels of melatonin, but violation as a result of oxidative modification of proteins the functional state of its receptors, providing regulation of the production of insulin and glucagon in the β and α-cells of the pancreas, leading to uncontrolled insulin secretion not only in daytime but also at night. The consequence of these processes is the development of insulin resistance and consequent impairment of glucose tolerance. Besides, β-cells being unable to adequately secrete sufficient amounts of insulin over long time to compensate for insulin resistance, it also contributes to hyperglycemia. To confirm the role of melatonin in the development of gestational diabetes data researchers set low melatonin secretion and the absence of its daily rhythm in the second and third trimesters of a given pregnancy complications, combined with the sleep disorder, the shortening of a night's sleep and quality features.[69,70] The changes with gestational diabetes, micro PHA production (microRNAs), which normally has a circadian rhythm.[71] It is found that the presence of melatonin receptor gene polymorphism and MTNR1B rs10830963 MTNR1B rs4753426 increases the risk of developing gestational diabetes.[72–74] This shows that women with GDM, exhibit reduced receptor binding ability GLYUT4 and glucose transport in adipose tissue and skeletal muscle.[71,75,76] Use of melatonin and stabilization of circadian rhythm, normalize metabolism optimized during pregnancy and fetal development.[28,49,77] Thus, the results of experimental and clinical studies have expanded our understanding towards the mechanisms of regulation regarding carbohydrate metabolism and energy metabolism, indicate the possibility of prediction of complications in future pregnancies with diabetes at the stage of family planning and timely implementation of preventive measures, including circadian rhythm normalization of sleep and wakefulness, energy metabolism, antioxidant status, and if necessary treatment with melatonina. In addition, the available data indicate the need for special attention to keeping in obstetric hospitals light conditions for the endogenous production of melatonin, as well as restrictions on the use of its suppressive drugs.[78,79] Increased in the last decade, the interest of researchers to study the physiological role of melatonin in the reproductive function, gave sample evidence that determine the optimal course of pregnancy, delivery and fetal development, making a promising development of new approaches to its use in obstetrics.

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Conflict of interest

Author declares that there is no conflict of interest.

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