



Mini Review

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Effect of Circadian Rhythm - Autonomic Nervous System - Endocrine Hormone Axis on The Occurrence and Development of Diabetes: A Review and Perspective

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Abstract

There are obvious circadian rhythms in organisms. In modern society, circadian rhythm disorders can be caused by factors such as shift work, staying up late for a long time, outbound tourism, psychological stress, various diseases and so on, and the disorders will regulate the physiological and biochemical functions of various tissues and organs through the autonomic nervous system, including the secretion and release of hormones, and then affect the occurrence and development of the disease further. At present, diabetes has become the sixth leading cause of death, and gradually tends to be younger. Considering the effects of systematic and holistic changes, such as circadian rhythm, autonomic nervous system and endocrine hormones, on the occurrence and development of diabetes, this paper summarizes the regulation of circadian rhythm-autonomic nervous system-endocrine hormone axis to blood glucose metabolism in order to find a new pathogenesis of diabetes and provide a new drug target for the treatment of diabetes.

Keywords: Diabetes, Circadian Rhythm, Autonomic Nervous System, Endocrine Hormone

Introduction

Diabetes is becoming one of the most common diseases except cardiovascular disease, and it is the sixth leading cause of death for human beings [1]. According to the estimates of the World Health Organization, there are at least 463 million people with diabetes in the world [2,3]. Among them, about 116 million in China, and about 4.2 million people died of diabetes and its complications in 2019. It is expected that by 2040, the number of cases will increase to 642 million [4]. The case rate of diabetes has increased rapidly in recent years. In addition to the absolute lack of insulin secretion, insulin resistance and other factors, circadian rhythm disorders as one of the pathogenic factors has gradually aroused people's attention. Epidemiologic study has shown that there is a significant correlation between circadian rhythm disorders and

increased risk of diabetes [5]. The disorder of circadian rhythm will disrupt the normal work of clock molecules in the brain, affect the endocrine regulation of the body through the autonomic nervous system, and then destroy the dynamic blood glucose balance. This paper systematically retrieved and summarized the regulation of circadian rhythm, autonomic nervous system and endocrine hormones to blood glucose homeostasis, in order to reveal the etiology of diabetes from a new perspective.

Discussion/Observations

Circadian Rhythm and its clock molecules

The circadian rhythm is common in most living things on the earth, which is synchronized with the 24-hour environmental cycle



of the earth [5]. The light source is a kind of signal that regulates the circadian rhythm by stimulating the suprachiasmatic nucleus (SCN) [6,7]. SCN has been proved to be the main pacemaker of circadian rhythm in mammals. It senses light through the retina-hypothalamus bundle (RHT), which makes mammals enter the circadian cycle. When SCN is damaged, the circadian behavior of diet and activity in rats will disappear. In mammals, there is a core clock feedback loop. BMAL1/CLOCK drives the transcription of PER (1-3) and CRY (1-2) by activating E-box enhancers. PER and CRY forms heterodimer translocated to the nucleus, and PER/CRY heterodimer inhibits the activity of CLOCK/BMAL1 in the night of circadian rhythm, thus forming a negative feedback loop. After that, the concentration of PER/CRY heterodimer decreases gradually and the loop enters a new circadian cycle [8,9].

Effect of Circadian Rhythm on Diabetes

Effect of clock molecules on diabetes

Clock molecules are vital for maintaining the balance of glucose metabolism in organisms. They regulate glucose metabolism at many levels. If the clock molecules are mutated or inactivated, the disorder of glucose metabolism will be induced, which may lead to diabetes. CLOCK mutant mice have typical characteristics of diabetes. Mutations in CLOCK will lead to hyperorexia and disruption of energy balance in mice, thus leading to diabetes [10]. Inactivation of BMAL1 and CLOCK inhibits diurnal changes in glucose and triglycerides, leading to hypoinsulinemia and diabetes [11,12]. Changes in CLOCK / BMAL1 downstream target genes can also cause diabetes, and Per3 knockout mice will develop advanced obesity and diabetes [13]. Cry1 and Cry2 knockout mice showed hypermetabolism, decreased insulin secretion and impaired glucose tolerance [14].

Effect of sleep on diabetes

The most direct factor of circadian rhythm disorders is sleep disorders. Since sleep is very important to life and the body needs enough sleep to run normally, sleep disorders will affect blood glucose metabolism [15]. Blood sugar levels change and fluctuate with changes in external conditions (activity / rest and eating / hunger) [16]. Epidemiological studies have shown that reduced sleep time can lead to an increase in the incidence of diabetes, and that reduced sleep time or lowered sleep quality will reduce the body's sensitivity to insulin and glucose tolerance [17]. Although less sleep can increase energy consumption due to increased waking time, it also leads to more food intake and weight gain at the same time [18]. Sleep can change the energy balance as well. The loss of sleep may greatly change the hypothalamic regulation mechanism that regulates appetite and energy metabolism, and the shortening of sleep time will lead to metabolic disorders, which leads to obesity, insulin resistance and diabetes [19]. A study shows that if a 2.5-year-old baby does not get enough sleep, it will be

obese around the age of 7 [20]. A study also showed that a lack of sleep can lead to impaired glucose tolerance and increase the risk of diabetes [21].

Regulation of Circadian Rhythm - Autonomic Nervous System to Blood Glucose

Autonomic nerves (parasympathetic nerve and sympathetic nerve) have obvious functions in regulating pancreatic islet hormone secretion [22]. Insufficient sleep and intermittent sleep can lead to increased activity of the sympathetic system, inhibit insulin secretion, and promote insulin resistance [23]. Increased sympathetic nerve function can lead to blood glucose disorders in patients with diabetes, while the concentrations of norepinephrine, epinephrine and cortisol increase in serum and urine. These hormones can promote gluconeogenesis and reduce insulin sensitivity [24-26]. When the sympathetic nerve is excited, the release of norepinephrine increases and binds to the receptors on vascular smooth muscle, resulting in peripheral vasoconstriction, decrease of skeletal muscle blood flow, decrease of skeletal muscle glucose uptake and utilization, and decrease of insulin sensitivity [27,28]. Sympathetic excitation can also stimulate fat decomposition and lead to an increase in free fatty acids, which may cause insulin resistance [29].

In an experiment of sympathetic ablation in the treatment of hypertension, a decrease in fasting blood glucose and an increase in insulin sensitivity were observed, which may be due to a decrease in the activity of the sympathetic nervous system, resulting in a decrease in insulin resistance [30,31]. Straznicky and others also found that long-term excessive activation of sympathetic nerves can lead to down-regulation of β -adrenaline metabolic reactivity and insulin resistance, which will further stimulate the activation of sympathetic nerve, thus forming a vicious circle and aggravating insulin resistance [32]. In patients with diabetes, sympathetic function is enhanced and parasympathetic function decreases [26]. Vagal stimulation can lead to weight loss and loss of appetite [33]. Nervi vagus, which is the pathway of peripheral metabolism and brain connection, is the main participant in regulating body weight and glucose homeostasis. The vagus nerves can directly innervate the pancreas to stimulate insulin secretion [34]. The vagal afferent neurons innervating the pancreas are sensitive to insulin and can transmit changes in pancreatic and systemic insulin levels to the brain [35]. In the case of hyperglycemia, the vagal activation reduces the release of glucose from the liver, while long-term hyperglycemia can induce insulin release stimulated by the vagus nerves and increase the activity of the vagus nerves [36].

Effect of Circadian Rhythm - Endocrine Hormone On Diabetes

Circadian clock molecules produce systemic rhythms directly or indirectly in a variety of endocrine hormones including melatonin,

insulin, glucagon, glucagon-like peptide 1 (GLP-1), catecholamine hormones, glucocorticoids, thyroid hormones and sex hormones, and then regulate blood glucose levels [37].

Effect of Circadian Rhythm - Melatonin on Diabetes

Melatonin is a kind of indole neuroendocrine hormone, which is mainly synthesized and secreted into the circulatory system by the pineal gland in the absence of light at night, acting as a "dark hormone" for the brain and body. At night, the synapses of the sympathetic nerve endings in the pineal gland release norepinephrine to stimulate the synthesis and secretion of melatonin, which increases the concentration of melatonin in human plasma at night by about 10 times. Under daytime light, the sympathetic nerve endings of SCN release the inhibitory neurotransmitter, γ -aminobutyric acid (GABA), and inhibit the synthesis of melatonin [38]. Melatonin is involved in the regulation of circadian rhythm and glucose levels [39]. There is a two-way regulation between circadian rhythm and melatonin. SCN regulates the circadian rhythm of melatonin synthesis according to optical signal reception. When the circadian rhythm is out of order, the synthesis and secretion of melatonin will be disordered. If the pineal gland is damaged, the level of melatonin in plasma will remain low, and the circadian rhythm will also be disordered [40].

Melatonin has been identified to be associated with elevated fasting blood glucose levels and an increased risk of diabetes [41]. Melatonin blocks glucose-stimulated insulin secretion, and glucose utilization is disrupted when melatonin synthesis is triggered, and its level rises in the body [42]. It has also been reported that glucose tolerance will decrease after acute administration of melatonin [43], but other studies have also shown that in normal pancreatic islets of chronic hyperglycemia or diabetes, melatonin receptor signal transduction in β -cells will reduce oxidative stress, resist β -cell apoptosis induced by proteotoxicity, and recover insulin secretion stimulated by glucose [44]. Effect of circadian rhythm - insulin, glucagon and GLP-1 on diabetes Insulin and glucagon, as the most important hormones to regulate the level of blood sugar, even though their secretions are mainly driven by eating, they also have a certain biological rhythm. There are peaks in insulin secretion in the early morning while troughs at night [45]. The biorhythm of insulin and glucagon secretion does not depend on the level of glucose, but the central biological clock regulates the secretion rhythm of insulin and glucagon through the autonomic nervous system and peripheral biological clock [46-48]. In healthy individuals, plasma glucose concentration remained within a narrow range of about 3.5 to 7.0 mmol / L throughout the day, mainly through insulin produced by the pancreas [49]. Knocking out BMAL1 clock gene in the mouse pancreas, insulin secretion and normal glucose homeostasis were disrupted, and plasma insulin concentration was decreased significantly after intraperitoneal

injection of glucose, thus resulting in hyperglycemia [50,51]. By knocking down the CLOCK gene in the human pancreas, it was found that the circadian rhythm of insulin secretion was disrupted and glucose-stimulated insulin secretion was also affected [52].

Glucagon, in contrast to insulin, increases plasma glucose levels by stimulating the liver to produce glucose. There was a circadian rhythm in the regulation of serum glucagon for the circulating glucagon level was the highest at 8:00 pm and the lowest at 8:00 am [53]. Generally speaking, insulin plays the role of glucose deposition and anabolism, while glucagon plays the role of glucose mobilization and catabolism [54]. When the level of plasma glucose is too low, the pancreas will release glucagon to the liver to promote glycogen decomposition and gluconeogenesis, inhibit glycogen formation, and increase blood glucose [55]. GLP-1 is an enterogenous hormone that regulates blood glucose and is secreted by endocrine L cells distributed in the distal ileum and proximal colon [56].

There is also a circadian rhythm in the regulation of GLP-1. GLP-1 secretion was decreased, and circadian rhythm was impaired in BMAL1 knockout mice [57]. Sara Janssen et al have shown that stimulating G protein-coupled receptor (GPCR) and/or ion-dependent nutritional transporters in intestinal endocrine cells can stimulate the release of GLP-1 [58]. GLP-1 acts on islet β cells in a glucose-dependent manner, promoting insulin gene transcription, increasing insulin synthesis and secretion, and inhibiting β cell apoptosis, thus increasing the number of islets β cells, inhibiting glucagon secretion, inhibiting gastric emptying, and reducing appetite and food intake. GLP-1 receptors are not only expressed in islet β cells, but also widely distributed in the brain, especially in the brainstem and hypothalamus of the central nervous system, including arcuate nucleus, paraventricular nucleus and dorsomedial nucleus. By stimulating the central reward system, it can increase the sense of satiety, reduce food intake, and have the effect of losing weight and reducing blood sugar [59].

Effect of Circadian Rhythm - Catecholamine Hormones on Diabetes

Catecholamine hormones, including norepinephrine, epinephrine and dopamine, are a kind of stress sympathicomimetic hormones produced by the adrenal gland. There is no obvious circadian rhythm in the secretion of catecholamines, but it has influence on blood glucose levels and islet function. When patients with diabetes suffer physical, mental or pathological stress, the adrenal medulla releases catecholamines, which can stimulate glucose production and reduce insulin levels, thus worsening diabetes [60,61]. Due to its sympathetic function, catecholamine hormones often inhibit appetite and reduce food intake [62]. However, this does not mean reducing blood glucose levels and improving insulin sensitivity and on the contrary, studies have

reported that stimulating the release of catecholamines can aggravate diabetes [63,64]. This may be that catecholamine hormones can directly act on skeletal muscle cells, promote muscle glycogen decomposition and increase blood glucose, while sympathetic nerve excitation causes peripheral vasoconstriction and decrease of skeletal muscle blood flow, which results in decreased glucose uptake and utilization and decreased insulin sensitivity of skeletal muscle under insulin stimulation [27,28].

Effect of Circadian Rhythm - Glucocorticoid on Diabetes

Glucocorticoid (GC) is secreted by the adrenal cortex under the control of the hypothalamus-pituitary-adrenal (HPA) axis, which plays an important role in glucose, lipid and protein metabolism and contributes to energy homeostasis. GC can regulate metabolism and also affect the circadian rhythm system. The first peak of GC secretion is in the period of time from 4:00 am to 5:00 am, and the second is from 6:00 am to 9:00 am, while the lowest level is at midnight [45]. There is a circadian rhythm in the content of glucocorticoid receptor (GR) in some tissues. CLOCK and BMAL proteins can acetylate the lysine residues in the hinge region of GR, selectively weakening the binding ability of GR to GC response elements, thus making the function of GR circadian. Glucocorticoids are widely used in anti-inflammatory and immunosuppressive therapy, but their side effects may cause or aggravate diabetes [65]. It is reported that the incidence of glucocorticoid-induced hyperglycemia is 12%, which may be related to insulin resistance, increased glucose tolerance and a decrease in the number of β cells caused by their dysfunction. The regulatory effect of glucocorticoids on glucose can be seen in multiple stages of the insulin signal cascade response, and the sensitivity of insulin can be reduced by 50% under the administration of glucocorticoids for 7 days in healthy volunteers [66,67].

Effect of Circadian Rhythm - Thyroid Hormones on Diabetes

Thyroid hormones are secreted from the thyroid under the regulation of the hypothalamus - pituitary axis to maintain normal metabolism, growth and development, including thyroxine (T4) and triiodothyronine (T3). Changes in photoperiod alter the transformation of hypothalamic thyroid hormone, and the circadian rhythm of blood thyroid hormone concentration is associated with the sleepwaking cycle, with peaks from midnight to 4:00 am and trough at 6:00 pm [68]. In one case report, the condition of patients with severe insulin resistance was significantly improved after the treatment of thyroid cancer with an inhibitory dose of thyroxine [69]. This is related to hypothyroidism leading to a decrease in gluconeogenesis. Physiological T3 can stimulate insulin secretion and protect pancreatic islets. T4 can increase the transport of alanine to hepatocytes and increase the production of metabolic

intermediates in the gluconeogenesis pathway, eventually converting alanine into glucose [70].

Effect of Circadian Rhythm - Sex Hormones on Diabetes

Sex hormones mainly include androgens secreted by the testis and estrogens and progesterones secreted by the ovary. The secretion of sex hormones is controlled by the hypothalamus - pituitary - gonadal axis, with circadian rhythm changes [71-73]. A study shows that androgens may have a different effect on the risk of diabetes in men and women, as lower androgen levels in men (overall and free) and higher androgen levels in women (overall and free) lead to an increased risk of diabetes [74]. Estrogens can protect pancreatic β cells from oxidative stress, amyloid toxicity, lipotoxicity and apoptosis, enhance insulin biosynthesis, reduce tissue inflammation and improve peripheral insulin sensitivity at the same time. Androgens are able to prevent visceral fat accumulation in men, promote male insulin sensitivity in skeletal muscles, and maintain male energy homeostasis in the brain [74,75].

Effect of Circadian Rhythm - Nervous System - Endocrine Axis on Diabetes

Due to the change of lifestyles in modern society and the increase of external factors, for example, stress, circadian rhythm disorder has become the norm [76]. The disorder of circadian rhythm will lead to the abnormal work of brain clock molecules, which acts on different tissues and organs through the changes of the autonomic nervous system of the human body, and then affects the secretion and release of hormones. Finally, the change of blood glucose level shows a certain biological rhythm [77]. The author combines circadian rhythm, autonomic nervous system and endocrine hormone into one, and proposes a new concept of blood sugar regulation by the circadian rhythm - autonomic nervous system - endocrine hormone axis to, in order to find the etiology of diabetes from the source.

Conclusion and Prospect

Since the discovery of insulin by Banting in 1920, insulin has been used only as an alternative therapy and has no cure for chronic diseases of diabetes. So far, there is no drug that can cure diabetes. The author believes that it is all because the 'cause' of diabetes has not been found, so we can only treat the symptoms rather than the etiology. Therefore, the author hopes to find the etiology of diabetes from the source, put forward the concept of circadian rhythm - autonomic nervous system - endocrine hormone axis, provide a theoretical basis for the prevention and etiological treatment of diabetes, and hope to develop corresponding drugs for the benefit of the majority of diabetic patients.

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Conflict of Interest

No conflict of interest.

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