REVIEW

The role of chronobiology and circadian rhythms in type 2 diabetes mellitus: implications for management of diabetes

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Abstract: Circadian clocks regulate cellular to organic and individual behavior levels of all organisms. Almost all cells in animals have self-sustained clocks entrained by environmental signals. Recent progress in genetic research has included identification of clock genes whose disruption causes metabolic abnormalities such as diabetes, obesity, and hyperlipidemia. Here we review recent advances in research on circadian disruption, shift work, altered eating behaviors, and disrupted sleep-wake cycles, with reference to management of type 2 diabetes.

Keywords: diabetes, clock gene, shift work, eating behavior, sleep loss

Introduction

Circadian rhythms of physiological functions have been shown to be regulated by endogenous molecular oscillators called circadian clocks. The master circadian clock resides in the suprachiasmatic nucleus (SCN) as a central regulator of the peripheral clock system, and is entrained directly by light.[1,2] Circadian clocks in peripheral cells are regulated by SCN via body temperature, humoral signals, and feeding in addition to light. The main mechanism of the molecular clock is composed of transcriptionally and translationally regulated feedback loop systems. Transcriptional activation by brain and muscle Arnt-like protein (BMAL1) and circadian locomotor output cycles kaput (CLOCK) up-regulate negative elements of Period (Per1, Per2, and Per3) and cryptochrome (Cry1 and Cry2) genes. Accumulation of Per and Cry proteins inhibit BMAL1/CLOCK activity (Figure 1). The expression cycle of clock genes forms an approximate 24-hour cycle. The second feedback loop involves the retinoic acid-related orphan receptor (ROR) (α, β, and γ) and REV-ERB (an orphan receptor encoded on the noncoding strand of the thyroid alpha gene) (α and β) proteins, members of a subfamily of nuclear receptor that recognizes cis-regulatory elements (ROREs) of target genes. RORs act as transcriptional activators and REV-ERBs are repressors. The BMAL1/CLOCK binds to E-box elements present in *Ror* and *Rev-erb* genes and activates their transcription.[3] RORs and REV-ERBs in turn control rhythmic transcription of the BMAL1 gene.[4,5]

Recent progress in basic research on circadian rhythms and metabolism has yielded discoveries of O-linked beta-D-N-acetylglucosamine (O-GlcNAc) signaling,[6] nicotinamide adenine dinucleotide (NAD+)-dependent sensors,[7,8] nicotinamide phosphoribosyltransferase (NAMPT),[9,10] silent mating type information regulation 2 homolog 1 (SIRT1),[11,12] peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α),[13] and 5′-adenosine monophosphate-activated protein kinase

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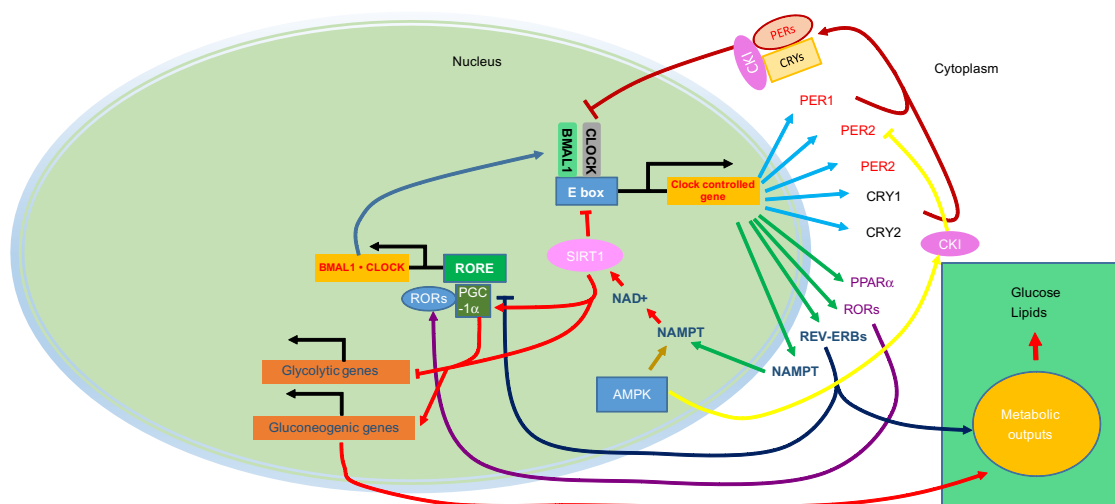Email kurose.takeshi@b4.kepco.co.jp

Figure 1 The mammalian core components of the clock system.
Notes: The circadian clock consists of transcription/translation feedback loops. The positive regulatory components are transcription factors CLOCK and BMAL1, which heterodimerize and bind to the E Box of clock target genes and activate downstream genes. These target genes are the period (Per 1, 2, and 3), cryptochrome (CRY1 and 2), REV-ERB, RORs, and other clock controlled genes.
Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; NAD+, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; CKI, casein kinase I; PPARα, peroxisome proliferator-activated receptor alpha; CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle Arnt-like protein; PGC1-α, peroxisome proliferator-activated receptor gamma co-activator 1-alpha.

(AMPK)[14] as key regulators in circadian systems that link the clock system and metabolism. Due to the large gap between basic and clinical research in this field, fundamental approaches from both directions are appropriate. In this review we discuss management of type 2 diabetes in terms of recent research in chronobiology.

Interaction between peripheral clock function and energy metabolism

The master central clock in the SCN is primarily entrained by light, and synchronizes peripheral clock components through neural and humoral mechanisms that are still obscure. With regard to glucose metabolism, several metabolic inputs from nutrient sensors operate as molecular clocks in peripheral tissues.

One example is the NAD+-dependent deacetylase SIRT1, an energy sensor with activity dependent on the intracellular NAD+/NADH ratio. Recently, SIRT1 has been thought to be a key regulator of the core clock machinery, since it binds to and inhibits the activity of CLOCK/BMAL1.[11,12] In addition, SIRT1 is known to play a key role in the regulation of gluconeogenesis, fat metabolism, insulin secretion, and apoptosis through its role in energy generation.[15,16] Nutrient-dependent regulation of SIRT1 and clock interaction thus regulates many metabolic targets including PGC-1α, peroxisome proliferator-activated receptor alpha (PPARα) and others.[17,8] AMPK is another cellular nutrient sensor linked

to the clock. AMPK is a stress kinase responding to depleted energy states, which is activated when the AMP-to-ATP ratio increases, causing increased ATP production and decreased ATP utilization.[18] Exercise also activates AMPK, to restore the energy used. Activation of AMPK by metformin induces PER2 degradation, through casein kinase I epsilon (CKIε), and a phase advance of clock gene expression.[14] In addition, Lamia et al has identified a consensus motif for phosphorylation by AMPK within CRY protein. Thus, AMPK destabilizes the core clock repressor CRY1.[19]

Metabolic transcription factors and transcriptional co-activators comprise feedback loops between the core clock and the peripheral tissues. For example, nuclear hormone receptors are ligand-activated transcription factors that regulate gene expression by interacting with specific DNA sequences upstream of their target genes, including REV-ERBα, RORs, and PPARs, which demonstrate circadian expression in peripheral tissues.[20] REV-ERBα regulates gluconeogenesis in hepatocytes, differentiation in adipocytes, and lipid metabolism and also represses BMAL1 transcription.[21,22] In addition, both RORα and PPARα regulate BMAL1 expression by regulating genes that control lipid metabolism.[23,24] REV-ERBs and RORs are highly related nuclear receptors, and are often expressed in common tissues such as the liver, adipose tissue, skeletal muscle, and the vasculature.[22] REV-ERBs have long been considered as true orphan receptors, but heme was identified recently as the ligand for both REV-ERBα and β.[21,25] The synthesis

of heme is linked to nutritional status through the regulation of delta-aminolevulinate synthase 1 (ALAS1) by the nuclear receptor co-activator PGC-1α.[26] This co-activator is induced by fasting and mediates the transition from glucose to fatty acid use as an energy source and has been shown to integrate the mammalian clock and energy metabolism.[13] As REV-ERBα is involved in the induction of adipogenesis, the known induction of adipocyte differentiation by heme[27] may also be mediated by this REV-ERBα.

Whether the nutrient itself regulates or otherwise affects circadian function is the important issue. There are many candidate nutrient signals entraining cues for peripheral clocks. Among these, glucose is considered to be a particularly potent cue for the clock system. Although the molecular mechanism of the entrainment of the clock system by glucose has been a difficult question, some clues to the answer have been found recently. Li et al[6] reported that glucose availability regulates cellular clock oscillation through the hexosamine/O-GlcNAc pathway. In addition, a possible link between fatty acid and circadian function has been postulated. Perturbation of metabolic homeostasis with a high-fat diet can also change the period of locomotor activity rhythm and induce alterations in the expression and cycling of circadian clock genes.[28]

Glucose metabolism and circadian rhythm

In addition to the major feeding inputs, there are 24-hour highly rhythmic changes in blood glucose levels induced by changes in insulin sensitivity and insulin secretory patterns.[29] In animal models, insulin release is rhythmically regulated by peripheral pancreatic β-cell clocks, even in isolated perifused condition.[30] The 24-hour pulsatile insulin secretion is observed in humans, and has been found to be set at a higher level in obese subjects and in type 2 diabetes patients and their first degree relatives without diabetes.[29,31] In recent experimental animal studies, global clock mutant mice (ClockΔ19) developed age-dependent hyperglycemia and obesity, but showed an inappropriately low concentration of insulin with enhanced insulin sensitivity.[32] Double Cry1 and Cry2 knockout mice also showed impaired insulin secretion, although their body weight was somewhat less than in control mice, and increased sympathetic tone was observed.[33] Recently, hyperglycemia induced by ablation of double *Cry* gene expression was shown to be mediated, at least in part, by hepatic gluconeogenesis due to hepatic over-expression of Cry by lowering blood glucose levels and improving insulin sensitivity in insulin resistant db/db mice.[34]

Furthermore, islet specific BMAL1 mutant mice showed normal weight, normal activity, and normal feeding, but significant hyperglycemia with impaired secretion of insulin due to impairment of exocytosis.[35] In addition, in diabetes-prone rats, disruption of circadian rhythms accelerates development of diabetes through pancreatic β-cell loss and dysfunction.[36] Interestingly, a recent in vitro islet study using rat pancreatic islets showed that islets exposed to continuous light were disrupted in circadian clock function, and showed diminished glucose-stimulated insulin secretion due to a decrease in insulin secretory pulse mass.[37] Accordingly, disruption of circadian rhythm could induce abnormal insulin release in susceptible individuals.

Insulin sensitivity also shows circadian changes, and clock gene disruption induces a lack of rhythmicity in insulin action and activity patterns.[38] Using hyperinsulinemic-euglycemic clamp, the authors found circadian rhythmicity in insulin action, which was abolished in BMAL1-knockout mice. Most of the counter-regulatory hormones that exert an effect such as anti-insulin, including glucagon,[39] catecholamine,[40] and cortisol,[41] also show circadian rhythm. Growth hormone shows a sleep-related surge that induces early morning insulin resistance.[42] In addition to these mechanisms, autonomic neural regulation from the hypothalamic SCN exerts effects on the liver.[43] Thus, insulin sensitivity is under close regulation of circadian control and its impairment has deleterious effects on glucose metabolism.

Timing of food intake and metabolism

In animal studies, the timing of food intake has been shown to be an important regulator of circadian rhythm and metabolic regulation; there is a strong association of weight gain with circadian timing of food intake. Mice fed a high fat diet only during the 12-hour light phase (corresponding to night-time for humans) gained significantly more weight than mice fed only during the corresponding 12-hour dark phase.[44] In addition, in mice, consumption of high fat meals at the end of the active phase (corresponding to evening time for humans), leads to increased weight gain, adiposity, glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and hyperleptinemia. Thus, night eating syndrome may promote the risk of obesity and metabolic syndrome.[45] Wu et al also reported that the first daily meal determines the peripheral clock phase, whereas the last daily meal tightly couples to lipid metabolism, adipose tissue accumulation, and body weight gain.[46]
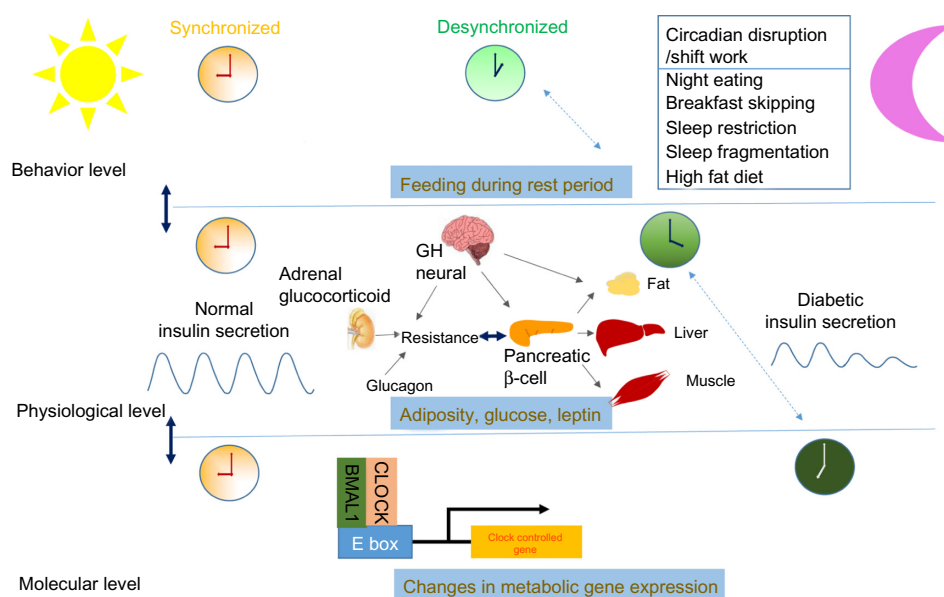
Figure 2 Behavioral factors that may affect the development of type 2 diabetes are influenced by shift work, eating behavior (breakfast skipping, night eating), and sleep loss (sleep restriction, sleep fragmentation).

Notes: These components affect circadian asynchrony. Accumulated evidence suggests that disruption of circadian synchronization between periods of rest and activity with feeding or fasting, and energy storage or energy utilization may be tightly linked to not only obesity, but also glucose metabolism, vascular reactivity, and lipid homeostasis. Reprinted from *Cell*, 134(5), Green CB, Takahashi JS, Bass J. The meter of metabolism. 728–742, Copyright © 2008, with permission from Elsevier.[75]

Abbreviations: GH, growth hormone; CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle Arnt-like protein.

Circadian rhythms and type 2 diabetes

The major issue regarding the role of the circadian clock in diabetes is whether disruption of CLOCK or BMAL1 directly leads to metabolic defects or whether the origin is indirectly related to clock function.[47,48] If disruption of the clock genes or clock mechanisms is directly involved in the development of diabetes, modern life-style itself has an increasingly pathological impact on the development of the disease. In addition to unusual patterns of sleep, unusual eating behavior such as skipping breakfast and night eating associated with shift work or other life-style disruptions of the day-night cycle may have a major pathological impact on the development of diabetes mellitus. In fact, two BMAL-1 haplotypes have recently been shown to be associated with type 2 diabetes and hypertension in a genetic association study.[49]

Shift work

In the manufacturing industry worldwide, 20%–25% of the employees are involved in shift work.[50] While there is no precise definition of shift work, most studies classify shift workers as those who regularly work outside the usual daytime shift hours.[47] Shift work is thought to be associated with several health problems, such as metabolic syndrome, diabetes mellitus, and cardiovascular disease that are possibly partly the result of impaired biological circadian rhythms.[50]

In an early cross-sectional Japanese male study, increased prevalence of diabetes mellitus was reported among shift workers (2.1% in shift workers and 0.9% in daytime workers) (Table 1).[51] In an 8-year cohort study with Japanese male industrial workers, rotating shift work was associated with a slightly higher risk of diabetes mellitus, but the effect did not reach statistical significance.[52] In addition, in a study of 2,860 Japanese male factory workers, the relative risk of diabetes mellitus for shift workers was 1.3~1.7, but these values also were not statistically significant.[53] While the early research on Japanese male subjects was inconclusive, in a study of female workers on rotating night-shift work, there was a significant association with type 2 diabetes mellitus in an age-adjusted model, although the authors state that the association was mediated by body weight.[54]

Furthermore, in a recent two-cohort study of female workers in the Nurse's Health Study, rotating night-shift work was associated with a modestly increased risk of type 2 diabetes mellitus.[55] In a prospective cohort study of middle-aged Swedish men and women with 8–10 years of follow-up, there was a positive association between shift work and type 2 diabetes mellitus in women (odds ratio [OR] 2.2 [95% confidence interval {CI} 1.0–4.7] adjusted for age, education, and psychological distress). This association also seems to be mediated by body mass index (BMI).[56] There was no association between shift work and type 2 diabetes in men

Table 1 Summary of the behavioral aspects of circadian rhythm in relation to development of type 2 diabetes mellitus

Authors	Year of publication	Methods	Main results	Ref no
Shift work				
Mikuni et al	1983	Japanese 9,000 males age-and weight-adjusted prevalence	Prevalence of diabetes 2.1% in all three shifts 0.9% in only day shifts	51
Kawakami et al	1999	Japanese 2,194 males 8-year prospective cohort study occurrence of NIDDM Diabetes criteria WHO	Age adjusted incidence per 1,000 person years Rotating shift 2.04 Day only 1.90	52
Morikawa et al	2005	Japanese 2,860 males 8-year prospective cohort study occurrence of diabetes HbA_{1c} 5.7%<	Diabetes incidence rate of 4.41/1,000 person years relative risk of diabetes mellitus two-shift 1.73. Three-shift 1.33	53
Kroenke et al	2007	62,574 US women 94% White 6-year prospective cohort study Nurses' Health Study II surveys ascertainment of type 2 diabetes	Duration of rotating shift Age adjusted relative risk 5–<10 years 1.59, 10 years 1.64 Multivariate-adjusted model 2 adjusted for BMI 5–<10 years 1.14, 10 years 0.98	54
Pan et al	2011	69,269 women aged 42–67 in Nurses' Health Study I (NHS I) 107,915 women aged 25–42 in NHS II 18–20 years cohort study	Pooled hazard ratios participants with >20 years of shift work 1.58 ($P<0.001$) adjusted for updated BMI participants with >20 years 1.24 ($P<0.001$)	55
Erikson et al	2013	3,205 women and 2,227 men aged 35–56 years 8–10 years population-based cohort study baseline normal OGTT	Odds ratio for shift work in women Age adjusted 2.3, multi-factor adjusted 1.9 Odds ratio for shift work in men Age adjusted 0.9, multi factor adjusted 0.8	56
Eating behavior				
Keski-Rahkonen	2003	Five birth cohorts of adolescent twins and their parents 16-year-old girls and boys (n=5,448) and their parents (n=4,660)	Adjusted odds ratios for BMI 25 or more Breakfast a few times a week: 1.41 Breakfast once a week or less often: 2.00	58
Cho et al	2003	NHANES III	Breakfast skippers and meat and egg eaters had higher BMI	59
Niemeir et al	2006	9,919 adolescents in Waves II (age 11–21) and III (age 18–27) of the National Longitudinal Study of Adolescent Health	Fewer days of breakfast consumption at Wave II and decreases in breakfast consumption between Waves II and III predicted increased BMI at Wave III	60
Odegaard et al	2013	3,598 participants from the community-based Coronary Artery Risk Development in Young Adults (CARDIA) study	Eating breakfast daily gained 1.9 kg less weight over 18 years ($P=0.001$) Hazard ratio for type 2 diabetes was 0.81 (0.63–1.05)	61
Morse et al	2012	714 tertiary care patients with type 1 and 2 diabetes	Patients with night eating behaviors were more likely to be obese (odds ratio 2.6) and to have two or more diabetes complications (odds ratio 2.6)	63
Sleep loss				
Vgontzas et al	2004	25 young, healthy, normal sleepers (12 men and 13 women), 1 week of sleep restriction (for only 2 hours)	24-hour secretion of IL-6 was increased by 0.8±0.3 pg/mL ($P<0.05$) in both sexes, TNF was increased only in men	70
Tasali et al	2008	Nine healthy volunteers (age 20–31 years; five men and four women). Experimental suppression of slow-wave sleep	Marked decreases in insulin sensitivity without adequate compensatory increase in insulin release with increased diabetes risk	71
Scheer et al	2009	Ten adults (5 female) underwent a 10-day laboratory protocol 12 hours out of phase from their habitual times	Decreased leptin (17%, $P<0.001$) Increased glucose (6%, $P<0.001$) Increased insulin (22%, $P=0.006$)	72

Note: The results are summarized in this table.
Abbreviations: NIDDM, non-insulin dependent diabetes mellitus; WHO, World Health Organization; OGTT, oral glucose tolerance test; NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; IL-6, interleukin 6; TNF, tumor necrosis factor; HbA_{1c}, glycated hemoglobin.

(OR 0.9 [95% CI 0.4–1.7] adjusted for age, education, and psychological distress). Therefore, shift work may contribute to the development of type 2 diabetes mellitus through obesity, especially in women, but the association may be mediated by obesity, as has also been suggested.[57]

Eating behaviors

Other problems of 24-hour contemporary life have been postulated and investigated, such as breakfast skipping and night eating. In a population-based study of adolescents and their parents, breakfast skipping was significantly associated with high BMI, not only in adolescents but also in their parents.[58] According to results from the Third National Health and Examination Survey (NHANES III) study with subjects 18 years or older, those who ate breakfast (especially those eating cooked cereal or quick bread) every day showed lower BMI compared to breakfast skippers.[59] In a prospective study of adolescents over a period of 5 years, breakfast skipping increased during the transition to adulthood, and was associated with increased weight gain.[60] Breakfast skipping is thus strongly associated with obesity. Recently, several reports have been published on the risk for type 2 diabetes related to breakfast skipping. In a cohort of 29,206 males in the Health Professionals Follow-Up Study followed for 16 years, breakfast omission was associated with an increased risk of type 2 diabetes mellitus in men even after adjustment for BMI. In addition, in over 18 years of cohort study with young adult men and women, frequent (4–6 days/week) or daily (7 days/week) breakfast consumption was significantly associated with a decreased risk of developing abdominal obesity, obesity, metabolic syndrome, hypertension, and also type 2 diabetes. Actually, in Black women, there was no significant association between breakfast frequency and incidence of type 2 diabetes, possibly because Black women have the highest rate of incidence of type 2 diabetes and the greatest mean level of BMI at baseline relative to the study population. The results are consistent and strongly inversely associated in Black men as well as in White men and women, even after adjustment for BMI.[61] Breakfast skipping is thus strongly associated with the incidence of type 2 diabetes mellitus. Other eating disorders such as night eating syndrome is also strongly associated with obesity, which strongly affects the clinical outcome of type 2 diabetes.[62] This disorder is also associated with morning anorexia and evening hyperphagia and insomnia. There is no clear definition of night eating syndrome, but patients who report eating >25% of their total daily food intake after regular suppertime (approximately after 9pm) may have night eating syndrome. Such night eating behavior is associated with obesity, higher glycated hemoglobin, and more diabetic complications.[63]

Sleep loss and diabetes

Sleep disorders (short duration and/or poor quality sleep) may have a profound impact on the development type 2 diabetes and obesity. There are many metabolic cues at the cellular level for clock machinery, but there is no direct evidence of the effects of disruption of the sleep-wake cycle itself on the clock system. However, since a disturbed sleep-wake cycle is often associated with a light phase shift, a changed or shifted light signal itself can regulate the master clock system. The magnitude of the effect of a phase shift or complete disruption of the sleep-wake cycle on human glucose metabolism is unclear. However, there is evidence of the deleterious effects of a shift change in sleep-wake cycles on glucose metabolism.

It has been shown in humans that the molecular clock is linked with sleep[64,65] in familial advanced sleep phase syndrome. This abnormal sleep syndrome is characterized by early sleep time and early-morning awakening.[66] In an animal study, wild-type mice prevented from sleeping during the first 6 hours of their normal inactive phase for 5 consecutive days (timed sleep restriction) showed significant transcriptional reprogramming of white adipose tissue, suggestive of increased lipogenesis, together with increased secretion of the adipokine leptin and increased food intake, hallmarks of obesity that are associated with leptin resistance. However, Per1/2 deficient mice showed blunted effects of this timed sleep restriction on food intake as well as on leptin levels and adipose transcription.[67] These experimental results suggest a causal relationship between sleep disturbances on clock function and metabolism. In addition, several epidemiological, observational studies indicate that chronic partial sleep loss can increase the risk of obesity and diabetes.[68,69] Laboratory studies in healthy volunteers have shown that experimental sleep restriction is associated with an adverse impact on glucose homeostasis. Insulin sensitivity decreases rapidly and markedly without adequate compensation in β cell function, resulting in an elevated risk of diabetes.[68–72] In a recent study on sleep restriction, only 2 hours restriction of sleep from 8 hours to 6 hours in young people was associated after 7 days with significant sleepiness, impairment of psychomotor performance, and increased secretion of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) which induce insulin resistance.[70] Although deep non-rapid eye movement sleep, also known as slow-wave sleep, is thought

to be the most restorative sleep stage, which coincides with hormonal changes that affect glucose regulation, there was a strong correlation between the magnitude of the reduction in short-wave sleep with the decrease in insulin sensitivity.[71] In addition to epidemiological and observational evidence, a recent experimental study of circadian misalignment in humans, which occurred when subjects ate and slept nearly 12 hours out of phase from their habitual times for a 10-day period, a protocol similar to shift work, showed systemically decreased leptin (−17%) and increased glucose (+6%) despite increased insulin (+22%). Furthermore, circadian misalignment caused three of eight subjects to exhibit postprandial glucose responses in the range typical of a prediabetic state.[72] As shown by forced manipulation of circadian rhythm, mimicking shift work or jet-lag caused impaired glucose tolerance in some but not all subjects, and hypoleptinemia in most patients. In addition, in a study of 4 hours sleep restriction for 4 days in healthy adults, the insulin concentration required to induce a half-maximal pAkt-tAkt response was nearly 3-fold higher during sleep restriction than during normal sleep, indicating that moderate sleep restriction can also induce an insulin-resistant state.[73] Recently, circadian typology, which consists of three chronotypes (morning-type [MT], neither-type [NT], evening-type [ET]), have been studied systematically.[74] About 40% of the adult population is classified in one of the two extreme groups, while 60% are NT. The chronotype is defined by biological markers such as sleep-wake cycle, body temperature, cortisol, and melatonin. These chronotypes should be considered for adjustment to shiftwork or jet-lag, as MT reported less sleep problems during day shift while ET reported more problems. This pattern was reversed during night work. Although these chronotypes may well have pathological impacts on type 2 diabetes development and metabolic diseases, more convincing evidence in future study is required to confirm their etiological significance.

Conclusion

As shown above, evidence that provides new insight into clock function and the pathophysiology of type 2 diabetes is accumulating rapidly. Disruption of circadian rhythms, such as that due to shift work, affects not only body weight and adiposity, but glucose metabolism itself. Since the magnitude of these effects in the present increase seen in the development of type 2 diabetes is obscure, more precise mechanisms and the relative importance of these factors in the development of type 2 diabetes should be investigated. To achieve this goal, it will be necessary to establish methodologies to measure parameters of circadian systems in feeding and glucose

and lipid metabolism.[75] In addition, it is also necessary to analyze the contribution of circadian gene variations in the development of type 2 diabetes. Clinical studies related to the development of type 2 diabetes are also needed to evaluate the health-compromising behaviors that affect circadian disruption with definitions that include chronotype or circadian typology.

According to the currently available data, diabetes patients should be warned about breakfast skipping and night eating syndrome in their diabetes education. Although it is very difficult to control these behaviors for every individual patient with type 2 diabetes, a socio-economical approach such as recommendations regarding the work environment may also be important. Although there is now insufficient evidence to evaluate the impact of these chronophysiological disruptions on the progression or pathophysiology of diabetes precisely, future focused research on these issues can answer these questions.

Disclosure

The authors have no conflicts of interest to declare.

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