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CIRCADIAN RHYTHM OF CARBOHYDRATE METABOLISM IN HEALTH AND DISEASE

Sorokin M.Yu. [1],
Pinkhasov B.B. [1, 2],
Selyatitskaya V.G. [1]

[1] Federal Research Center for Fundamental and Translational Medicine (Timakova str. 2, Novosibirsk 630060, Russian Federation)
[2] Novosibirsk State Medical University (Krasny Ave. 52, Novosibirsk 630091, Russian Federation)

Corresponding author:
Maxim Yu. Sorokin,
e-mail: biokvant@bk.ru

ABSTRACT

The article presents a review of the main circadian mechanisms regulating carbohydrate metabolism and their role in maintenance of energy homeostasis; the molecular genetic structure of the circadian system is also discussed. The role of adipose tissue and other organs and systems in the maintenance of circadian rhythm of carbohydrate metabolism, both in health and in obesity and diabetes, is highlighted. Particular attention is paid to diurnal rhythms of endocrine factors responsible for metabolic patterns of hormones such as cortisol, growth hormone and melatonin. Gender differences in the circadian regulation of energy and carbohydrate metabolism are also discussed, as well as their changes in different age periods. Article provides detailed review of the mechanisms of glucose utilization, reactivity of the pancreatic islets and peripheral insulin sensitivity shifts at different time periods of the day in people with normal body weight, android and gynoid types of obesity, both in women and men. Protective factors of energy metabolism circadian regulation structure preventing the development of diabetes mellitus and cardiovascular disease in individuals with so-called "metabolically healthy" obesity type are discussed. Article provides a review of various pathways of circadian rhythm disturbances, mechanisms of their development, as well as exogenous and endogenous factors leading to carbohydrate metabolic circadian rhythm misalignment, such as shift work, untiming of natural and artificial lighting, jet lags, sleep disorders. Represented data contribute to a new look at the pathogenesis of obesity and carbohydrate metabolism disorders in various types of obesity in men and women, that provides basis for searching for new effective methods of prevention and treatment of these conditions, elaboration of evidence-based diets and physical activity recommendations, as well as approaches to their medical treatment.

Key words: *carbohydrate metabolism, circadian rhythms, insulin, glucose, diabetes mellitus, obesity, adipose tissue*

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ЦИРКАДНЫЙ РИТМ УГЛЕВОДНОГО ОБМЕНА В НОРМЕ И ПРИ ПАТОЛОГИИ

Сорокин М.Ю. [1],
Пинхасов Б.Б. [1, 2],
Селятицкая В.Г. [1]

[1] ФГБНУ «Федеральный исследовательский центр фундаментальной и трансляционной медицины» (630060, г. Новосибирск, ул. Тимакова, 2, Россия)
[2] ФГБОУ ВО «Новосибирский государственный медицинский университет» Минздрава России (630091, г. Новосибирск, Красный просп., 52, Россия)

Автор, ответственный за переписку:
Сорокин Максим Юрьевич,
e-mail: biokvant@bk.ru

РЕЗЮМЕ

В статье представлен обзор сведений об основных механизмах циркадной регуляции углеводного обмена, а также её роли в поддержании энергетического гомеостаза, рассмотрена молекулярно-генетическая структура циркадной системы. Освещена роль жировой ткани и других органов и систем в циркадном ритме углеводного обмена, как в норме, так и при ожирении и сахарном диабете 2-го типа. Особое внимание уделено суточной ритмике эндокринных факторов, определяющих метаболические паттерны таких гормонов, как кортизол, соматотропный гормон, мелатонин. В статье отдельно обсуждаются гендерные различия циркадной регуляции энергетического и углеводного метаболизма, а также их изменения в различные возрастные периоды. Проведён подробный обзор механизмов изменения утилизации глюкозы, реактивности инсулярного аппарата поджелудочной железы и чувствительности периферических тканей к инсулину в разное время суток у лиц с нормальной массой тела, андроидным и гиноидным типами ожирения, как у женщин, так и у мужчин. Обсуждены защитные факторы в структуре циркадной регуляции энергетического метаболизма, препятствующие развитию сахарного диабета и сердечно-сосудистых заболеваний у лиц с так называемым «метаболически здоровым» типом ожирения. Рассмотрены различные варианты нарушений циркадных ритмов, механизмы их возникновения, а также экзогенные и эндогенные факторы, приводящие к нарушениям циркадного ритма углеводного обмена, такие как сменная работа, нарушение естественного и искусственного освещения, смена часовых поясов, расстройства сна. Приведённые сведения способствуют формированию нового взгляда на патогенетические механизмы развития нарушений углеводного обмена при различных типах ожирения у мужчин и женщин, что даёт основания для поиска эффективных методов профилактики и лечения этих заболеваний, определения научно-обоснованных режимов питания и физических нагрузок, а также подходов к их медикаментозной терапии.

Ключевые слова: *углеводный обмен, циркадные ритмы, инсулин, глюкоза, сахарный диабет, ожирение, жировая ткань*

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INTRODUCTION

There is more and more information concerning the essential role of not only central but also peripheral oscillators acting in metabolically active organs in the regulation of glucose homeostasis to ensure circadian coordination of key metabolic processes. Integral work of central and peripheral oscillators allows the organism to predict the development of events related to the day-night cycle, including processes related to the periodization of sleep-wakefulness, hunger-satiety cycles of the organism. In this regard, obtaining new knowledge related to blood glucose homeostasis as a key energy substrate is one of the fundamental tasks for understanding the mechanisms of metabolism regulation in the human body in health, as well as for determining pathogenetic approaches to the treatment of such diseases as obesity, dyslipidemia, atherosclerosis, type 2 diabetes mellitus and others.

Circadian rhythms are periodically repeating patterns of physiologic processes every 24 hours. Cyclic processes occurring in the human body determine the equilibrium both within the organism and its equilibrium with the environment, which provides adaptation to the environmental conditions. Circadian rhythm is generated endogenously by a genetically encoded molecular clock with a periodicity of about a day [1].

Currently, more than 300 physiological functions and processes are known to have circadian rhythm, including: body temperature, motor performance, sensitivity of the organism to environmental factors; different levels of biologically active substances in body tissues and organs, as well as in biological fluids; intensity of metabolic processes, as well as providing cells, tissues and organs with energy and plastic resources [2, 3]. A circadian clock, influencing the expression of synthesis and hormone secretion involved in the metabolism regulation, contributes to the maintenance of body weight adequate to external conditions [4, 5].

One of the most striking examples of circadian rhythms are the stable circadian and ultradian rhythms of blood glucose level dynamics, which have developed in the course of evolutionary development under the influence of organism's peculiarities of functioning in the environment. Glucose homeostasis represents a model of energy metabolism circadian control, enhancing the efficiency of this substrate usage. So, while during activity, blood glucose is predominantly of dietary origin, during rest, glucose is gradually recruited from glycogen in the liver and maintains the required level in the blood within a relatively narrow range of concentrations [6]. During this process, liver glycogen content undergoes large daily fluctuations necessary to maintain blood glucose levels, as glycogen synthesis and breakdown change during periods of wakefulness/feeding and rest/starvation, respectively [7, 8].

The circadian model of carbohydrate metabolism neurohumoral regulation formed during phylo- and ontogenesis is highly reliable because it is a multilevel and self-regulating system [3]. This system regulating glucose homeostasis is represented by both a central biological clock located in the hypothalamus and a peripheral circadian clock in organs and tissues such as muscle, adipose tissue, liver, and pancreas.

Discordance in the circadian clock can lead to significant disorders in the endocrine glands rhythms, which play a leading role in the realization of most physiological functions. The resulting hormonal disorders affect a range of metabolic responses, and the effects on glucose and lipid homeostasis lead to the development of such disorders as metabolic syndrome, obesity and type 2 diabetes [4, 6]. Adipose tissue accumulation leads to changes in daily fluctuations in body temperature, heart rate, blood pressure, fasting glycemia. Further disorders of carbohydrate metabolism in the form of type 2 DM development contribute to the aggravation of metabolic disorders, which leads to even greater changes in the structure of circadian rhythms in the body [9].

CIRCADIAN CONTROL OF ENERGY METABOLISM

Endogenous circadian rhythms of metabolism are reproduced by a multi-oscillatory system consisting of a central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus, as well as the peripheral clocks represented in virtually all organs, tissues, and cells of the human body [10]. SCN functioning is triggered primarily by light signals via the retinohypothalamic tract. Further, through nerve and/or hormonal pathways, the SCN transmits temporal signals to other brain regions, particularly the epiphysis, as well as to peripheral organs such as the adrenal glands, muscles, adipose tissue, pancreas, liver, and gastrointestinal tract [10]. The central clock uses hormones such as cortisol, melatonin, STH, leptin, and synaptic projections, particularly the autonomic nervous system, as signals that regulate metabolism [11, 12].

Peripheral tissues, by integrating SCN signals with environmental factors and behavior (including nutrition, light, sleep, and physical activity), as well as with their own autonomous rhythms, maintain the circadian rhythm of the body's energy metabolism [13]. It has been shown in experimental models that (almost) all cells in the body express the molecular mechanism of the circadian clock, and the hunger-satiety cycle is one of the main synchronization timers for the peripheral clocks [14]. Thus, the rhythm of food intake largely controls the circadian expression of liver genes [15].

Molecular regulation of energy metabolism circadian rhythms is provided by a set of genes that trigger and maintain the clock mechanism of the organism as a whole. Autonomous intracellular rhythms are maintained at the molecular level by circadian genes and proteins that form a transcriptional-translational feedback loop (TTFL). The main negative transcriptional-translational feedback loop includes core clock genes such as *CLOCK, BMAL1* (also known as *ARNTL*), *PER* and *CRY* [16]. TTFL operates in a ~ 24-hour cycle, activating a rhythmic cascade of transcriptional and post-transcriptional events involving thousands of tar-

get genes [17]. In total, about 10 % of gene transcripts show circadian periodicity and, moreover, even more proteins undergo oscillations due to circadian rhythms at the post-transcriptional and post-translational levels [17]. Thus, circadian rhythms are generated endogenously in the body and persist for quite a long time even in the absence of external time cues [1]. Since different stimuli determine the rhythm of the central and peripheral clocks, both systems can be desynchronized whenever their respective timers are out of sync. In this regard, synchronization of photic (light) and non-photic (non-light) stimuli is necessary for the circadian system to work more accurately and coherently.

CIRCADIAN RHYTHMS OF CARBOHYDRATE METABOLISM IN NORMAL

The circadian rhythms of carbohydrate metabolism are fairly well studied in healthy individuals. Numerous studies have found diurnal variation in glucose tolerance with a maximum in the morning hours and reduced glucose tolerance in the evening [18–21]. The above diurnal variations are independent of the route of glucose entry into the body and are characteristic of both oral and intravenous glucose or insulin tolerance tests [22, 23] and mixed-feeding conditions [24]. Daily fluctuations in glucose tolerance are largely determined by the diurnal rhythm of β-cell reactivity, insulin secretion and its clearance. It has been shown that β-cell reactivity is higher in the morning than at other times of the day [18, 22], while secretion rate and insulin levels in response to glucose or food intake are most significant in the afternoon and evening [25]. Insulin clearance also varies by day: its extraction by the liver has been shown to be lower in the morning, relative to the evening [25].

The diurnal rhythm of carbohydrate metabolism is also determined by the peripheral sensitivity of tissues to insulin, primarily muscle [26, 27], liver [28], and adipose [24, 29]. Regarding the latter, only subcutaneous adipose tissue has been shown to undergo a circadian rhythm of insulin sensitivity with the highest amplitude of insulin sensitivity, 54 % higher at midday relative to midnight [29]. The results of our own studies with the oral glucose tolerance test (OGTT) at different times of the day indicate that in both men and women with normal body weight, evening time is characterized by a physiological increase in insulin resistance, manifested by a decrease in the rate of glucose utilization compared to the morning hours. Gender features of the carbohydrate metabolism circadian rhythm consisted in lower glucose tolerance in the morning in men relative to women. The explanation for this may be the preferential accumulation of visceral adipose tissue in men compared to the proportion of subcutaneous adipose tissue, as determined by the ratio of waist circumference to hip circumference [30]. It is visceral adipose tissue that largely determines the level of free fatty acids (FFAs) in the blood. The predominant alternate use of carbohydrates and fats in energy metabolism is confirmed by the fact that FFA levels are also subject to diurnal fluctuations and are consistent with the diurnal rhythms of glucose homeostasis [18, 24].

As mentioned above, effective regulation of carbohydrate-fat metabolism is supported by a number of counterinsulatory hormones, such as somatotropic hormone, the level of which is in a pronounced relationship with glycemic levels during nighttime sleep (10:00 PM – 2:00 AM) [31]. Cortisol is also responsible for circadian fluctuations in glycemia and insulinemia. Hydrocortisone infusion is known to dramatically suppress insulin secretion and increase peripheral insulin resistance in about 4–6 hours, and maintains these effects up to 12–16 hours after administration [32]. The effects of melatonin are also reflected in the circadian balance of regulators in the form of increased secretion of counterinsulatory hormones, predetermining increased insulin resistance and glucose tolerance in the evening and at night [33]. Conversely, increased daytime insulin sensitivity and increased pancreatic glucose sensitivity coincide with an anabolic orientation of energy metabolism. It has also been suggested that melatonin may directly affect the expression of clock genes [34]. For example, one of the melatonin effects is not only the regulation of the expression of circadian genes of the transcription-translation feedback loop in cells of the central nervous system and β-cells of the pancreas, but also an increase in their sensitivity to the action of Glucagon-like peptide-1 (GLP-1), which in turn stimulates insulin secretion [35].

Analyzing the changes in glucose tolerance and insulin sensitivity in the circadian rhythm, it can be assumed that the physiological significance of the phenomenon of insulin resistance lies in the activation of lipid oxidation in peripheral tissues in the evening and night hours, which is necessary for the functioning of muscle and fat cells and is also aimed at reducing lipotoxicity [36]. Thus, the increase in lipid utilization and the switch of energy metabolism to fat oxidation in the evening is the presumed cause of hyperglycemia and determines the daily rhythm of glucose levels. The biological meaning of switching to fat metabolism in the late phase of the circadian cycle lies in the expediency of restoring the structure, reserves and cell function of peripheral tissues, as well as in getting rid of unspent excess fat stores to avoid fat degeneration and lipotoxicosis. The oxidation products accumulated during the day inhibit glycolysis and the delivery of glucose into the cells. Perhaps one of the key roles in this process is played by leptin, the secretion of which is characterized by a cosine curve with a peak in the middle of the night [37]. It is known that leptin is able to induce in somatic cells the synthesis of enzymes involved in the non-oxidative metabolism of FFAs. In turn, leptin deficiency or developing resistance to it leads to a switch of FFA metabolism to the pathway of synthesis of long-chain fatty acids and their esterification into triglycerides. The resulting increased lipid content in peripheral tissues can lead to adipose degeneration, lipotoxicosis, and cellular apoptosis [38]. We believe that it is this protective function of leptin against excessive

fat accumulation that defines its basic biological meaning. Based on the above, it can be assumed that it is leptin that plays a key role in regulating the switch from carbohydrate to fat metabolism during the transition from light to dark time. Thus, the accumulation of adipose tissue and insulin resistance are elements of the system of energy metabolism regulation, formed in the course of evolution and contributing to the survival and reproduction of offspring in extreme conditions.

FACTORS LEADING TO DISORDERS OF CIRCADIAN RHYTHM OF CARBOHYDRATE METABOLISM

Shiftwork

There is increasing evidence that shifts in circadian rhythms caused by an inappropriate combination of key external factors, such as shift work, exposure to bright light at night, sleeping during the day, disordered eating, low motor performance during the day, lead to metabolic disorders and the formation of pathological conditions in the form of increased levels of glucose, insulin, triglycerides, the development of obesity and type 2 diabetes mellitus (DM), and accelerated aging [39–41].

A meta-analysis of observational studies showed that people who work shifts have a 9 % increased risk of developing type 2 DM compared with those without a history of shift work [42]. In a longitudinal study using cohorts of nurses, this risk also depended on the length of shift work, increasing by 5 % for every 5 years of shift work [43]. It has also been shown that workers with rotation shifts were even more likely to develop type 2 DM than workers with a fixed night schedule [42].

Natural and artificial light disturbance and change of time zones

Another risk factor for circadian rhythm disorder is irregularities in lighting, both natural and artificial. Epidemiologic evidence suggests that exposure to bright light in the evening or at night increases the risk of metabolic disease. In a cross-sectional study of more than 100,000 women, bright room lighting during sleep was strongly associated with higher BMI, waist circumference, and waist to hip circumference ratio [44]. In addition, in a prospective cohort study, older adults exposed to light at night (≥ 3 lux) demonstrated a 10 % increase in body mass index (BMI) over 10 years [45]. In another study, increased exposure to light in the evening (18–38 lux) was associated with a 51 % increased risk of developing type 2 DM [46], while a phase delay of every hour in light above 500 lux was associated with a 1.3 kg/m^2 increase in BMI [47]. In a cohort study involving 43,722 women, artificial light at night during sleep significantly influenced the risk of weight gain and the development of obesity, especially in women who had a light or TV on in the room during sleep [48]. Insolation disorder is associated with impaired melatonin production. Exposure to bright light during the daytime has been shown to increase melatonin secretion at night [49]; therefore, lack of bright light during the daytime may weaken the central clock rhythm and, hence, lead to metabolic disorders. In contrast, evening or nighttime exposure to bright light suppresses melatonin production, resulting in significant changes in hormonal balance [12]. Decreased melatonin levels can lead to the development of food addiction, manifested by increased appetite, episodes of compulsive eating behavior, and elements of night eating syndrome. In modern society, the influence of social factors on the timing of meals and the maintenance of circadian rhythms of sleep and wakefulness is great. Clear examples include nighttime eating with shift work schedules and postponing meals when time zones change. An increase in caloric intake in the evening and night hours is often accompanied by an increase in total daily caloric intake, as well as a shift in preference toward foods rich in rapidly digestible carbohydrates. For example, one study showed a prevalence of refined carbohydrates and high-calorie meals in the diet of individuals working the night shift [39]. Another study (n = 98) showed decreased levels of melatonin and serotonin and an inverse relationship of their levels with all types of eating disorders in individuals with metabolic syndrome [50]. The results of another study including 100 patients with metabolic syndrome demonstrated a shift in the nocturnal peak of melatonin without a confirmed decrease in its levels [51].

Another common type of circadian rhythm disorders is jet lag, quantified as a discrepancy between sleep and wakefulness times on weekdays and weekends with discrepancies in social and biological time [52]. It has been found that people experiencing jet lag (approximately 69 % of the population [52]) have a 1.75-fold higher incidence of type 2 DM and prediabetes compared to individuals who do not change time zones [53]. Moreover, individuals with an evening chronotype were at a 2–2.5-fold higher risk of developing type 2 DM compared to those with a morning chronotype [54].

Sleep disorders

Another of the mechanisms explaining metabolic changes in circadian misalignment are sleep disorders. According to a number of studies, excess body fat is associated with a number of circadian sleep rhythm disorders [55]. It has been shown that episodes of late falling asleep can lead to circadian misalignment and exacerbate insulin resistance [56]. Phase shifts in sleep timing, even when sleep duration is kept constant, also cause circadian shifts leading to metabolic dysfunction. Sleep deprivation worsens glycemic outcomes in patients with and without DM [57]. Not only shorter (< 6 h) but also longer (> 9 h) sleep duration has been shown to be unfavorably associated with insulin resistance. Although the association between insufficient sleep and DM is more or less understood, little is known about how excessive time spent sleeping or hypersomnia (10–12 hours) increases the risk of developing diabetes [58]. The link between sleep disturbances and diabetes is two-way: chronic sleep dis-

turbances increase the risk of developing insulin resistance, and diabetes worsens sleep quality. When the diurnal rhythm of going to sleep is shifted, melatonin peak shifts to the beginning of awakening, the total duration of sleep decreases, and due to insulin resistance in the morning hours, there is an increase in postprandial glycemia at lunchtime. This is because the circadian system influences phase I insulin secretion through the SCN and melatonin receptors (MT1 and MT2). Consequently, the increase in fasting and postprandial hyperglycemia on the background of circadian misalignment is mainly due to the increase in insulin resistance, rather than due to a decrease in β-cell function [59].

Diet violation

An important factor that meaningfully affects circadian rhythm is food intake. There is now no doubt that meal timing plays one of the key roles in maintaining daily homeostasis of glycemic levels [60]. Several studies have reported that delaying the meal phase has adverse metabolic consequences, even when food intake is limited to daytime hours. Changing lunch time from 01:00 PM to 04:30 PM increased glucose increment by 46 %, and decreased carbohydrate oxidation in the fasting state [61]. Late dinner induces nocturnal glucose intolerance and reduces fatty acid oxidation and mobilization, especially in those who fall asleep early [62]. Another study showed that an abrupt shift in dinner time from 07:00 PM to 10:30 PM increased post-breakfast glucose levels the next morning by 7–8 % and increased 24-h glucose levels by 4 mg/dL, although it had no effect on 24-h energy expenditure [63]. A nighttime meal, even if it consists of low glycemic index foods, is associated with a more significant increase in glycemia and insulinemia compared with an equivalent meal in the morning hours [61].

In a randomized cross-over study, it was shown that late dinner time led to increased nighttime melatonin concentrations and decreased glucose tolerance in *MTNR1B* melatonin receptor gene carriers [64]. The melatonin role in this process is supported by the observation that significant impairment of glucose tolerance at late dinner was observed only in carriers of the rs10830963 SNP allele variant of the *MTNR1B* gene of the melatonin receptor [64], associated with a high risk of developing type 2 DM [65]. This conclusion is further supported by placebo-controlled trials demonstrating that administration of exogenous melatonin in the morning and evening reduces glucose tolerance [66], and that this effect is six times more pronounced in carriers of the rs10830963 SNP allele of the *MTNR1B* gene than in non-carriers [64, 67].

Improper timing of meals can negatively affect the course of type 2 DM. Patients with type 2 DM who consumed more than 25 % of their daily energy in the evening hours had worse glycemic control, higher levels of glycosylated hemoglobin, and more complications of diabetes [68]. Late meal timing may impair glucose tolerance for a number of reasons: (1) eating during an unfavorable circadian phase; (2) eating concurrently with increased melatonin concentrations; and (3) late meal timing causes internal misalignment (main working hypothesis). According to the latter hypothesis, misalignment of food intake may lead to dissociation of central and peripheral clocks in metabolically active tissues [69], which has been confirmed experimentally [70]. However, to date, there is no direct evidence that internal desynchrony per se negatively affects glucose control [71], suggesting that the first two mechanisms may also be important. Anyway, late meal time can be considered as a risk factor for carbohydrate metabolism disorders [10]. These data may serve as a basis for recommending that patients with carbohydrate metabolism disorders eat earlier in the day and refrain from eating later in the day.

Changing the distribution of calories between meals (even if meal times have not changed) also affects metabolic risk factors. According to various authors, increased consumption of caloric food at lunchtime and evening contributes to the accumulation of visceral adipose tissue, the development of liver steatosis, abdominal obesity and disorders of carbohydrate metabolism [71]. G.K.W. Leung et al. suggested that daily glycemia fluctuations also depend on the distribution of consumed carbohydrates with different glycemic index during the day. Indeed, diurnal fluctuations in blood glucose concentrations were maximized when a higher carbohydrate meal followed a lower carbohydrate meal [71]. This fact is important to take into account in the training and organization of nutrition of persons with carbohydrate metabolism disorders.

Thus, the most significant risk factors for the development of carbohydrate metabolism disorders associated with circadian dysfunction include irrational distribution of caloric intake during the day, late breakfast and dinner, shift in bedtime, shortened sleep duration, exposure to artificial light in the evening, as well as too short and long intervals between meals.

CIRCADIAN RHYTHMS OF CARBOHYDRATE METABOLISM IN PATHOLOGY

Obesity

Most studies that have focused on carbohydrate metabolism rhythms have not considered obesity types and gender differences [5, 9]. At the same time, these factors are among the key determinants that determine the pathogenesis of metabolic syndrome and carbohydrate metabolism disorders. It is well known that when it comes to obesity, it is largely gender that determines the regional distribution of adipose tissue, in turn influencing cardiometabolic risk factors [72].

The accumulation and distribution of adipose tissue in different depots differs significantly between men and women, which is reflected in the development timing of metabolic and associated disorders. A comparative analysis of gender differences in fat accumulation in ontogenesis has allowed us to establish that in all age periods, subcutaneous distribution of fatty tissue predominates in wom-

en, while in men, in most cases, its accumulation in the abdominal region is greater [73, 74]. However, the dynamics of adipose tissue accumulation still has a dependence on age. In the case of overweight and obesity at a younger age, for example, the gynoid type dominates in males. In older age groups (by the end of the first period of adulthood) in males, active accumulation of fat in the abdominal region leads to an equal incidence of gynoid and android types of obesity, after which the android type of obesity begins to predominate [73].

In women, the gynoid type predominates in the presence of overweight and obesity until the end of the second period of adulthood, and thereafter, as age increases (including in old age), there is an increase in the occurrence of the android type of obesity [74]. What is interesting is that the age at which the android type of obesity begins to predominate occurs about two decades later in women than in men. This largely determines the fact that obese men are characterized by an earlier onset of carbohydrate metabolism disorders and cardiovascular diseases, while in women these disorders begin to occur much more frequently at the end of the reproductive period. This ultimately has an overall impact on longer life expectancy in women [73].

Recently, more and more attention has been paid to the study of so-called "metabolically healthy obesity", in which individuals with a characteristic phenotype lack metabolic abnormalities [75, 76]. The properties of "metabolically healthy" were found to be more characteristic of gynoid obesity with a high ratio of subcutaneous to abdominal fat. These individuals with a lower type of fat distribution are less characterized by hyperglycemia, hypoadiponectinemia, and insulin resistance, which are precursors to the development of diabetes mellitus and cardiovascular disease [21].

Women with different types of obesity were found to have different diurnal rhythms of glycemia and insulinemia. For example, women with gynoid type of obesity are more characterized by functional hyperinsulinemia provoking postprandial hypoglycemia. The latter, as we have shown earlier, occurs due to increased glucose utilization in peripheral tissues, which suggests that in this phenotype glucose is the main source of energy and substrate of lipogenesis in adipose tissue during light and dark hours of the day [21].

In women with android type obesity, the pattern of the glycemic curve during OGTT is similar to that of women with normal body weight, both in the morning and in the evening. However, comparable glucose levels in this type of obesity are achieved at the cost of significant postprandial hyperinsulinemia. During OGTT, android-type obese women had 4-fold higher levels of immunoreactive insulin (IRI) at the 60th minute of the test in the morning compared with normal-weight women, and 2-fold higher levels in the evening. This significant difference is the result of insulin resistance due to the high metabolic activity of visceral adipose tissue. An interesting fact is that in the group of women with android type of obesity, a more pronounced increase in blood glucose levels at the 60th minute of the test in the evening occurred in the setting of lower insulin levels than when a similar OGTT was performed in the morning. Apparently, this phenomenon is indicative of the developing functional exhaustion of the insular apparatus in the afternoon [77], which is a precursor to type 2 DM.

Thus, in both types of obesity there are disorders in the diurnal rhythms of carbohydrate metabolism, but they are mediated by different mechanisms. In gynoid obesity carbohydrate load provokes hyperinsulinemia and hypoglycemia, and in android obesity – insulin resistance, hyperglycemia and compensatory hyperinsulinemia, which determines the peculiarities of the pathogenesis of the obesity different types and carbohydrate metabolism disorders development.

Type 2 diabetes mellitus

A large number of studies have found that the rhythms of glucose tolerance, insulin levels, and insulin sensitivity characteristic of healthy individuals may be impaired, inverted, or absent in individuals with type 2 DM [23, 29]; these patterns may also change in older age [25]. Studies with hyperglycemic clamp in individuals with type 2 DM have demonstrated an inverted glucose tolerance profile, with glucose tolerance improving throughout the day while awake [25].

In a study with 24-hour glucose infusion to adult patients with type 2 DM and obese non-diabetic individuals with comparable BMI, glucose levels were found to be highest in the morning and lowest in the evening [78]. Moreover, the amplitude of glycemic fluctuations was approximately 2-fold higher in individuals with type 2 DM compared with those with obesity. While increased glycemia at night correlated with increased cortisol levels, increased insulin secretion at night corresponded to increased glucose levels only in obese subjects but not in those with type 2 DM. In fact, no temporal rhythms of insulin secretion rate were detected in subjects with type 2 DM. These differences in the rhythms of glycemia and insulinemia fluctuations may be due in part to differences in the timing and amplitude of the cortisol rhythm in individuals with diabetes compared to healthy ones [28].

Two other studies of patients with type 2 DM have shown a lack of rhythmicity in muscle glycogen stores [25] and peripheral insulin sensitivity [79]. Nevertheless, adults with type 2 DM show distinct rhythms of hepatic glycogen accumulation and hepatic insulin sensitivity [78]. As a result, overall insulin sensitivity in individuals with type 2 DM reaches a maximum at about 7:00 PM. And a minimum in the morning. This rhythm of liver sensitivity to insulin may explain the well-known "dawn phenomenon" (fasting hyperglycemia). Increased endogenous glucose production during the night hours also contributes to the fasting/morning hyperglycemia observed in type 2 DM [79].

Thus, circadian rhythm disorders are also accompanied by carbohydrate metabolism disorders, playing a role in the pathogenesis of metabolic diseases. The present data demonstrate that shifts in circadian rhythms caused by untimely exposure to light, sleep, and meals impair glycemic

control and increase the risks of obesity and type 2 DM. Whether interventions that restore normal circadian rhythm can actually prevent or have a favorable effect on the course of metabolic diseases remains completely unclear.

Perhaps the differences between glucose metabolism in individuals with type 2 DM and without carbohydrate metabolism disorders may be related to impaired functioning of the central biological clock of the SCN in type 2 DM. In particular, the number of arginine-vasopressin-immunoreactive neurons (AVIN), VIP neurons (VIPN) and glial fibrillary acidic protein immunoreactive (GFAP-ir) astroglial cells are significantly reduced in the SCN among type 2 DM patients compared to healthy individuals [80].

CONCLUSION

Thus, circadian rhythms of carbohydrate metabolism are determined by diurnal variations in a large number of metabolic processes, including β-cell sensitivity, peripheral insulin sensitivity, insulin clearance, and the amount of fat and its ratio in various depots. Circadian rhythms of carbohydrate metabolism were formed in phylogenesis under the influence of natural factors of the human environment, which determine physiological needs and functional energy expenditure necessary for the realization of life activity processes. The circadian rhythm of carbohydrate metabolism, first of all, predetermines the phasicity of glucose usage as an energy substrate. So, in the morning and afternoon, its usage is determined by: light, awakening, hunger, hormonal regulators (cortisol, insulin), motor performance, food intake and other regulatory factors. In the evening and at night, physiologic insulin resistance promotes a switch to fat metabolism to rid somatic cells of excess lipids and prevent lipotoxicity.

In current conditions, when a person is characterized by hypodynamia; excessive and extended practically for the whole time of day consumption of nutrients, and, above all, refined carbohydrates; light stress; psychoemotional stress associated with the release of glucocorticoids, both central and molecular mechanisms of circadian rhythms maintenance are disturbed, which, in turn, increases the negative impact of exogenous factors on human metabolism parameters, forming a vicious circle of the pathological process risk factor formation. In this regard, the question arises, what is primary: disorders of circadian rhythms, which contribute to the development of metabolic pathology, or they are secondary and only strengthen the metabolic disorders formed under the influence of exogenous factors? The answer to this question will largely help to find pathogenetic approaches to dietary and drug correction of carbohydrate metabolism in the treatment of diseases and conditions such as obesity, DM, dyslipidemia, atherosclerosis and other endocrine-exchange disorders.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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Information about the authors

Maxim Y. Sorokin – Postgraduate at the Laboratory of Endocrinology, Federal Research Center for Fundamental and Translational Medicine, e-mail: biokvant@bk.ru, https://orcid.org/0000-0003-2384-3759

Boris B. Pinkhasov – Dr. Sc. (Med.), Head of the Department of Pathological Physiology and Clinical Pathophysiology, Novosibirsk State Medical University; Leading Research Officer at the Laboratory of Endocrinology, Federal Research Center for Fundamental and Translational Medicine, e-mail: pin@centercem.ru, https://orcid.org/0000-0002-4579-425X

Vera G. Selyatitskaya – Dr. Sc. (Biol.), Professor, Chief Research Officer, Head of the Laboratory of Endocrinology, Federal Research Center for Fundamental and Translational Medicine, e-mail: ccem@centercem.ru, https://orcid.org/0000-0003-4534-7289