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Untimely oxidative stress in β-cells leads to diabetes – Role of circadian clock in β-cell function

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Abstract

Diabetes results from a loss of β-cell function. With the number of people with diabetes reaching epidemic proportions globally, understanding mechanisms that are contributing to this increasing prevalence is critical. One such factor has been circadian disruption, with shift-work, light pollution, jet-lag, increased screen time, all acting as potential contributory factors. Though circadian disruption has been epidemiologically associated with diabetes and other metabolic disorders for many decades, it is only recently that there has been a better understanding of the underlying molecular mechanisms. Experimental circadian disruption, via manipulation of environmental or genetic factors using gene-deletion mouse models, has demonstrated the importance of circadian rhythms in whole body metabolism. Genetic disruption of core clock genes, specifically in the β-cells in mice, have, now demonstrated the importance of the intrinsic β-cell clock in regulating function. Recent work has also shown the interaction of the circadian clock and enhancers in β-cells, indicating a highly integrated regulation of transcription and cellular function by the circadian clock. Disruption of either the whole body or only the β-cell clock leads to significant impairment of mitochondrial function, uncoupling, impaired vesicular transport, oxidative stress in β-cells and finally impaired glucose-stimulated insulin secretion and diabetes. In this review, we explore the role of the circadian clock in mitigating oxidative stress and preserving β-cell function.

Keywords

Circadian clock; Islet; β-cell; Insulin; Oxidative stress; Diabetes; Bmal1; Nrf2

Conflicts of interest

There are no potential conflicts of interest.

1. Introduction

There is a growing burden of T2D, reaching epidemic proportions. The WHO estimated in 2014 that there are 422 million people with diabetes in the world with the prevalence almost doubling in the last 4 decades [1]. Diabetes is a result of a loss, or decrease, in insulin action. In type 1 diabetes (T1D) there is an autoimmune destruction of pancreatic insulin-producing β-cells, while in type 2 diabetes (T2D) there is often significant insulin resistance with varying degrees of β-cell dysfunction. Thus a decrease in β-cell mass or β-cell function, or both, underlie all forms of diabetes. Obesity is a common risk factor for diabetes and the frequent glucolipotoxicity seen with diabetes and obesity is a well-accepted cause of worsening β-cell dysfunction, there are many other environmental factors that are less well understood, contributing to ongoing β-cell dysfunction. One such factor is disruption of the normal circadian rhythm. The importance of having a normal circadian rhythm and the association with disease, if disrupted, has been known for a long time, especially in at-risk populations, such as in shift-workers [2] with rotational or night shift work. Strong associations between shift-work and risk for metabolic dysfunction, obesity and diabetes have been reported [3–6], with a cumulative excess risk of up to 60% of T2D [6,7]. *ARNTL* (also referred to as *BMAL1*), an essential core clock gene, is associated with type 2 diabetes (T2D) [8]. Interestingly, its expression is significantly downregulated in diabetic human islets [9]. In addition, genome-wide association studies have implicated *MTNR1b and Cry2,* circadian rhythm related genes, in T2D and impaired β-cell function [10–15].

However, it is only recently that with a better understanding of both β-cell dysfunction and the molecular mechanisms of the circadian clock, are there mechanistic connections being made to better understand how circadian disruption leads to diabetes and specifically β-cell dysfunction. With modern day lifestyle and constant work-related disruption of the body circadian rhythms, understanding the molecular pathways mediating circadian regulation of β-cell function is critical and urgently need for addressing this prevalent public health concern. In this review, we will present these interactions with a focus on how the circadian clock affects β-cell function and oxidative stress response.

2. The molecular clock

The circadian rhythm is established by the core components of the molecular clock. The molecular clock comprises of a transcription/ translational feedback loop comprised of the non-redundant transcription factor Bmal1 (Brain and Muscle Arnt like 1, or Arntl) that forms a heterodimer with another transcription factor, Clock (Circadian locomotor output cycles kaput), or its homologue Npas2, to bind to E-box elements in the promoters of target genes (clock-controlled genes). Four of these target genes (*Per1*, *Per2, Cry1* and *Cry2*) encode proteins that translocate to the nucleus as heterodimers, to inhibit transactivation by Bmal1/Clock on their own promoters, and on those of other clock-controlled genes. The levels of Per1, Per2, Cry1 and Cry2 are also regulated by phosphorylation-mediated degradation. This slow rise in the levels of these proteins, thus sets up a feedback loop that gives rise to oscillations in the expression levels of clock-controlled genes – the circadian rhythm that has a ~ 24 h period. [16–25]. Reverbα and Reverbβ are transcriptional repressors that have E-box elements in their promoters and are clock-controlled genes. In

addition, they negatively regulate *Bmal1* [26–29] to accord *Bmal1* expression a circadian rhythm adding another layer of robustness to the core molecular clock.

3. Central and peripheral clocks

Most cell types, especially those that are differentiated, display robust clock oscillations in their gene expression [30]. These circadian oscillations in gene expression have also been demonstrated in pancreatic islets [31–36] and islets maintained, in culture, ex vivo [34]. The endogenous, or free-running, rhythm in the expression of clock-controlled genes can be entrainable by internal stimuli, such as from the circadian pace-setter located in the suprachisamatic nucleus (SCN) of the hypothalamus or by other external cues. The highly interconnected network of neurons, in the SCN, receive direct input from the retina via the retino-hypothalamic tract. Light is the primary driver of circadian oscillations in the SCN while temperature has also been shown to affect it [37]. On light exposure, the molecular events of transcriptional and post-translational events are set in motion, which result in the circadian oscillations of the expression of clock controlled genes in the SCN. These are communicated to the rest of the body (peripheral clocks), including the β-cells, through neurohumoral pathways [38,39]. While there have been mechanistic studies to characterize the nature of this communication between the central SCN clock and the liver peripheral clock [40], these are lacking for β-cells. Nevertheless, it has been recognized that those tissues, such as the liver, pancreas (including β-cells [41]), muscle etc. are also significantly influenced by, not only the cues from the central clock, regarding the time of the day, but also by nutritional cues [40–44], such as the time and nature of these nutrient cues. When the timing of food is uncoupled from the normal light/dark cycle, many of the metabolically active tissues, such as the liver, reset their circadian oscillations to align with the nutrient cues, indicating the dominance of these cues for these tissues [45,46]. Similarly, activity has also been shown to regulate peripheral clocks [47,48]. This is represented in Fig. 1.

4. Circadian clock regulation of metabolism

The circadian clock regulates whole-body metabolism [49] and this has been demonstrated in human studies, both epidemiological and interventional studies, and in animal models with circadian gene gain-of and loss-of-function studies. Targeted disruptions of clock genes result in striking metabolic disturbances [33–36,45,50–59], highlighting the central role of circadian regulation of cellular metabolism. ~ 10% or more of all transcripts have a circadian rhythm [30,60,61] that is tissue-specific, while a third of all nuclear receptors that play critical roles in metabolic homeostasis [26,62], display circadian rhythm. Furthermore, circadian control of various metabolic pathways appears to be most apparent on rate-limiting steps [60], compelling evidence that it is required for normal homeostasis. Interestingly, metabolic sensors, such as Sirt1, [63–65], AMPK [66] and PGC-1α [67,68] feed back to the core clock. Similar circadian rhythms of transcripts have been recently reported in β-cells regulating insulin secretion [69].

5. Circadian clock and β-cell function

β-cell clock has been studied for over a decade in rodents with a robust oscillation of core clock genes (Fig. 2), with more recent studies demonstrating their existence and function in human islets [70–72]. Indeed, a large number of transcripts in β-cells are rhythmic and are under circadian regulation [34,69,73]. Loss-of-function studies of the components of the core molecular clock in β-cells demonstrated its requirement for normal function (Table 1). We and others have demonstrated that β-cell-specific deletion of Bmal1, embryonic period onwards, which abrogates all rhythmic activity of the β-cell intrinsic clock, leads to profound β-cell dysfunction and diabetes [34–36,69,74]. Loss of circadian function in β-cells led to impaired substrate oxidation, a decrease in glucose-stimulated mitochondrial ATP production, impaired vesicular trafficking all resulting in a significantly blunted glucose-stimulated insulin secretion, the hallmark of β-cell failure seen in diabetes. Similarly, there is a profound effect on β-cell function even if the intrinsic β-cell clock is disrupted only in the adult life [69,75]. Mice with a loss-of-function of the β-cell clock induced only during adult life, have a blunted compensatory β-cell hyperplastic response in response to diet-induced insulin resistance, supporting evidence for the intrinsic circadian clock regulating β-cell proliferation [75]. All this provides convincing evidence that normal circadian oscillations and a functioning cell-autonomous β-cell circadian clock are essential throughout life to maintain normal β-cell function.

6. β-cells and oxidative stress

The primary function of β-cells is to sense glucose and secrete proportional amount of insulin [76]. This is achieved by an intricate cellular signaling machinery that, at its core, is composed of an uptake of glucose and subsequent oxidation of glucose to generate ATP. The levels of ATP are sensed by the ATP-dependent potassium channels to regulate membrane depolarization and insulin granule exocytosis. Thus, insulin secretion is tightly linked to plasma glucose levels in the body [77]. This synchronization requires that the glucose uptake into the β-cell be tightly coupled to ATP production, via increased oxygen consumption and mitochondrial oxidative phosphorylation. Since, mitochondrial oxidative metabolism is a large source of intracellular reactive oxygen species (ROS, including superoxides, hydrogen peroxide ec.); β-cells are exposed to potentially damaging amounts of intracellular ROS. In addition, other extra-mitochondrial sources of ROS, including the NADPH oxidase system, have also been shown to be important in β-cell oxidative stress [78]. To compound this, β-cells comparatively have a lesser anti-oxidant capacity, only 15–38% of the ROS scavenging ability [79,80] of most metabolic tissues, such as the liver, putting them at risk for ROS-induced oxidative stress. Indeed this has been hypothesized to be one of the important underlying causes of β-cell failure in many forms of T2D [81].

7. Circadian regulation of β-cell oxidative stress

The regulation of oxidative stress by the circadian clock and Bmal1 has been proposed in the context of the premature aging phenotype seen in mice with global Bmal1 deletion [82–84], and based on conserved E-boxes in the promoters of many antioxidant genes, it was proposed that Bmal1 and the molecular clock control antioxidant genes [82]. Many of the

antioxidant enzyme systems that defend against the damage induced by ROS are regulated by the leucine-zipper transcription factor, Nrf2 (*Nfe2l2*). We and others have shown that Nrf2 expression has a circadian oscillation and is directly under the control of Bmal1 and the circadian clock in β-cells [36] and in other tissues [85,86]. Indeed, in β-cells, there is a circadian oscillation of many critical antioxidant genes that are targets not only of Nrf2, but also Bmal1 (Fig. 2) and are dysregulated with circadian disruption [36,87]. These include genes in the sestrin family (*Sesn2*), peroxiredoxin family (*Prdx3*) and critical components of the glutathione system (*Gclc* and *Gclm*) [36]. Circadian disruption, thus leads to a dysregulation of mitochondrial function with increased ROS production [36], which when coupled with a decrease in antioxidant gene expression due to an impaired Nrf2 response, results in oxidative stress and β-cell dysfunction. To compound this, increased oxidative stress leads to an upregulation of Ucp2 in the β-cell, initially as a protective mechanism to diminish ROS production in the mitochondria by uncoupling substrate oxidation to phosphorylation of ADP to generate ATP. This uncoupling that result in a loss of oxidative phosphorylation, while beneficial in mitigating mitochondrial ROS production, has detrimental effects in β-cell function. An uncoupled β-cell is unable to couple glucose oxidation with ATP production and loses glucose-stimulated insulin secretion, an essential function. These changes have been demonstrated both in genetic and environmental models of circadian disruption [36]. Thus circadian disruption in the β-cell leads to increased ROS production, uncoupling, decreased antioxidant gene expression, and oxidative stress and culminates in significant impairment in β-cell function and diabetes.

8. Conclusion and future directions

Circadian disruption has become an integral part of modern lifestyle, with increasing number of people in occupations that demand shift-work and travel across time-zones. With mounting evidence demonstrating significant metabolic perturbations with circadian disruption, it has become imperative to decipher the molecular mechanisms underlying circadian regulation of pancreatic β-cells and understand how they interact with other tissues, to regulate whole body metabolism. Recent studies demonstrate that the circadian clock is critical for normal β-cell function and this regulation involves almost all aspects of β-cell biology (pictorially depicted in Fig. 3). However, there remain many questions that need to be answered in future studies. For instance, how does the circadian clock regulate how β-cells adapt and what are the mechanisms underlying acute and chronic adaptation? What is the tipping point when these adaptive mechanisms become pathological? How do β-cells interact with other organs and the central clock? What are the pathways that can be leveraged to prevent, mitigate and reverse circadian disruption induced dysfunction. While the answers to these questions will give us a better understanding about the interactions of the circadian clock and beta cell biology, other studies must be carried out concurrently to translate findings in pre-clinical models to clinical application to prevent and cure circadian disruption induced diabetes.

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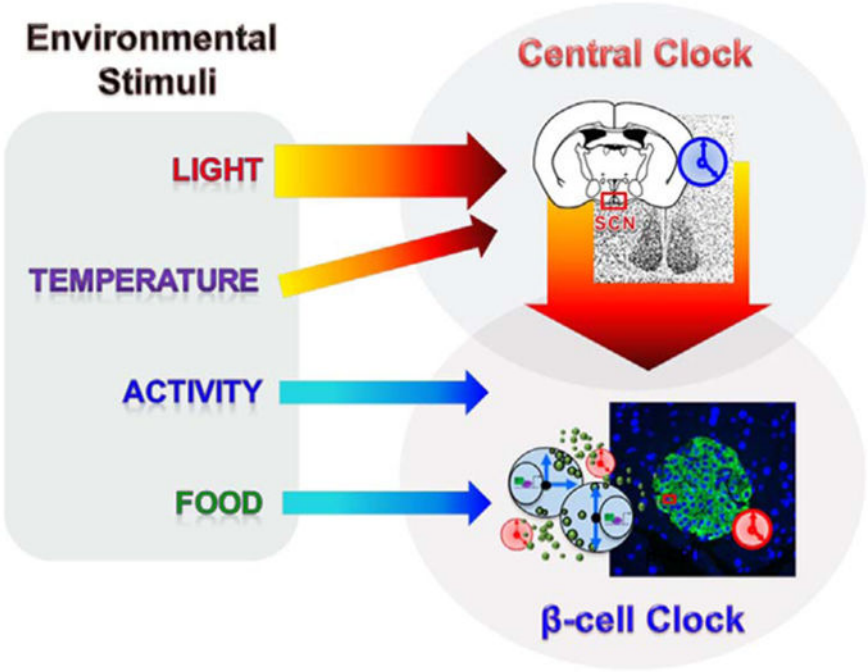

Fig. 1. Interaction of β-cell clock with the central clock and environmental cues

The central clock is entrained by external cues, of which light is the primary entraining signal. Other entraining signals include activity, temperature and food. The central clock regulates the β-cell clock via neurohumoral outputs.

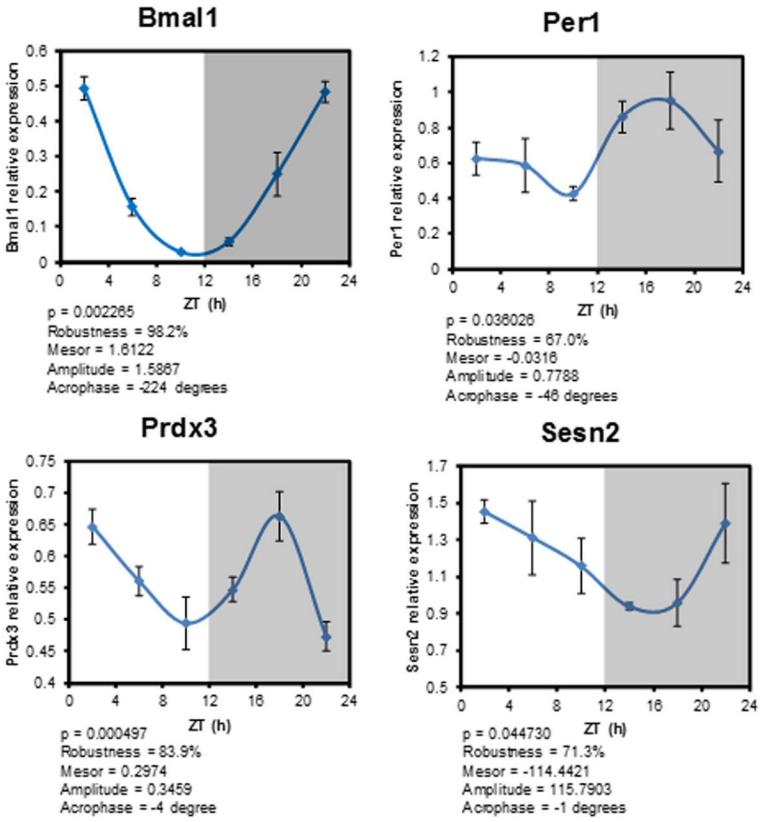

Fig. 2. Core clock and antioxidant gene oscillations in pancreatic islets

Relative gene expression of Bmal1, Per1 (core clock genes) and of anti-oxidant genes, Senstrin2 (Sesn2) and Peroxiredoxin 3 (Prdx3), are shown after normalization to house keeping genes, Tbp (TATA box binding protein) and topl (topoisomerases I). qRT-PCR from isolated islets that were collected every 4 h is shown. ZT is Zeitgeber time with ZT-0 being when lights are turned on at 7 A.M. Each time point represents islets collected from 4 mice. The gene expression data were fitted to a cosine function (using Acro software V3.5 Dr. Refinetti) and the cocinar parameters are presented below each panel.

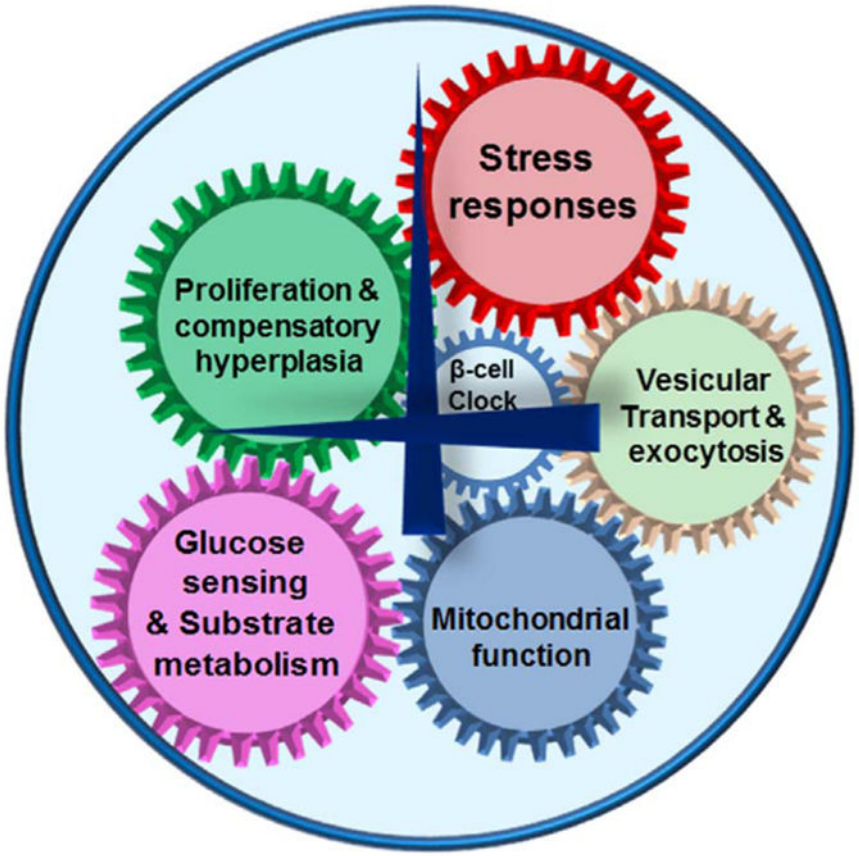

Fig. 3.

Circadian control of β-cell function. The intrinsic β-cell clock regulated many cellar process critical to normal function, including, glucose sensing and substrate metabolism, mitochondrial function, stress responses, insulin secretion by exocytosis and proliferation. Hence, circadian disruption leads to as failure of stimulus-secretion coupling, poor insulin secretion and diabetes.

Table 1

Genetic models of core clock gene disruption affecting β-cell function and glucose metabolism.

Gene disrupted	Metabolic phenotype	Refs.
Bmal1 (Global)	Impaired gluconeogenesis, adipocyte differentiation, hyperlipidemia, glucose intolerance	[34,50]
Bmal1 – since birth (Pancreas using Pdx-1 Cre)	Hyperglycemia, hypoinsulinemia, glucose intolerance, β-cell dysfunction	[34,35]
Bmal1 – since birth (β-cell specific using Rip-Cre)	Hyperglycemia, hypoinsulinemia, glucose intolerance, β-cell dysfunction	[36]
Bmal1 – only in adult (β-cell specific using Mip-Cre/ERT)	Impaired compensatory hyperplasia in response to diet-induced obesity	[75]
Bmal1 – only in adult (β-cell specific using Pdx1-CreER)	Hyperglycemia, hypoinsulinemia, glucose intolerance, β-cell dysfunction	[69]
Clock (Global)	Hypertriglyceridemia, hypercholesterolemia, hyperglycemia, hyperleptinemia	[52]
Cry1&2 (Global)	Glucose intolerance	[55]