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Circadian Rhythm Disruption: A Molecular Link Between Diabetes Mellitus and Neurodegenerative Diseases

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ABSTRACT

Circadian rhythms are the body's natural clock. They regulate numerous physiological functions, including hormonal cycles, metabolic pathways, and immune responses. Proteins like BMAL1, CLOCK, PERIOD (PER), and CRYPTOCHROME (CRY) are in charge of circadian rhythms. They work with the daily cycle of day and night to control insulin levels, keep energy levels stable, fight off free radicals, and start inflammation. But genetic differences, getting older, living an unhealthy lifestyle, and too much time spent in front of screens can all throw this balance off. These types of issues can lead to diabetes mellitus, which causes oxidation, problems with mitochondria, and strange insulin signaling in pancreatic β-cells. This stretches and weakens the nervous system, allowing pathways to diabetes to cross, such as chronic inflammation, possible redox, and mitochondrial dysfunction that cause energy imbalances at the cellular level. This intersection clarifies the heightened incidence of neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), among individuals with diabetes. Evidence supports this correlation, demonstrating that individuals with circadian misalignment—characterized by harmful eating habits and timing, stress, excessive screen exposure, inadequate sleep, and extended working hours—are impacted. Investigations at molecular, cellular, and systemic levels identify circadian disruption as a pivotal link between neurodegeneration and diabetes. By investigating the function of protein molecules within the β-cell and neuronal systems, it clarifies how their dysregulation cultivates a degenerative milieu.

Circadian rhythm, biological clock, CLOCK-BMAL1, PER-CRY, type 2 diabetes mellitus, neurodegeneration, Alzheimer's disease, Parkinson's disease, oxidative stress, mitochondrial dysfunction

1.Introduction

The circadian rhythm, which lasts about 24 hours, is a basic biological process that controls many physiological functions in most living things (Zhang et al., 2014). The suprachiasmatic nucleus (SCN) in the brain is the main pacemaker that keeps this internal clock running. It keeps different parts of the body in sync with the light-dark cycle outside (Panda et al., 2002). The circadian clock functions at the molecular level via intricate interactions among clock genes and proteins that create transcriptional-translational feedback loops, thereby maintaining rhythmic gene expression throughout the organism (Takahashi, 2017). Changes to this fragile system, whether they are caused by genetics, lifestyle choices like shift work, or getting older, can have serious effects on health (Knutsson, 2003). Diabetes Mellitus (DM), a chronic metabolic disorder marked by hyperglycemia, has attained epidemic levels worldwide, impacting millions and presenting a substantial public health challenge (World Health Organization, 2023; International Diabetes Federation, 2023). Predictions indicate a substantial increase in its prevalence in the upcoming years (Institute for Health Metrics and Evaluation, 2023; India Times, 2024). The population of the world is also getting older, which is leading to more neurodegenerative diseases like Alzheimer's Disease (AD) and Parkinson's Disease (PD) (GBD 2019 Dementia Forecasting Collaborators, 2022). There is more and more evidence that these conditions are strongly linked in both an epidemiological and mechanistic way, even though they may not seem related at first. Individuals with Type 2 Diabetes Mellitus (T2DM) exhibit a significantly elevated risk of developing neurodegenerative diseases, indicating the presence of shared pathophysiological mechanisms (PubMed, n.d.). Recent studies indicate that the disruption of circadian rhythms constitutes a significant molecular connection between diabetes mellitus and neurodegenerative disorders. This review aims to elucidate the intricate molecular mechanisms through which circadian dysregulation affects the pathogenesis of diabetes mellitus (DM) and neurodegenerative diseases, highlighting the common pathways and potential therapeutic targets that arise from this relationship.

2.Methodology

2.1.Data extraction.

This review employed a systematic literature search strategy to identify studies examining the relationship between circadian rhythm disruption, type 2 diabetes mellitus (T2DM), and neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). The databases that were searched were PubMed, Scopus, and Web of Science. To make sure it was still relevant, works published between 2000 and 2025 were included.

2.2.Circadia rhythm and its molecular mechanism

A complicated network of molecules that work in opposite ways controls the mammalian circadian clock. This network creates cycles of physiological and gene expression activities that last about 24 hours. The transcription-translation feedback loop (TTFL) is the main part of it. The transcription factors CLOCK (or its paralog NPAS2) and BMAL1 form a heterodimer through the loop to bind DNA at E-box elements and start transcription of the Period (PER1–3) and Crytochrome (CRY1–2) genes (Ko & Takahashi, 2006; Lowrey & Takahashi, 2011). The PER and CRY proteins accumulate in the cytoplasm until they arrive at the nucleus, where they inhibit CLOCK–BMAL1 activity, consequently halting their own transcription. After destruction, repression is lifted, and the cycle starts over, creating 24-hour cycles that last on their own. This core loop works better with accessory regulatory loops. CLOCK–BMAL1 also turns on the nuclear receptors REV-ERBα/β, which stop Bmal1 from being transcribed, and RORα/β/γ, which start it. This creates a second level of feedback (Cho et al., 2012). NFIL3 also has an effect on other transcription factors, like those in the PAR-bZip family. These factors help fine-tune how genes are expressed in tissues over time. Circadian timing is intimately associated with chromatin remodeling and epigenetic regulation, alongside transcription factors. CLOCK possesses intrinsic histone acetyltransferase activity; however, in conjunction with cofactors such as CBP/p300, MLL1, and the deacetylase SIRT1, it modifies chromatin states and facilitates the recruitment of RNA polymerase II (Lowrey & Takahashi, 2011). Genome-wide studies confirm that rhythmic CLOCK, BMAL1, and their repressor binding initiate waves of transcription, thus synchronizing cellular physiology. Circadian proteins are also very important for controlling metabolism. CLOCK and BMAL1 help keep mitochondria healthy and protect them from oxidative stress. PER and CRY help keep redox balance and break down glucose. If these loops don't work right, they can cause oxidative stress, lower insulin secretion, and make it harder to use energy. This illustrates the strong connection between circadian regulation and metabolic homeostasis (Takahashi, 2017; Knutsson, 2003; Panda et al., 2002). The circadian clock also has an effect on nuclear receptors, which are in charge of metabolic pathways. For example, PPARα is a transcription factor that regulates the metabolism of lipids and the oxidation of fatty acids. It has a circadian rhythm and works with CLOCK–BMAL1. Circadian proteins synchronize metabolic processes with the environmental light–dark cycle via these interactions, thereby facilitating optimal nutrient utilization and energy storage (Okabe et al., 2024; Zhang et al., 2013). The circadian system encompasses more than just the master clock in the suprachiasmatic nucleus (SCN). Peripheral clocks in organs like the liver, pancreas, fat tissue, and brain make sure that the activities of certain tissues are in sync with the needs of the whole body. This coordination makes sure that the intake of nutrients, the storage of energy, and the activity of neurons are all perfectly in sync. When central or peripheral clocks are not in sync, the resulting misalignment causes metabolic dysregulation and raises the risk of neurological disease (Videnovic et al., 2014; Zhang et al., 2014)., 2014).

Figure 1 illustartion of circadian cycle

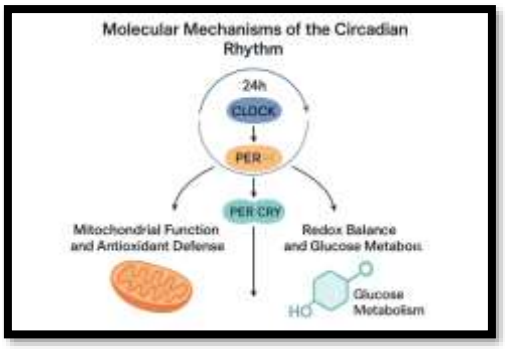

Figure 2 Circadian rhythm:molecular mechanism

2.3. Type 2 diabetes mellaitus:A global trend.

Type 2 diabetes mellitus (T2DM) is presently a considerable and escalating global public health issue. The disorder is marked by insulin resistance, disrupted glucose metabolism, and persistent hyperglycemia, leading to systemic vascular damage, oxidative stress, mitochondrial dysfunction, and low-grade inflammation. These pathological processes not only lead to typical complications in the kidneys, eyes, heart, nerves, and vessels, but they also impact the brain, making it vulnerable to neurodegenerative diseases. Recent epidemiological data shows that there were more than 800 million people with diabetes around the world in 2022. This is more than four times as many as there were in 1990. This means that the disease is spreading more quickly, especially in countries with low and middle incomes. Right now, about 10.5% of adults around the world are thought to have diabetes. If things keep going the way they are, the number of people affected will go up from a few hundred million to more than one billion by 2050, which is what projections say will happen. It's very scary that more than half of people with diabetes don't know they have it or aren't getting treatment. In India, for instance, there were about 212 million people with diabetes in 2022, but almost 62% of them were not getting treatment. Public health officials say that these trends will keep going without stronger preventive steps, like changing how people live, better screening, and fair access to care. This will cause more pain for individuals and more costs for the economy (World Health Organization, 2023; International Diabetes Federation, 2023; Institute for Health Metrics and Evaluation, 2023; India Times, 2024; PubMed, n.d.).

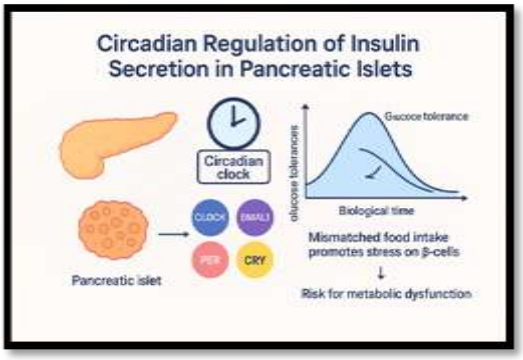

Figure 3 Circadian regulation in daibetes

2.4.Parkinson's diseases.

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of α-synuclein aggregates. It clinically presents with motor symptoms (tremor, rigidity, bradykinesia) and non-motor symptoms including cognitive impairment, depression, and autonomic dysfunction. It is becoming more and more clear that metabolic disorders like T2DM raise the risk of PD and make the disease worse faster. Insulin resistance can interfere with neuronal insulin signaling, worsen oxidative stress and mitochondrial dysfunction, and elevate α-synuclein accumulation. Epidemiological research demonstrates that individuals with Type 2 Diabetes Mellitus (T2DM) undergo expedited motor deterioration, an earlier manifestation of Parkinson's disease dementia, and more pronounced non-motor symptoms relative to those without T2DM. Researchers are testing new treatments that change metabolic pathways, such as GLP-1 receptor agonists, to see if they can protect the brains of people with PD. These treatments might make the disease go slower (PubMed, 2024; The Guardian, 2024).

2.5.Alzheimer's diseases.

Alzheimer's disease (AD) is the most prevalent form of neurodegenerative dementia. Memory loss, cognitive impairment, and the slow death of neurons are all signs of it. The main neuropathological features are extracellular amyloid-β plaques, intracellular neurofibrillary tangles of hyperphosphorylated tau, synaptic dysfunction, and brain atrophy. Type 2 diabetes mellitus markedly affects the vulnerability to and advancement of Alzheimer's disease. In

T2DM, chronic hyperglycemia, insulin resistance, advanced glycation end products, and inflammation disrupt brain glucose homeostasis, hinder mitochondrial function, and promote pathological amyloid-β aggregation and abnormal tau phosphorylation. These processes result in synaptic loss and a swift deterioration of cognitive function. Neuroimaging studies reveal significant hippocampal atrophy, reduced cortical glucose uptake, and various structural and functional impairments in diabetic patients, resembling the pathology of Alzheimer's disease. Clinical or preclinical trials are looking into some antidiabetic drugs, like GLP-1 receptor agonists and maybe others, to see if they can lower amyloid levels, protect neurons, and slow down cognitive decline (PubMed, 2024; Neurology.org, 2023).

2.6.Circadian rhythm disruption leading to diabetes melliatus.

This increase in type 2 diabetes mellitus (T2DM) is a result of changes in modern lifestyles that disrupt natural circadian rhythms. The heightened utilization of artificial light, erratic work schedules, and reduced sleep have rendered circadian rhythm disruption (CRD) the primary etiology of metabolic disease. Both laboratory and population studies indicate that diminished or disrupted sleep swiftly diminishes glucose tolerance and reduces insulin sensitivity (Knutsson, 2003). A regular lack of sleep, even if it's not too bad, can make the sympathetic nervous system too active, raise cortisol levels in the evening, and mess up hormones that control appetite. All of these things can lead to insulin resistance and weight gain. Obstructive sleep apnea, shift work, and "social jet lag" are examples of how sleep patterns that are not working right or are broken can directly raise the risk of diabetes and obesity (Knutsson, 2003). Circadian regulation of metabolism involves the connection of the master clock in the suprachiasmatic nucleus (SCN) with peripheral oscillators located in the pancreas, liver, muscle, and adipose tissue (Panda et al., 2002). These tissue clocks control how much glucose is taken up, how much insulin is released, and how lipids are broken down in a circadian way. Under normal circumstances, insulin sensitivity and glucose tolerance reach their zenith in the morning, whereas efficiency diminishes in the evening. Circadian desynchrony—like eating late at night or working through the night—makes the body metabolize nutrients at times that aren't ideal. This can cause glucolipotoxicity, lipid buildup in the wrong tissues, and stress on pancreatic β-cells (Takahashi, 2017). This correlation is strongly supported by evidence from animal studies: the deletion of central clock genes (CLOCK, BMAL1, PER, or CRY) causes β-cell dysfunction and speeds up the onset of diabetes (Takahashi, 2017). Human genetic studies have also associated polymorphisms in circadian genes with heightened susceptibility to T2DM (Zhang et al., 2014; Zhang et al., 2013). These observations underscore that diabetes is not merely a consequence of caloric imbalance or physical inactivity, but also a condition marked by disrupted biological rhythms.

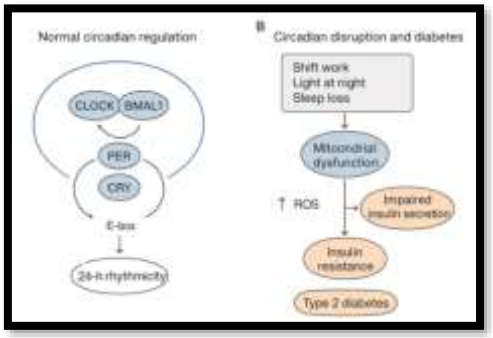

Figure 4 Molecular mechanism:Circadian rhythm disruption leading to diabetes melliatus.

2.7. Circadin rhythm disruption leading to neurodegenration.

At the molecular level, circadian proteins function as central controllers of antioxidant defense, mitochondrial integrity, oxidative stress, chronic inflammation, and mitochondrial dysfunction mount, collectively compromising neuronal health (Videnovic et al., 2014).

- **CLOCK:** Forms a transcriptional complex with BMAL1 to control genes that defend against oxidative stress and maintain mitochondrial metabolism. CLOCK loss of function reduces antioxidant enzyme expression, resulting in an overabundance of reactive oxygen species (ROS), mitochondrial dysfunction, and progressive neuronal damage.
- **BMAL1:** Important for redox homeostasis and mitochondrial biogenesis, as well as in restraining inflammatory signaling in glial cells. Its loss drains glutathione stores, increases oxidative stress, and induces prolonged release of pro-inflammatory cytokines from astrocytes and microglia that generate a toxic environment for neurons.
- **PER proteins (PER1, PER2, PER3):** Regulate mitochondrial respiration and oxidative stress responses. PER2 specifically couples circadian timing to oxygen sensing pathways. Decreased PER activity leads to efficiency loss in energy metabolism, increased ROS, and enhanced susceptibility to apoptosis, eventually compromising synaptic plasticity and cognitive resilience.
- **CRY proteins (CRY1, CRY2):** Inhibit runaway CLOCK–BMAL1 action, support DNA repair, and restrain NF-κB–driven inflammatory cascades. Deficiency in CRY reduces antioxidant protection and provokes hyperactivation of immune pathways in glial cells and resulting chronic neuroinflammation and neuronal degeneration

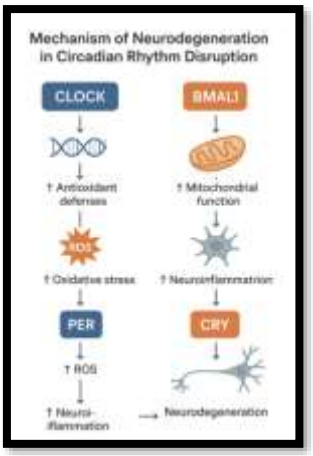

Figure 5 Mechanism of neurodegenration in Circadain rhythm disruption

3.Result.

3.1. Linking the traid: circadian rhythmn disruption-diabetes-neurodegenration.

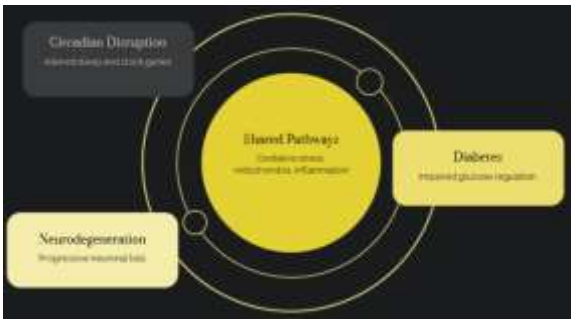

Figure 6 Shared pathways of diabetes and neurodegenration in circadain disruption

Circadian rhythms coordinate cellular and systemic functions by synchronizing central and peripheral clocks with the external light-dark cycle. When things like shift work, not getting enough sleep, or not eating on a regular basis throw off these rhythms, the metabolic and neuronal systems get out of sync, which can cause long-term health problems. Circadian disruption in metabolism impedes the temporal regulation of insulin sensitivity, glucose uptake, and β-cell functionality. Insulin secretion and glucose tolerance are typically maximized in the morning; however, desynchrony compels nutrient processing to occur during suboptimal phases, leading to glucolipotoxicity, β-cell stress, and systemic insulin resistance. Experimental data indicate that the elimination of core clock proteins (CLOCK, BMAL1, PER, CRY) expedites oxidative stress, mitochondrial dysfunction, and β-cell failure, consequently heightening vulnerability to type 2 diabetes mellitus (Takahashi, 2017; Knutsson, 2003; Panda et al., 2002; Zhang et al., 2013). Analogous molecular anomalies are evident in the nervous system. CLOCK and BMAL1 help the mitochondria work properly and protect against oxidative damage. On the other hand, PER and CRY control how the body reacts to stress and how it balances oxidative stress. Their disruption leads to the buildup of reactive oxygen species (ROS), damage to mitochondria, and overactivity of glial inflammatory pathways. Consequently, neurons undergo oxidative damage, impaired synaptic plasticity, and chronic neuroinflammation—pathological features of Alzheimer's, Parkinson's, and associated neurodegenerative disorders (Videnovic et al., 2014). .

These pathways together identify a common mechanism:

- **Circadian misalignment** → impaired CLOCK/BMAL1/PER/CRY function.
- **Metabolic consequence** → β-cell dysfunction, insulin resistance, and hyperglycemia.
- **Neurological consequence** → oxidative stress, glial activation, and neuronal death.

Therefore, circadian disruption is a unifying upstream driver that links diabetes and neurodegeneration. The restoration of circadian alignment by lifestyle adjustment (sleep regularity, timed feeding, light exposure) or pharmacological targeting of clock proteins presents a dual therapeutic approach: enhancing glycemic control while slowing or preventing neurodegenerative decline.

4.Discussion.

Circadian rhythm disorder (CRD) is a common cause of diabetes and neurodegenerative diseases. When clock center proteins (CLOCK, BMAL1, PER, CRY) don't work right, it hurts the mitochondria, the body's defenses against free radicals, and the body's ability to keep its metabolism in sync. This results in oxidative stress, inflammation, and inadequate insulin secretion (Takahashi, 2017; Knutsson, 2003; Panda et al., 2002; Zhang et al., 2013; Zhang et al., 2014). The same processes that change the way synapses work and cause neuroinflammation also link metabolic problems to cognitive problems (Videnovic et al., 2014; Panda et al., 2002). Epidemiological studies substantiate this by demonstrating that shift workers have an increased likelihood of developing diabetes, and that individuals with diabetes are more prone to Alzheimer's and Parkinson's diseases (Videnovic et al., 2014). Treatments that restore circadian synchrony—such as sleep maximization, temporal feeding, light exposure, and chronotherapy—provide dual benefits for metabolic and neurological health (Okabe et al., 2024; Zhang et al., 2014). Subsequent investigations must integrate molecular insights with clinical results. Comprehensive human studies utilizing wearable sensors, continuous glucose monitoring, and neuroimaging are imperative for the real-time tracking of circadian rhythms. Clinical trials of clock-modulating drugs (REV-ERB agonists, ROR modulators, SIRT1 activators) are essential to evaluate their effectiveness in postponing metabolic decline and neurodegeneration (Takahashi, 2017). Furthermore, interdisciplinary tools that integrate chronobiology, endocrinology, and neuroscience will be essential for formulating personalized chronomedicine strategies customized to individual circadian profiles. In conclusion, circadian rhythm disruption (CRD) is not merely an adjunct to lifestyle but a contributing factor in chronic disease; therefore, circadian regulation signifies a potential therapeutic target for the preservation of both metabolic and cognitive function.

5.Conclusion.

Circadian rhythms are a natural biological system that connects outside stimuli with inside physiological processes. Their dysfunction disrupts glucose homeostasis and β-cell function, while concurrently intensifying oxidative stress, inflammation, and neuronal damage, thereby establishing a connection between diabetes and neurodegenerative diseases. The convergence of these processes establishes circadian misalignment as a principal causative factor of chronic disease, rather than a mere secondary consequence of modern lifestyle. This viewpoint introduces innovative therapeutic strategies: readjusting circadian alignment via lifestyle alterations, pharmacological treatments, and chronotherapy may improve glycemic control while concurrently slowing neurodegenerative advancement. Subsequent research will concentrate on converting mechanistic insights into clinical applications, employing real-time monitoring and personalized chronomedicine to enhance outcomes in both metabolic and neurological fields. Therefore, circadian biology ought to be considered a therapeutic target, rather than merely a background element, for the comprehensive management of diabetes and neurodegenerative disorders."

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