REVIEW
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Circadian Etiology of Type 2 Diabetes Mellitus

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The epidemic of Type 2 diabetes mellitus necessitates development of novel therapeutic and preventative strategies to attenuate expansion of this debilitating disease. Evidence links the circadian system to various aspects of diabetes pathophysiology and treatment. The aim of this review will be to outline the rationale for therapeutic targeting of the circadian system in the treatment and prevention of Type 2 diabetes mellitus and consequent metabolic comorbidities.

Pathophysiology of Type 2 Diabetes Mellitus

The prevalence of Type 2 diabetes mellitus (T2DM) has reached epidemic proportions and is estimated to afflict over 400 million people worldwide (174). Moreover, the incidence of diabetes is expected to continue to rise and, in the U.S. alone, is projected to affect nearly one in three people by the year 2050 (8). These alarming projections suggest that there is an urgent need for the development and implementation of novel preventative and treatment strategies to combat the rise in T2DM prevalence worldwide. T2DM manifests through the development of fasting and postprandial hyperglycemia, which is the primary contributor to the induction of numerous life-threatening complications and co-morbidities (153). The etiology of hyperglycemia in T2DM is a complex multifactorial process (127). However, it can be distilled to progressive impairments in insulin sensitivity (i.e., insulin resistance) and a corresponding failure of pancreatic islets to maintain appropriate insulin output to compensate for the decline in insulin sensitivity (i.e., islet failure) (55) (FIGURE 1). Pathophysiological manifestations of insulin resistance and islet failure are evidenced early in the evolution of the disease and are imperative for its full development (28).

Insulin resistance manifests as a reduction in insulin's ability to activate the cellular insulin signaling cascade and consequently stimulate insulin-mediated cellular processes. The pathophysiology of T2DM is primarily driven by induction of skeletal muscle, hepatic, and adipose tissue insulin resistance (27). Since skeletal muscle is the major organ responsible for postprandial glucose disposal, insulin resistance in skeletal muscle severely restricts the capacity for glucose clearance in patients with T2DM (102). At the cellular level, muscle insulin resistance expresses due to *1*) impaired insulin-mediated recruitment of GLUT4 glucose transporter proteins to the plasma membrane, *2*) attenuated capacity for glycogen storage, *3*) reduction in glucose oxidation, and *4*) impaired mitochondrial function (27). In the liver, insulin resistance is associated with excessive rates of hepatic glucose production during fasting, attributed in part to failed insulin-mediated suppression of gluconeogenesis (84). Liver insulin resistance is also associated with failure to suppress hepatic glucose production in the postprandial state due to impaired suppression of gluconeogenesis and glycogenolysis (127). Finally, adipose tissue insulin resistance is characterized by defective insulin-mediated glucose transport, a decreased capacity for lipid uptake, and a failure to suppress lipolysis and inflammation, resulting in elevated plasma free fatty acids (FFAs) and cytokines (145).

At the cellular level, induction of insulin resistance is largely attributed to ectopic lipid accumulation in insulin-sensitive tissues (i.e., liver, skeletal muscle, and adipose tissue) (133, 145). In muscle and liver, ectopic lipid deposition due to obesity-induced intracellular accumulation and consequent trafficking of lipid signaling intermediates (i.e., ceramides and diacylglycerols) plays a major contributory role in impaired activation of the cellular insulin signaling cascade (133, 145). Specifically, intracellular diacylglycerols and ceramides contribute to insulin resistance through deleterious effects on activation of insulin signaling molecules such as insulin receptor substrate 1 and 2 (IRS-1 and -2). This process is mediated through activation of atypical serine/threonine kinases such as protein kinase C θ (133, 145). In addition, obesity in T2DM is also associated with impaired adipocyte metabolism resulting in *1*) excessive lipolysis and consequent increase in plasma free fatty acid levels, and *2*) excessive production and secretion of pro-inflammatory cytokines (i.e., TNF-α, Il-6, etc.), which are thought to originate from activated adipose tissue macrophages (51).

Thus aberrant adipose tissue metabolism in T2DM directly contributes to insulin resistance in target tissues through an increase in lipid accumulation or indirectly through cytokine-mediated disruption of the insulin signaling cascade in the liver and skeletal muscle (51) (FIGURE 1).

Pancreatic islet failure is a characteristic pathology in T2DM and, together with insulin resistance, is required for the establishment of hyperglycemia (18, 24) (FIGURE 1). The primary manifestation of islet failure in T2DM patients is the loss (or inappropriate activation) of glucose-stimulated insulin secretion and impaired suppression of glucagon release (55, 72). Impaired glucose-stimulated insulin secretion is attributed to the induction of β-cell secretory dysfunction and loss of β-cell numbers (i.e., β-cell mass) (55, 88). Loss of β-cell mass in T2DM patients has been attributed to increased β-cell apoptosis and the development of β-cell dedifferentiation (10, 157). The etiology of β-cell secretory dysfunction and loss is highly complex. Cumulative evidence points to induction of intracellular oxidative and/or endoplasmic reticulum stress brought on by increased exposure to toxicity associated with hyperglycemia/hyperlipidemia and/or islet amyloid peptide oligomers (IAPP) (42, 114, 136). Mechanisms underlying impaired suppression of glucagon release are not well understood, with limited evidence pointing toward an increase in α-cell numbers and alterations in α-cell function in diabetes (72, 91, 139).

T2DM is a complex metabolic disease driven by interactions among diverse environmental and genetic susceptibilities (148). Although genetic factors clearly play a contributory role in the pathogenesis of T2DM, environmental and epigenetic factors appear to be the primary contributors to the recent rise in T2DM prevalence (35). In this regard, more recent evidence suggests that environmental conditions associated with disruptions of normal circadian rhythms are associated with increased incidences of T2DM. Specifically, the incidence of T2DM is substantially increased in individuals experiencing night work and shift work; an observation consistent across a variety of professional industries (64, 65, 75, 99, 111, 154). Similarly, acute circadian disruption induces alterations in glucose metabolism, which promotes a diabetogenic state within days/weeks of exposure to circadian misalignment under a variety of clinical laboratory settings (11, 21, 74, 95, 119, 135, 141). In addition, genetic polymorphisms and variants in key circadian transcripts are associated with metabolic disorders and an increased incidence of obesity, hyperglycemia, and T2DM (37, 81, 140, 168).

In summary, there is an urgent need for the development of novel therapeutic and preventative strategies to attenuate expansion in T2DM prevalence worldwide. In this regard, there is an impressive amount of consistently growing evidence from epidemiological, clinical, and animal-based research linking the circadian system to various aspects of T2DM pathophysiology and treatment. The aim of the current review will be to describe emerging physiological and molecular insights into the role of the circadian system in the pathophysiology of metabolic abnormalities associated with the development of T2DM. In addition, a particular emphasis will be placed on the discussion of the therapeutic potential of targeting key components of the circadian system for the treatment and prevention of metabolic dysfunction.

Circadian Organization, Molecular Structure, and Entrainment

The majority of organisms have evolved optimal physiological functionality under environmental

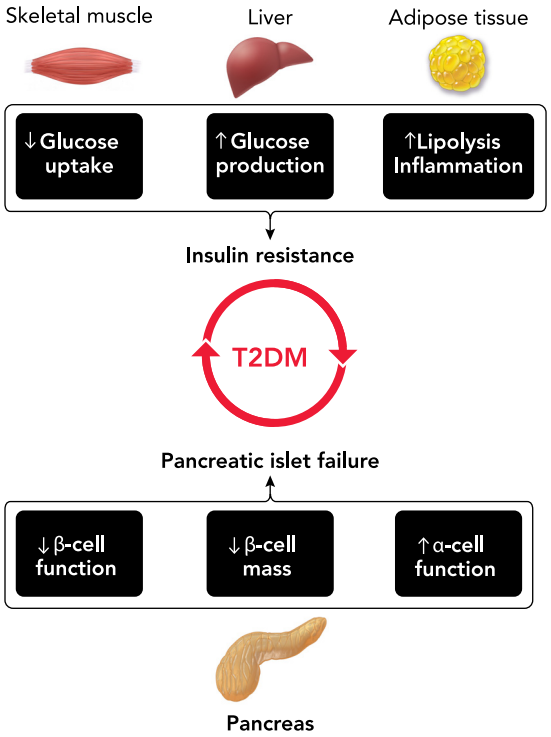

FIGURE 1. **Pathophysiology of Type 2 diabetes mellitus**
Type 2 diabetes (T2DM) is a complex metabolic disease in which the pathophysiology involves an interaction between genetic predisposition and environmental triggers. Hyperglycemia develops as a result of pancreatic islet failure in lieu of systemic insulin resistance. Islet failure in T2DM is associated with a deficit in β-cell mass and function and increased glucagon secretion. Insulin resistance in T2DM primarily manifests at the level of skeletal muscle, liver, and adipose tissue, and is characterized by impaired insulin-stimulated glucose disposal, failure to suppress hepatic glucose production, and elevated adipose tissue lipolysis and inflammation.

conditions created by daily changes in the light-dark (LD) cycle. The driving force behind biological adaptation to changes in LD cycle is precipitated by the evolutionary development of the circadian (*circa diem*, about a day) system. The primary utility of the circadian system is to promote adaptation and organismal fitness in response to 24-h environmental cycles (e.g., wake/sleep, fasting/feeding, etc). A key aspect of circadian physiology is its intrinsic nature, suggesting the presence of an internal cell-specific temporal program that anticipates and regulates behavioral, physiological, genetic, and metabolic cycles appropriate for the outside environment (112). Thus evolutionary origins of the circadian system appear to be selected to promote organismal adaptation to diurnal changes in oxidative environment, UV-mediated DNA damage, as well as optimal diurnal regulation of cellular energetics and metabolism (112, 158). Indeed, a functional circadian system has been shown to provide a clear fitness advantage to organisms from diverse living phyla such as plants (29), bacteria (167), yeast (19), and mammals (26, 63).

Circadian System Organization in Mammals

Given the fundamental importance of the circadian system in mammalian physiology, circadian rhythmicity permeates all levels of mammalian organization from behavior to hormonal secretion, temperature regulation, as well as molecular regulation of gene transcription and translation (124, 155, 156). To provide efficient and precise coordination of circadian timing throughout the body, the circadian system is organized as a multi-level hierarchical oscillator network (FIGURE 2). The pacemaker or "master clock" is localized to a subset of bilateral neurons in the suprachiasmatic nucleus (SCN) of the hypothalamus (56, 97, 123, 151). Indeed, SCN neurons appear to determine the period of an organism's circadian rhythms and are essential for the generation of circadian rhythms in most physiological and behavioral functions (56, 97). Light is the most salient stimulus responsible for the entrainment of the SCN clock to daily changes in LD cycles (47). Entrainment of the SCN

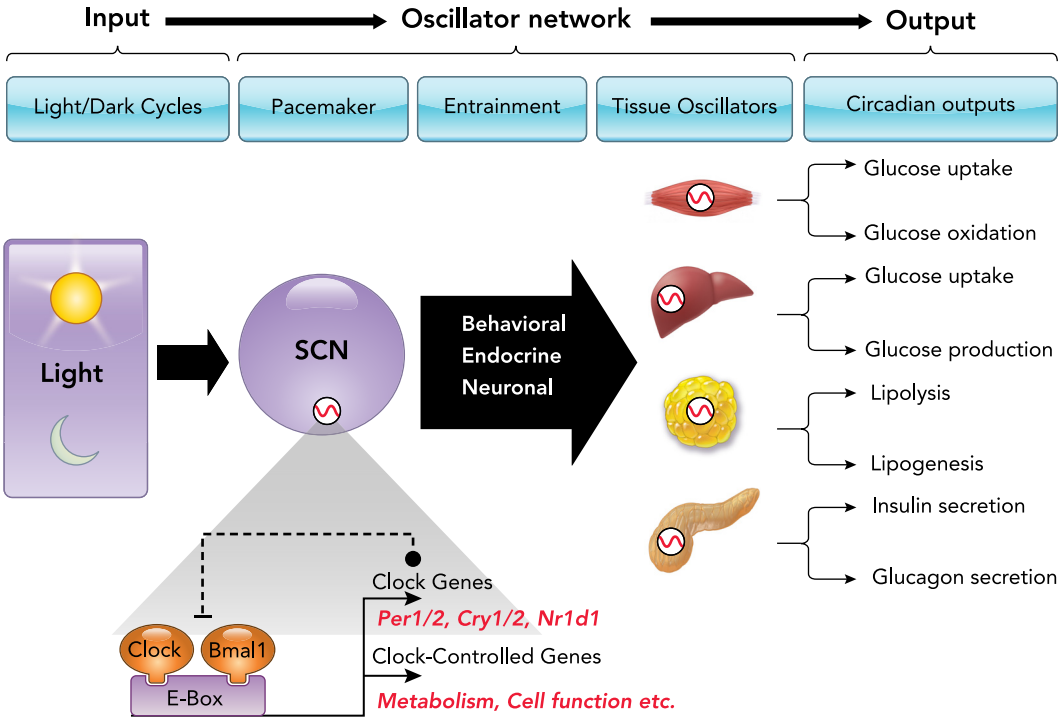

FIGURE 2. **Organization and molecular structure of the mammalian circadian system**
To provide efficient coordination of circadian timing, the mammalian circadian system is organized as a multi-level hierarchical oscillator network. Changes in the LD cycle are perceived by specialized ganglion cells in the retina, synchronizing the central pacemaker of the circadian system in the SCN to the solar day. The main function of the SCN clock appears to coordinate and synchronize cell-autonomous circadian oscillators present in a wide array of peripheral tissues (e.g., skeletal myocytes, hepatocytes, adipocytes, and pancreatic islet cell subtypes) via a combination of neuronal, humoral, and behavioral cues, thus integrating a complex multi-level hierarchical oscillator network. The molecular make up of circadian oscillators consists of the transcriptional activators CLOCK and its heterodimer BMAL1, along with repressor genes that encode period (PER1, 2) and cryptochrome (CRY1, 2) proteins. This regulatory mechanism ensures the generation of 24-h cycles of transcription and translation. Specifically, the CLOCK:BMAL1 heterodimer is essential for the generation of circadian rhythms of transcription through DNA binding to conserved promoter regions (E-boxes) of numerous clock-controlled genes critical for regulation of diverse cellular functions and metabolic pathways.

clock to environmental cycles is mediated via direct retinal projections from the specialized melanopsin-enriched photoreceptors (4). It is important to note that light-mediated circadian neuronal pathways are distinct from conventional phototransduction mediated by rods and cones, which further emphasizes the unique nature of the circadian system in mammalian physiology (36).

Self-sustainable and cell-autonomous circadian oscillators are also present in a wide array of peripheral tissues/cells including tissues critical for metabolic control such as skeletal myocytes, hepatocytes, adipocytes, and pancreatic islet cell subtypes (132) (FIGURE 2). These cell-autonomous oscillators are capable of sustaining 24-h circadian rhythms in cell-specific functions without continuous input from the SCN (170). However, the main function of the SCN clock appears to be to coordinate and synchronize tissue circadian oscillators via a combination of neuronal, humoral, and behavioral cues, thus integrating a complex multilevel hierarchical oscillator network (FIGURE 2).

To date, the exact physiological mechanism by which the SCN synchronizes peripheral oscillators remains an area of active investigation. However, accumulating data shows that the SCN engages multiple biological routes to regulate phase entrainment and circadian physiology of peripheral tissue oscillators. Specifically, both parasympathetic and sympathetic branches of the autonomic nervous systems mediate SCN-dependent entrainment of circadian rhythms (57, 97, 162). For example, circadian rhythms in hepatic glucose production and ambient glycemia rely on SCN-mediated autonomic control of the hepatic circadian clock (66). The SCN also regulates entrainment of peripheral oscillators indirectly through modulation of fasting/feeding cycles, which is particularly apparent in cell types responsive to daily nutritional challenges (e.g., pancreatic islets and hepatocytes) (25, 121). Although the exact mechanisms mediating feeding-induced circadian entrainment of peripheral oscillators are unknown, combinations of gut-related hormonal factors and food-related metabolites have been proposed (98). Finally, the SCN also synchronizes circadian rhythms through regulation of temperature and hormonal rhythms (e.g., glucocorticoids) (68, 137). Overall, the SCN plays a central role in orchestrating the entrainment of peripheral oscillators while utilizing redundant signaling mechanisms to fine tune the temporal regulation of diverse circadian rhythms in mammals (FIGURE 2).

Molecular Mechanisms of Cell-Autonomous Circadian Clocks

The molecular makeup of the SCN and peripheral circadian oscillators is essentially identical and consists of a cell-autonomous transcriptional-translational feedback loop regulated by a set of core "clock" genes (FIGURE 2). Pioneering work by Hardin, Hall, and Rosbash first identified the *Period* (*Per*) gene as a core component of the circadian oscillator loop in *Drosophila*, thus providing early mechanistic insights into the function of the circadian clock (44, 45). In mammals, the core of the circadian clock comprises the transcription factors CLOCK and its heterodimer BMAL1 (also known *Arntl* or *Mop3*), and repressor genes that encode period (PER 1,2) and cryptochrome (CRY 1,2) proteins (155, 156). Secondary regulatory loops involving the nuclear receptors Rev-erbα/β and RORα/β provide additional molecular stabilization and control by acting as respective transcriptional repressors and activators of *Bmal1* (115). Together, this regulatory mechanism ensures the generation of robust 24-h cycles of transcription and translation with varying phases of expression. Specifically, the CLOCK-BMAL1 heterodimer activates transcription of target genes via DNA binding to conserved promoter regions (E-boxes). This includes recruitment and interaction with histone acetyltransferases (e.g., p300), methyltransferases (e.g., MLL1), histone demethylases (Jarid1a), and cell-specific enhancers (e.g., PDX1 in β-cells) to enhance chromatin accessibility and thus promote transcriptional activation of target genes (155). Indeed, up to 20% of the genome in the majority of studied cell types display some form of regulatory oversight by the circadian clock, which includes regulation of transcription, translation, mRNA degradation, micro-RNA turnover, and splicing (155). Notably, a great proportion of clock-controlled genes are involved in the regulation of cellular metabolism (31, 67). Thus alterations in glucose homeostasis and the propensity for obesity and diabetes were one of the earliest phenotypical observations noted in clock gene mutant mouse models (128, 161).

Circadian Clocks as Cell-Specific Regulators of Glucose Homeostasis

Role of Skeletal Muscle Circadian Clocks in Glucose Homeostasis

Both in vitro and in vivo studies have clearly demonstrated the presence of robust self-sustainable and autonomous circadian oscillators in skeletal myocytes (43, 104). Most notably, robust circadian rhythmicity exists for nearly every aspect of skeletal muscle physiology critical for proper regulation of glucose homeostasis. This includes circadian variations in skeletal muscle GLUT4 glucose transporter expression and translocation (30), glucose uptake and oxidation (32, 73), glycogen deposition (73), mitochondrial oxidative capacity (163), as

well as protein (17) and lipid metabolism (78). For example, peak physiological activity in skeletal muscle glucose uptake and oxidation coincides with the onset of active/feeding circadian cycles in both mouse and human experiments, which is consistent with the primary role of the circadian system to enhance metabolic flexibility (73, 163). Importantly, circadian rhythms in skeletal muscle functions (e.g., glucose uptake) persist in isolated muscle cells in vitro, thereby suggesting transcriptional control by the endogenous circadian clock mechanism (32, 104). Moreover, T2DM is associated with disruptions in circadian control of muscle glucose uptake and oxidation, thus implicating impairments in the circadian clock as a contributory factor to the pathophysiology of skeletal muscle insulin resistance in diabetes (5, 32, 82).

The most compelling evidence for the key role of the biological clock in the regulation of skeletal muscle physiology comes from studies in *Bmal1* knockout mouse models. *Bmal1* is a critical clock gene essential for proper functionality of the core circadian clock (9). Indeed, *Bmal1* is the only nonredundant clock gene deletion that results in ablation of behavioral, physiological, and molecular circadian rhythms (63, 90). Significantly, whole body deletion of *Bmal1* is characterized by a striking reduction in skeletal muscle mass, function, and mitochondrial density, which is reversed upon muscle-specific transgenic rescue (2, 63, 90). In recent years, skeletal muscle-specific *Bmal1* knockout mouse models were developed to delineate its role in the regulation of glucose metabolism. Interestingly, both embryonic and adult muscle-specific *Bmal1* knockouts primarily exhibit profound loss in glucose and insulin tolerance attributed largely to impaired insulin-stimulated glucose uptake akin to pathology common to insulin-resistant patients with T2DM (30, 46, 50).

At the cellular level, loss of glucose uptake due to *Bmal1* deletion is associated with the reduction in the expression and plasma membrane translocation of GLUT4 glucose transporters mediated through decreased expression of TBC1D1, a key protein involved in GLUT4 translocation from the cytoplasm to the plasma membrane (30, 46). Notably, diminished glucose transport is also seen in skeletal muscle of T2DM patients (102). Furthermore, muscle *Bmal1* deletion also attenuates the expression and enzymatic activity of key metabolic enzymes essential for glucose metabolism (e.g., *hexokinase*) and subsequent glucose oxidation (e.g., *pyruvate dehydrogenase*), which diverts cellular metabolism toward greater lipid utilization and storage. This further recapitulates the phenotypical changes observed in skeletal muscle of patients with T2DM (30, 46). Overall, there is strong experimental evidence that the skeletal muscle circadian clock is a key regulator of insulin-mediated glucose transport, uptake, storage, and oxidation, and when disrupted, contributes to the development of T2DM.

Role of Hepatic Circadian Clocks in Glucose Homeostasis

The liver is one of the main organs responsible for circadian control of daily glucose homeostasis (106). Under fasting conditions, diurnal fluctuations in the rate of hepatic glucose production dictate circadian variations in blood glycemia. Thus ablation of the SCN (or liver-specific) circadian clock abolishes circadian rhythms in blood glucose concentrations and results in disrupted glucose homeostasis (1, 58). The liver also contributes to circadian control of postprandial glucose metabolism since circadian changes in the rate of hepatic glucose production are also key determinants of diurnal cycles in insulin sensitivity and meal tolerance (6, 22, 130). Moreover, key metabolic and enzymatic determinants of hepatic glucose production (i.e., rates of gluconeogenesis, glycogenolysis, and glycogen storage) all have been shown to exhibit robust circadian variations in humans and a variety of animal models (60, 73, 82, 110).

At the cellular level, hepatocytes exhibit distinct circadian oscillations in transcription, translation, and morphological features such as cell size and volume (3, 89, 100, 146, 166). Specifically, hepatocytes exhibit circadian expression patterns for metabolic genes essential for regulation of hepatic glucose uptake and storage (e.g., *Glut2* and *Gck*), hepatic glucose production (e.g., *Pepck* and *Gcgr*), as well as cellular processes involved in hepatic lipid oxidation and storage (e.g., *Cpt1* and *Lipin1*) (67, 100). In addition, the hepatic proteome (both nuclear and cytoplasmic) is also subjected to significant diurnal regulations, particularly in biological processes involved in DNA repair, proliferation, ribosomal biogenesis, and protein intracellular transport (166). It is important to point out that fasting-feeding cycles appear to be the main timing signals regulating many daily rhythms in hepatic function and related diurnal oscillations in hepatic transcriptome and proteome (3, 89, 152, 164). Thus, when assessing mechanisms responsible for the generation of circadian rhythms in the liver, a distinction should be made between clock-dependent and clock-independent (i.e., feeding-driven) circadian rhythms, both of which contribute to the generation of diurnal oscillations in the liver.

Chromatin immunoprecipitation combined with deep sequencing studies (ChIP-Seq) have shed some light on potential molecular targets and mechanisms guiding clock-controlled transcriptional regulation

in hepatocytes (62, 126). Specifically, Rey and colleagues (126) identified a genome-wide map corresponding to over 2,000 BMAL1 binding sites in the liver. Importantly, the most prominent binding sites were enriched for promoter regions of genes regulating hepatic glucose (e.g., *Glut2* and *G6pc*) and lipid (e.g., *Agpat6* and *Dgat2*) metabolism, thus further implicating hepatic clocks as key mediators of glucose homeostasis (126). In accordance with this finding, liver-specific deletion of *Bmal1* in mice results in the loss of circadian regulation of genes essential for regulation of hepatic glucose metabolism, such as glucose transporter *Glut2*, leading to dysregulation in systemic glycemia and glucose tolerance (67). More recently, Jacobi and colleagues (53) extended these findings to demonstrate that hepatic *Bmal1* orchestrates intracellular mitochondrial dynamics (fission and mytophagy) and plays an essential role in the regulation of hepatic oxidative capacity. Consequently, liver-specific deletion of *Bmal1* recapitulates hepatic pathology in T2DM characterized by increased oxidative stress, loss of insulin signaling, ectopic lipid accumulation, and hepatic insulin resistance (53).

Hepatic clocks also orchestrate the regulation of cellular metabolism through "indirect" pathways mediated through activation of transcription factors and other transcriptional and translational regulators (12, 40, 138, 171, 172). ChIP-Seq studies show "transcriptional regulation" as the most enriched annotated functional cluster of BMAL1 binding sites in the liver, which includes 82 DNA transcription factors and 18 liver-expressed nuclear receptors (126). Specifically, hepatic clocks regulate lipid and cholesterol metabolism through BMAL1:CLOCK-mediated transactivation of *Klf10* (Kruppel-like transcription factor) and nuclear receptor *Pparα* (peroxisome proliferator-activated receptor α) (12, 40). Interestingly, *Klf10* and *Pparα* also regulate *Bmal1* promoter activation, thus underscoring a complex interrelationship between the circadian clock and hepatic metabolism (12, 40). Finally, studies also show that circadian clock repressor proteins (e.g., CRY 1 and 2, and PER2) coordinate circadian control over hepatic glucose metabolism through posttranslational regulation of cAMP signaling and nuclear receptor function (138, 171). For example, Zhang et al. (171) eloquently demonstrated that circadian expression of CRY1 inhibits activation of key gluconeogenic enzymes through direct binding and inhibition of the hepatic glucagon receptor Gsα subunit, whereas hepatic overexpression of *Cry1* resulted in attenuated gluconeogenesis and lowered glycemia in diabetic mice. Overall, accumulating data highlights hepatic clocks as essential transcriptional/translational regulators of hepatic glucose production, uptake, and insulin sensitivity, thus underscoring their potential as therapeutic targets in T2DM (160).

Role of Adipocyte Circadian Clocks in Glucose Homeostasis

White adipose tissue (WAT) serves a dual purpose in the regulation of glucose homeostasis through its role as both an energy store and through its diverse endocrine-related functions. WAT are central energy stores harboring triglycerides (TGs), which are utilized through the process of lipolysis [i.e., the breakdown of TGs into free fatty acids (FFAs) and glycerol]. Thus proper regulation of lipolysis and its counterpart, lipogenesis, is critical in maintaining normal glucose homeostasis, as excess circulating FFAs contribute to ectopic lipid accumulation and consequent development of insulin resistance in T2DM (145). Indeed, circadian variations in plasma free fatty acids concentrations have long been described in humans (14), a phenomenon recently ascribed to circadian changes in the activation of adipose tissue insulin signaling cascade (13).

Due to robust diurnal changes in mammalian energy demands, adipose tissue processes including lipolysis, adipogenesis, and metabolic inflammation have been shown to be regulated by the circadian clock (142, 143, 169). Consistently, induction of obesity due to excessive levels of plasma triglycerides and free fatty acids are characteristically observed in *Clock* and/or *Bmal1* mutant mice (128, 161). Furthermore, studies done in both rodents and humans have identified rhythmically expressing clock-controlled genes in various adipose tissue depots (77, 143, 175), revealing circadian expression profiles for thousands of genes critical for proper regulation of adipocyte metabolism (175). For example, in one study, the release of FFAs and glycerol was shown to be clock-regulated due to transcriptional regulation of two key lipolysis pacemaker enzymes (e.g., *Atgl* and *Hsl*) by the BMAL1 and CLOCK heterodimer (144). Moreover, *Bmal1*-deficient mice demonstrated a lower capacity of adipocytes to synthesize polyunsaturated fatty acids due to lower expression levels of two key genes involved in FFA elongation and desaturation, *Elovl6* and *Scd1*, which were shown to be also transcriptionally controlled by *Bmal1* (101).

In addition to serving as an energy depot, adipose tissue has been considered one of the largest endocrine organs in the body due to its unlimited growth potential and capacity to secrete various hormones and cytokines. The number of adipokines known to be secreted by adipocytes in obesity and diabetes has expanded to include leptin, adiponectin, resistin, visfatin, and omentin, in addition to inflammatory cytokines such as TNF-α,

IL-6, and MCP-1, among others (83). One of the most well-regarded sources of proinflammatory cytokines in obesity-induced insulin resistance comes from adipose tissue macrophages (ATMs) (51, 79). Under diabetic conditions, ATMs are shown to undergo a switch from anti-inflammatory M2 macrophages to proinflammatory M1 macrophages, which are known producers of proinflammatory cytokines such as TNF-α, IL-6, and IL-12 (79). Although the role of the circadian system in controlling adipose tissue inflammation is not well understood, accumulating evidence suggests that perturbations in circadian pathways can elicit inflammatory responses. For example, obese circadian-disrupted mice showed enhanced adiposity associated with increased expression of key adipose inflammatory markers such as macrophage-1 antigen (MAC1) and TNF-α in WAT (33). Furthermore, clock-disrupted (*Per2* mutant) macrophages demonstrated enhanced proinflammatory activation under LPS conditions and increased M1 macrophage polarization in WAT (169). Interestingly, these findings were further recapitulated in obese mice with *Per1/2*-disrupted myeloid cells mediated through macrophage downregulation of *PPARγ*, a key clock-regulated transcription factor involved in M2 macrophage polarization (169). Overall, compelling evidence suggests that multiple aspects of adipose tissue biology (e.g., insulin sensitivity, lipolysis, lipogenesis, inflammatory pathways, etc.) are controlled by the circadian clock, disruption of which leads to enhanced adiposity, insulin resistance, and an increased susceptibility for the development of T2DM.

Role of Islet Circadian Clocks in Glucose Homeostasis

In humans, circadian variation in glucose and meal tolerance has long been recognized as a hallmark feature of glucose homeostasis (14, 69, 130). Indeed, enhanced glucose tolerance manifests at the onset of the active circadian cycle and is associated with a greater insulin secretory response to glucose and β-cell-specific secretagogues (14). In support of these early observations, classic studies by Boden and colleagues utilized a 72-h glucose clamp protocol to demonstrate robust feeding and glycemia-independent circadian insulin secretory patterns in humans (7). Furthermore, circadian rhythms in glucose-stimulated insulin secretion persist in vitro in cultured isolated human (and rodent) pancreatic islets as well as in purified β-cell populations, suggesting regulatory oversight by the cell-autonomous circadian clock (103, 105, 108). Although circadian regulation of the α-cell glucagon response is much less understood, studies also show circadian variations in glucagon secretion in vivo, in cultured islets, and in purified α-cells in vitro (85, 129, 130).

The presence and function of the cell-autonomous circadian clock in pancreatic islets has been explored and confirmed by multiple groups utilizing a method to track islet cell bioluminescence in vitro with clock gene luciferase fusion constructs (e.g., *Per1*:LUC and *Per2*:LUC) (87, 107, 108, 116–118, 121). Collectively, these studies show that islet cells *1*) exhibit robust autonomous circadian rhythms in clock gene expression with a distinct ~24-h period, phase, and amplitude of circadian oscillations, and *2*) the SCN appears to entrain the phase of circadian clocks in islets via modulation of the feeding behavior (121). It was also demonstrated that the function of islet circadian clocks is perturbed on exposure to circadian disruption induced by changes in the photoperiod and/or exposure to obesogenic diets (117, 118). Finally, more recently, Petrenko and colleagues have employed a novel triple reporter mouse model to show the presence of robust cell-autonomous circadian oscillators in purified populations of β- and α-cells, which were notably characterized by distinct phases in transcriptional and functional oscillations (108).

At the cellular level, islet cell clocks orchestrate circadian oscillations in the transcriptome akin to other metabolically active cell types (i.e., liver and skeletal muscle) (103, 108, 122). Indeed, a large proportion of transcripts in mouse islets (up to a third) exhibit statistically significant circadian profiles (103). Circadian-expressed transcripts in islets cells are predominantly enriched for biological pathways regulating insulin secretion and exocytosis (e.g., SNARE interactions, vesicular transport, and exocytosis), mitochondrial function, ER protein processing and transport, as well as transcripts involved in the regulation of cell turnover (e.g., DNA replication and DNA damage and repair response) (103, 108, 122). Importantly, purified populations of islet cell subtypes have been recently shown to display a subset of α- and β-cell-specific circadian transcripts with respective peak expression during either the inactive/fasting or active/feeding circadian cycle corresponding to peak secretion of glucagon and insulin (108).

At the molecular level, recent work by Perelis et al. (103) eloquently demonstrated that circadian control of insulin secretion and islet transcriptional regulation is orchestrated by rhythmic DNA binding of the CLOCK:BMAL1 heterodimer with the key islet transcription factor, PDX-1, along with concurrent recruitment of islet cell-specific enhancers. Consequently, given the widespread importance of circadian clocks for regulation of islet transcription and hormonal secretion, multiple groups have now shown induction of glucose

intolerance, hyperglycemia, and impaired glucose-stimulated insulin secretion in pancreas and β-cell-specific clock gene mutants (71, 87, 103, 120, 131). Moreover, β-cell-specific clock disruption also compromises the β-cell's replicative capacity and promotes DNA damage-induced apoptosis, likely attributed to an increased intracellular oxidative environment and induction of ER stress (70, 120). Taken together, islet circadian clocks appear to play an essential role in the regulation of β- and α-cell function and turnover. Consequently, clock-disrupted islets recapitulate both functional and morphological abnormalities associated with islet failure in T2DM.

Circadian System as a Novel Therapeutic Target in T2DM

Growing evidence suggests that therapeutic strategies designed to enhance circadian clock function may be beneficial for the prevention and treatment of metabolic disorders such as T2DM. First, as outlined in the current review, cell-autonomous circadian clocks orchestrate the regulation of physiological functions required for maintenance of normal glucose homesosis (e.g., skeletal muscle glucose uptake, hepatic glucose production, adipose tissue lipolysis, and islet cell function) (30, 46, 53, 103, 142). Correspondingly, phenotypical characteristics of many clock gene mutant mice recapitulate the pathophysiology commonly observed in patients with T2DM, such as insulin resistance, excessive hepatic glucose production, ectopic fat accumulation, impaired insulin secretion, and β-cell loss (30, 46, 53, 103, 120, 142). Second, pathogenesis of obesity and T2DM per se is linked with impairments in circadian regulation both at the level of central and peripheral circadian oscillators (16, 39, 61, 92, 134). Thus development of obesity and T2DM in humans is evidenced by disrupted circadian physiology (5, 54, 69, 82, 86, 125, 150). Indeed, obese diabetic rodents are characterized by disrupted behavioral and metabolic circadian rhythms associated with suppression of CLOCK-BMAL1 transactivation and impaired function of circadian oscillators in peripheral tissue (e.g., liver, skeletal muscle and islets) (48, 61, 118). Moreover, ectopic expression of CLOCK and BMAL1 in insulin-sensitive tissues has been shown to reverse insulin resistance in skeletal muscle and liver, reduce lipolysis in adipocytes, and improve glucose tolerance in mouse models of T2DM (76, 142, 173).

The first circadian-based therapeutic tested for antidiabetic efficacy was melatonin, a hormone synthesized and secreted from the endocrine cells in the pineal gland (93). Circadian melatonin production and secretion is driven through direct neuronal inputs from the SCN (94), and thus circadian secretion of melatonin has been described as a hormonal output of the central circadian clock (109). Indeed, exogenous melatonin administration exerts direct effects on the SCN and peripheral circadian oscillators through ubiquitously expressed melatonin receptors (38). Subsequently, timed melatonin supplementation is effective in enhancing global circadian rhythms in both rodents and humans (15, 147). Importantly, melatonin supplementation in rodents has proven to be effective in reducing adiposity and attenuating both hepatic and skeletal muscle insulin resistance by direct enhancement of the cellular insulin signaling cascade (41, 96). Furthermore, in isolated T2DM islets, activation of melatonin signaling has been shown to attenuate induction of the oxidative and endoplasmic reticulum stress and improve glucose-stimulated insulin secretion and β-cell survival (23, 159). Although some initial clinical studies in humans reported beneficial effects of melatonin treatment for glycemic control in patients with T2DM, additional well-controlled clinical trials are required to elucidate the potential efficacy of melatonin for the prevention and treatment of T2DM in humans (34).

In recent years, an increased emphasis has been placed on the development of small-molecule chemical enhancers of circadian system with goals of augmenting clock-regulated physiological outputs (20, 165). Subsequently, a number of chemical compounds specifically targeting the core circadian oscillator have been developed with documented efficacy in modulating metabolic function in pre-clinical studies. Specifically, Nobiletin (a naturally occurring flavonoid) has been recently identified as a clock amplitude enhancer, actions of which are mediated through ROR nuclear receptor activation (48). Importantly, chronic administration of Nobiletin in two distinct obese/T2DM mouse models resulted in restoration of oscillatory patterns in circadian and metabolic gene expression in the liver and corresponding phenotypical improvements in glycemia, glucose tolerance, insulin resistance, and ectopic fat accumulation (48). Another recently discovered chemical modulator of the circadian system, Rev-ERB-α/β agonist, also has been shown to modulate circadain metabolic gene expression and improve glycemia, lipidemia, and ectopic fat accumulation in mice (149). Moreover, Hirota and colleagues identified a small molecule CRY activator (KL001) that interferes with ubiquitin-mediated CRY degradation, resulting in CRY stabilization and lengthening of the circadain period (49). Importantly, KL001 administration was shown to attenuate glucagon-induced gluconeogenic flux in isolated hepatocytes in vitro and also to improve glucose intolerance in obese insulin-resistant

mice in vivo (49, 52). Finally, beneficial metabolic effects ascribed to chemical modulators of Rev-ERB-α/β and CRY were not associated with enhanced circadian clock amplitude, which underscores that more studies are needed to fully understand mechanisms underlying physiological effects of clock-modifying chemical compounds (49, 52).

Concluding Remarks

Mammalian circadian physiology is highlighted by exceptional stability in time-based regulation of numerous biological functions displaying a near-24-h temporal resolution period with minimal coefficient of variance (112). However, physiological benefits of the circadian system are diminished when external environmental cycles deviate from the norm (i.e., 24 h) as is becoming more and more prevalent in today's society (80). This produces the state often characterized as circadian misalignment or disruption (26, 59, 113), a condition strongly associated with metabolic dysfunction and development of obesity and T2DM (11, 21, 64, 65, 74, 75, 95, 99, 111, 119, 135, 141, 154). The current review highlights extensive clinical and pre-clinical data supporting the essential role of circadian system in the regulation of metabolic function and glucose homeostasis. This work also provides strong rationale for therapeutic targeting of circadian system in the treatment and prevention of T2DM and consequent metabolic comorbidities. Future studies are urgently needed to identify and characterize mechanisms of action of novel chemical and endogenous modifiers of mammalian circadian system, with potential to augment clock-regulated metabolic and glucose-responsive physiological processes. ■

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