

The Beat Goes On: The Impact of Circadian Rhythms on insulin resistance

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Abstract:

Metabolic activities are interfered by circadian rhythm, orchestrated by the central clock suprachiasmatic nucleus (SCN) in hypothalamus and peripheral clocks in other tissue and organs. In this review, how both circadian and non-circadian genes within these organs and tissues can mutually influence circadian rhythms, potentially inducing or exacerbating insulin resistance at the cellular level is outlined. Furthermore, to delves into the impact of environmental factors beyond atypical light exposure and jet lag on the expression of genes related to peripheral clocks, emphasizing the demand for precise control experiments and the application of sophisticated statistical models for analyzing results. The expression anomalies of circadian-related genes across diverse organs may instigate varying degrees of metabolic disturbances, culminating in diverse intensities of insulin resistance. Besides, this review critically examines the effects of circadian rhythm disruptions on insulin resistance, incorporating both existing and potential pharmacological interventions that address these metabolic dysfunctions through multiple pathways. It proposes innovative experimental approaches and hypotheses aimed at enhancing our understanding of circadian influences on metabolic health.

Keywords: Circadian rhythm; insulin resistance; SCN; genes.

1. Introduction

With the continuous development of society, type 2 diabetes has become one a significant health challenge, contributing to obesity through metabolic dysregulation and elevated blood glucose levels. Type 2 diabetes is the disease which is considered as diabetes mellitus with high blood glucose level plus inefficient insulin utilization by body cells judged by specialized tests. In addition to the unique insulin resistance, i.e., where moderate doses of insulin fail to lower blood glucose levels adequately, type 2 diabetes shares certain characteristics with other diseases, such as cardiovascular disease, nonalcoholic fatty liver disease, and deficient metabolic syndrome [1]. The most direct cause of insulin resistance is the direct mutation or deletion of the insulin receptor gene located on chromosome 19 such as a mutation from Cys²⁸⁴ residue to Tyr residue in the insulin receptor α -subunit [2]. Ironically, compared to rare genetic disorders, the prevalent societal stressors and diverse environmental factors disrupting circadian rhythms, coupled with erratic behavioral patterns, posing a more common risk to the development of insulin resistance and even type 2 diabetes. Disruptions in gene expression regulation, whether from internal or external sources, can compromise the quantity and quality of gene

products.

Organisms form a biological clock in order to adapt to the surrounding environment and. rationally utilize the surrounding resources to facilitate their own life activities. Multicellular animals have developed significant circadian rhythms over the course of their development and evolution and have retained characteristics that adjust in response to environmental variations. As for higher mammals, like human, rodents, felidae, canidae etc., SCN exists in the hypothalamus of the brain that receive photic signals directly from the retina as the role of master clock, which transmits rhythmic information to peripheral organs and tissues by means of diverse circadian oscillators [3]. Non-SCN endogenous clocks are also modulated by non-photic signals no matter internal or external. Synchronization of central clock and peripheral clock ensures stable sleep and normal metabolic functioning of the body, but it is relatively fragile in nowadays abnormal lifestyles. Excessive stress leads to insomnia, or human subjective initiative to stay up late at night to “enjoy lives” as well as a certain lux of light at night to interfere with the SCN superimposed on the irregularity of the eating/fasting cycle, like late-night snacks, no time to eat three meals etc., is likely to cause disruption of the central circadian clock or an untimely increase in the concentration of

blood glucose, and ultimately disrupt the synchronization of endogenous clocks in the periphery, and an imbalance of metabolism triggers insulin resistance and ultimately the formation of type 2 diabetes mellitus, not to mention internal signal interference due to certain diseases caused by the absence or mutation of non-circadian rhythm clock genes. Insulin resistance severity is expected to vary with the disruption of circadian rhythms under different situations directly or diffusely relevant to circadian rhythms. This thesis mainly reviewed recent research over the past 10 years, focusing on understanding how circadian rhythms impact insulin resistance mechanisms, with the aim of identifying potential medications.

2. Circadian rhythms affecting insulin resistance via different mechanisms

2.1 Gene abnormalities related to circadian rhythms affecting insulin resistance

2.1.1 MTNR1B gene enhancing insulin resistance

Abnormalities in circadian genes affect insulin resistance directly. The shift of circadian rhythm gene melatonin receptor type 1B (*MTNR1B*) gene interferes with the postoperative recovery associated with insulin resistance symptoms in patients, thus giving rise to suspicions of accelerating the progression of insulin resistance in the body. One of *MTNR1B* gene's single nucleotide polymorphisms (SNPs) is rs10830963, the CC change to CG or GG will lead to impaired melatonin signaling and its rhythmic abnormalities [4]. Logically, once melatonin signal has problem, human bodies' metabolic disturbances appear which is caused by melatonin's secretion in diurnal circadian fashion and its combination with melatonin receptor 1 exerts regulation on α -cells and β -cells in pancreatic islet [5]. In response to figure out whether the rs10830963 SNP affect the postoperative physiological indicators of individuals who have undergone dietary restriction measures, Pacheco et al. [6] and de Luis et al. [7] exploited different experimental intake-related measures. Make short of long, no matter sole and specialized treatment for control group or SNP group such as designed diets everyday supplement which confirms individuals' overall energy expenditure less than daily calorie absorption or facultative handling method like taking the same tablets, following a low-fat diet, and undergoing biliopancreatic diversion (BPD) surgery in every group; SNP group, i.e. CG group or GG group, all of their blood insulin concentration and homeostatic model assessment of insulin resistance (HOMA-IR) indexes were higher than those of the C allele group statistically considering time period and genotype still after same cure. These trial findings comprehensively demonstrate that regardless of the type or degree of

external interference, the rs10830963 SNP consistently possesses the ability to induce insulin resistance in the human body, equivalent to an enhancer of insulin resistance levels. Nevertheless, in the context of obtaining medical ethics approval, conducting controlled experiments tailored to individuals with currently normal BMI but with the rs10830963 CG or GG genotype, aiming to customize diets with varying fat content and assessing their blood physiological parameters, still holds its reasonable justifiability.

2.1.2 Genes in transcription-translation feedback loop (TTFL) SNP-inducing insulin resistance

The insulin resistance caused by circadian genes associated with the negative arms of the circadian rhythm's transcription-translation feedback loop (TTFL) is attributed to single SNP or multiple SNPs even including introns. Cryptochromes (*Cry*) 1 gene is TTFL's negative arm of core clock genes [8], Dashti et al. [9] revealed through controlled experiments that, regardless of Mediterranean or North American populations, individuals homozygous for the C allele of *CRY1* rs2287161 genotype showed a positive correlation between high carbohydrate intake and higher HOMA-IR, which was statistically compelling; in contrast, carriers of the major G allele (GG + CG), whether the high and low carbohydrate intake groups were defined based on a median baseline of 49.14% carbohydrate intake as a percentage of daily total energy absorption, all showed no significant differences in HOMA-IR [9]. Period Circadian Regulator (*PER*) 3 gene also belongs to TTFL's negative arm genes, Park et al. [10] discovered series of *PER3* SNPs including synonymous variant rs228669 and intron variant rs17031578 initiate Korean mature male and female's high HOMA-IR value which is generally higher than 2 though no statistical significance in male; but the most astonishing detection is 4 minor homozygote SNPs: alleles AA rs10930781, alleles AA rs2364720, alleles TT rs10188107, and alleles CC rs4243387 that all listed intron variants in nuclear factor erythroid 2-related factor (*NFE2L*) 2 gene in Park et al.'s research is in the equal situation with HOMA-IR results for *PER3* SNPs. Hinge on past studies showed *NFE2L2* mediates the regulation of *PER3* expression by binding to the stress response element (STRE) motif, thereby leveraging iron and lipid metabolism to manage indirect regulation of blood glucose metabolism [11] while *NFE2L2* alone mutation causes contradictory adipogenesis through different pathways, an inferred denouement that circadian clock TTFL negative arm genes' SNPs and their regulatory elements' SNPs of expressed genes' superimposition is capable of collectively engendering insulin resistance. In summary, weeding out exogenous non-dietary interference, if the circadian

rhythm regulation involving the negative or positive arms directly affects saccharides metabolism, then a single SNP is sufficient; on the other hand, if the SNP just affects the genes of the negative or positive arms expression or other substances such as lipid metabolism, then multiple different gene SNPs need to coexist to generate the literally defined insulin resistance. Of course, the impact of alone SNP or numerous SNPs on insulin resistance in different ethnicities should be prioritized for investigation.

2.2 External environmental factors interrupting with the circadian clock and affecting insulin resistance

Exploration of the effects of non-jet-lag social circadian disruption on insulin resistance has been more gradual and refined than jet-lag studies of circadian disruption in humans or in mice used as photic sources as interference. Exploiting controlled experiments and reference data from the intravenous glucose tolerance test (IVGTT), Leproult et al. [12] illuminated that for adult participants with circadian rhythm disorders who worked shifts, the reduction in insulin sensitivity (SI) was doubled compared to those who maintained a regular nighttime bedtime, demonstrating that circadian dysregulation occurring in shift work may raise the risk of diabetes independently of sleep deprivation [12]. The subjects in this experiment had a strongly disrupted circadian rhythm (8.5 hour phase shift). Although the effect of the ready availability of snacks in the control and disordered groups on the absolute control of the experimental variables did not unduly interfere with the final results, the authors of the paper constructed a slightly flawed model of the subjects, as the sleep duration of the subjects on the subsequent 8 days was 5 hours, which is less than the theoretical average duration of a normal circadian rhythm in adults. The segment that figuring out whether a condition of sleep deprivation is indispensable to trigger a superimposed elevation of insulin resistance in non-photic-emitting circadian disorders in humans is missing. On the basis of morningness–eveningness score, Rawat et al. [13] divided observed adolescent subjects to 3 groups as several sleep time for cross-sectional studies, a progressive relationship was spotted: diet, especially alcohol, along with other social pressures, synergistically delay sleep onset, ultimately leading to elevated HOMA-IR levels, indicating high insulin resistance. This reveals how extrinsic environmental factors disrupt the circadian clock and affect the macro process of insulin resistance, but it does not refute the hypothesis that insufficient sleep is a necessary cornerstone for abnormal circadian rhythms leading to insulin resistance. Chen et al. [14] eliminated the necessity of diverse sleep durations as precursors to enhanced circadian disruption and increased

insulin resistance by constructing appropriate linear and logistic regression mathematical models, with separate models for sleep duration and sleep timing. In their unaccompanied sleep timing model, they found a positive correlation between HOMA-IR index in Mexican adolescents with sleep durations ranging from 8 to 9.5 hours and the midpoint of the sleep period on weekdays and weekends. Additionally, the results indicated that females exhibited statistically significant differences in insulin sensitivity disruption compared to males. This provides a statistical reference framework for the study of weak disruptive factors (phase shift <2 hours) such as social factors on circadian rhythms. Most crucially, Chen et al. [14] clue that midpoint gets one hour late in weekdays is going to initiate 1.3 times higher odds of high HOMA-IR. Even though raw number is contained in midpoint models' 95% CI, approximative rising insulin resistance parameter as to Leproult et al. [12] outcomes exclude the scenario where insufficient sleep served as a precursor to enhance the circadian rhythm phase shift leading to increased insulin resistance in the body. This demonstrates that rational mathematical model construction makes experimental results for non-jet-lag social circadian disruption on insulin resistance more plausible.

2.3 Drugs modulating divergent organs circadian rhythms deformity and attenuating insulin resistance

Referring Ribble et al. [15] and Stenvers et al. [16] graphical and textual conclusions, Figure 1 shows general pathways and components involved in the TTFL and insulin sensitivity across various organs. Due to the conditions for lung deterioration-induced insulin resistance are stringent, and this is a just emerging area of research. Treatment targeting insulin resistance triggered by non-congenital circadian rhythm imbalance still primarily focuses on peripheral organs such as the liver, pancreas, and skeletal muscles. The existing or potential research directions for drug development are as follows:

2.3.1 Gut cells

Gut cells do not have insulin receptors on their own but they transport glucose in humanity circulatory system, downregulating the excessive expression of *Bmal1* gene or *Clock* gene in gut cells to reduce the absorption of glucose in the intestinal lumen and decrease the efficiency of glucose entry into the bloodstream. But traditional drug design is impracticable as a high likelihood of causing malnutrition exist in this way, target protein is necessary.

2.3.2 Pancreatic β -cells

Pancreatic β -cells also do not have insulin receptors, excessive *Bmal1* and *CLOCK* gene expression trigger high

insulin concentration in blood and gradually provokes insulin resistance in liver, skeletal muscles etc., drugs for amending *Cry* or *Per* genes' expression attenuation in pancreatic β -cells, so as positive arm in TTFL initiates normal insulin expression, transcription and secretion level, insulin sensitivity also returns to normal.

2.3.3 Skeletal muscle

Skeletal muscle clock genes intercede insulin sensitivity in more convoluted ways, which involves a series of enzymes including SIRT1 and HDAC3, but all of the pathways collaboratively control an entire metabolic process: GLUT4s are translocated on cellular membrane and transport glucose in cells and finalize its conversion to ATP in mitochondrion. Scientists can develop drugs like Hydrocortisone that can reset the circadian rhythm of genes *Bmal1*, *Per1*, *Per2*, and *Cry2* to normal rhythms [17]. Oppositely, they can design drugs targeting GLUT4 in skeletal muscle cells for correct translocation and appropriate glucose transportation or devise drugs which can penetrate cells membrane and act as catalyst in the metabolic pathways for ATP generation in mitochondria to directly maintain normal insulin sensitivity in skeletal

muscle cells.

2.3.4 Liver

Liver, humanity's biggest detoxification organ, its cells are prone to metabolic issues, TTFL in liver cells not only contain mitochondrion functional fission and fusion but also the coordinator of gluconeogenesis. Crash in liver cells' circadian rhythm clock is usually not caused by independent gene, existing or crafted medication must possess the ability to restore the normal oscillatory cycle of at least TTFL core genes expression in order to take effect. Fortunately, targeting diverse chemical exposures, capsaicin ameliorates [18], ursolic acid [19], and nobiletin [20] regulate the expression levels of multiple circadian genes, re-establishing their cyclic oscillations, especially genes related to TTFL, in addition to their ability to clear free radicals within liver cells and restore their mitochondrial function. Indeed, one drawback exists: nobiletin and capsaicin ameliorates is relied on *Bmal1* regular expression while whether this situation fits in ursolic acid is unidentified. The exploration of treatment options for patients with *Bmal1* defect leading to insulin resistance is a challenging and daunting task.

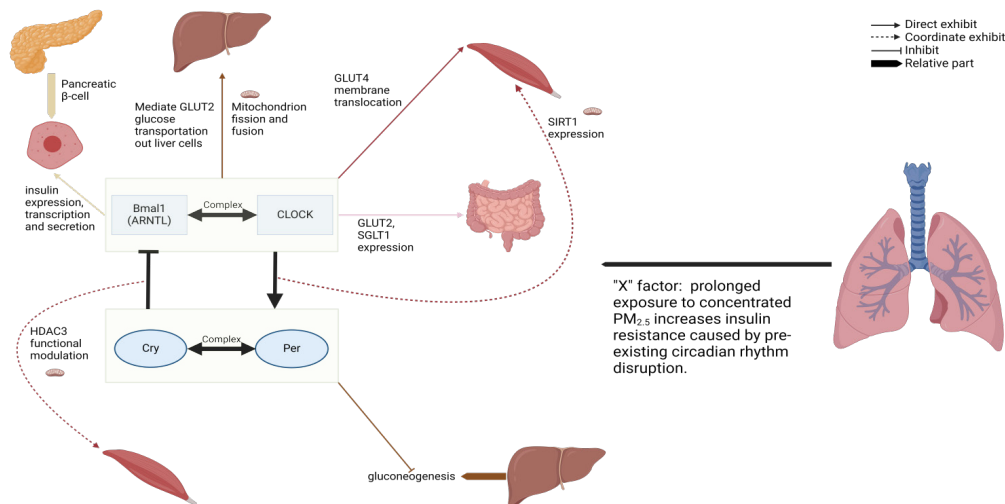


Fig. 1 TTFL genes effects on insulin sensitivity related metabolic pathways in five organs.

Pancreas, liver, gut and skeletal muscles series of physiological activities with biomolecular components maintain standard insulin sensitivity governed by TTFL positive and negative arms genes, lungs serve as catalyst organs for severe insulin resistance if human bodies get long time exposure in concentrated $PM_{2.5}$ with insulin resistance already present. Line legends are shown in the figure. Muscle legend in figure is considered as skeletal muscle. GLUT: Glucose Transporter, SIRT1: Sirtuin 1, SGLT1: Sodium-Glucose Transporter 1, *Bmal1*: Brain and Muscle Arnt-like protein 1, *CLOCK*: Circadian Locomotor Output Cycles Kaput, *Cry*: Cryptochrome, *Per*: Period, HDAC3:

Histone Deacetylase 3

3. Summary

Variations in the genes associated with these clocks can interact with various external factors in complex ways. Notably, a solitary SNP within the central clock's genes can trigger significant disruptions in circadian rhythms without being mitigated by dietary factors. The operation of peripheral clocks can be influenced by an undefined multitude of SNPs, alongside the qualitative and quantitative aspects of dietary intake. The intricate interplay between these genetic variations and non-light related en-

vironmental factors necessitates the adoption of rigorous epidemiological research methodologies. Furthermore, organs pivotal to insulin sensitivity are implicated in diverse manners, underscoring the dual focus in pharmacological innovation on either normalizing the circadian rhythms of relevant organs or addressing cellular defects within organs crucial for insulin and glucose metabolism.

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