Vol 10 | Issue 1 | 2020 | 7-19.

e-ISSN 2248 - 9169
Print ISSN 2248 - 9150

International Journal of
Experimental Pharmacology

www.ijepjournal.com

ROLE OF CIRCADIAN RHYTHM ON PATHOPHYSIOLOGY OF TYPE II DIABETIES MELLITUS

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ABSTRACT

Circadian rhythms are synchronized according to internal biological clocks related to the sleep cycle. This cycle is coordinated by the suprachiasmatic nucleus and controls important biological processes, including sleep-wake cycle, hormone secretion, body temperature regulation, feeding/energy homeostasis and cell-cycle regulation. Clock gene is an essential regulator of circadian rhythms. These clocks composed of autoregulatory transcription/translation feedback loops of the expression of central clock gene especially CLOCK and BMAL-1. Disruption of these clock gene leads to various metabolic disorders such as obesity and Type II diabetes mellitus. Various factor such as molecular, physiological and behavioral level affect the Type II diabetes mellitus.

Keywords: Circadian rhythm, clock gene, diabetes mellitus, CLOCK, BMAL-1 gene.

INTRODUCTION

Every living creature are directed by the 24-hrs light and dark cycle delivered by earth rotation. Rhythms are found from unicellular to multicellular organisms in plants, animal, and humans. Mammalian body is described by a complex time structure of biological rhythms, which is a basic component of homeostasis. Biological rhythm is a regular variation in biophysical or biochemical processes with time, happening in an anticipated way. The most studied rhythm is the one which has a period of approximately 24hrs, known as circadian rhythm. The environmental factors that keep up the periodicity of a biological rhythm are the light-dark, sleep-activity and of feeding-fasting periods [1]. The first scientific observation of circadian rhythm was made in 1729 by the French astronomer Jean Jacques d'Ortous de Mairan, who set the Mimosa plant in a light tight dark room and saw that the plant kept on unfold its leaves in the morning and close them at evening [2,3]. Circadian rhythms (Latin, circa: approximate; dies: day) refer to physiological process that happen with a repeating time of approximately 24 h and ensure that internal physiology is synchronized with the external environment [4,5]. These rhythms are known to control significant biological processes, including sleep-wake cycle, hormone secretion, body temperature regulation, feeding/energy homeostasis, and cell-cycle regulation [6].

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Mechanism of Circadian timing system

The suprachiasmatic nucleus was demonstrated to be required for every day rhythms in both animal and human behavior [7].The circadian timing system is made out of a central clock in the suprachiasmatic nucleus (SCN) situated in the hypothalamus of the brain and peripheral clocks in other brain areas and peripheral tissues all throughout the body, including muscle, adipose tissue and liver [8]. SCN gets input pathways for light and other stimuli that are significant in the synchronization of the pacemaker to the earth; output rhythms are in turn regulated by the pacemaker [9]. Direct (retinohypothalamic) and indirect (retinogeniculate) photic information to the SCN

originates from the retina [10]. Retinohypothalamic photic information begins from the ganglion cells of the retina (which contain melanopsin, and are viewed as the essential photoreceptors for the circadian system), nonphotic information originates from the raphe nuclei, while different afferents originate from the pons, medulla, basal forebrain and posterior hypothalamus [9]. In any case, non-photic prompts, for example, social interaction, nourishment, or exercise can also serve as Zeitgebers that change or reset the timing of the clock. These Zeitgebers give input to the SCN, which at that point forms the information and, through complex neurological pathways, eventually impacts behavioural, hormonal, and biochemical yields that synchronize peripheral tissues to central timing.

Suprachiasmatic Nucleus

The master circadian clock

The SCN is a bilateral structure comprising of thousands of neurons (45,000–50,000 in people and ~20,000 in rodents) that is situated in the anterior hypothalamus directly on top the optic chiasm and next to the third ventricle. Circadian clocks are entrain by both photic and non-photic signals [11]. SCN controls the daily rhythm in sleep-wake behavior [12,13] by means of its associations with hypothalamic area, for example, sub paraventricular zone, the ventrolateral preoptic area and the dorsomedial hypothalamus [14].The central clock is answerable for the circadian regulation of multiple components of energy expenditure, for example, the sleep-wake cycle[12,13] diet-induced thermogenesis[15], resting energy expenditure.

The circadian timing system

The circadian timing system is composed of a central clock in the suprachiasmatic nucleus (SCN) located in the hypothalamus of the brain and peripheral clocks in other brain areas and peripheral tissues. The circadian rhythms in these clocks are generated by a molecular transcriptional- translational feedback loop. The light signal, reaching the SCN via the retina and the retinohypothalamic tract, is the most important Zeitgeber for the SCN. The SCN synchronizes peripheral clocks through neural, endocrine, temperature and behavioral signals. BAT, brown adipose tissue; WAT, white adipose tissue (shown in figure 1).

Molecular mechanism of the circadian clock

Core clock additives are genes whose protein products are necessary for the generation and regulation of circadian rhythms within individual cells throughout the organism. Circadian rhythms are determined genetically with the aid of a core set of clock genes, inclusive of three Per genes (the period homolog 1 gene, Per1; the period homolog 2 gene, Per2; the period homolog 3 gene, Per3), the circadian locomotor output cycles kaput gene, clock; the cycle gene, BMAL-1, and two plant cryptochrome gene homologs (the cryptochrome 1 gene, cry1 and the cryptochrome 2 gene, cry 2) [17]. Those genes and their product interact to form transcription-translation feedback loops that offer the molecular basis of circadian rhythmicity. Throughout the day, clock interacts with bmal-1 to activate transcription of the Per and Cry genes, ensuing in excessive ranges of those transcripts. Per-Cry proteins translocate to the nucleus and inhibit clock-bmal1-mediated transcription. At some point of the night time, the Per-Cry repressor complex is degraded, and the cycle begins again (Figure: 2). Circadian clock genes control a significant share of the genome. It is predicted that about 10% of all expressed genes are under regulation of the clock genes. Moreover, peripheral tissues comprise independent clocks. It's likely that peripheral clocks are synchronized by an input directly from the SCN or SCN mediated messages. Several first-rate critiques are available for extra precise evaluation of the molecular regulation of the circadian system [18,19].

Diabetes Mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. It may be due to impaired insulin secretion, resistance to peripheral actions of insulin, or both. According to the International Diabetes Federation (IDF), approximately 415 million adults between the ages of 20 to 79 years had diabetes mellitus in 2015. DM is proving to be a global public health burden as this number is expected to rise to another 200 million by 2040 [20]. Chronic hyperglycemia in synergy with the other metabolic aberrations in patients with diabetes mellitus can cause damage to various organ systems, leading to the development of disabling and life-threatening health complications, most prominent of which are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications leading to a 2-fold to a 4-fold increased risk of cardiovascular diseases. It is well known that some individuals are genetically prone to the disease, and studies have shown that a disrupted sleep/ wake cycle can increase an individual's chance of developing diabetes. Insulin is secreted in a predictable daily (i.e., circadian) pattern from the pancreas, and a functional biological clock is necessary for proper insulin release. In addition, studies have shown that diabetes affects some the genes which regulate the circadian rhythm, such as period, clock, and bmal1.

Pancreas

The pancreas releases insulin in a daily rhythm, i.e., in a circadian pattern [21]. The pancreatic clock is synchronized to the light–dark cycle [22] by means of signs got from the central brain clock in the SCN that incorporate autonomic neuronal signs [23] melatonin release glucocorticoid release and changes in body temperature [24,25]. CLOCK and BMAL1 initiate the transcription of genes associated with insulin biosynthesis, insulin transport

and glucose-stimulated insulin secretion [26] (Figure: 4). Disruption of the pancreatic clock causes inadequate insulin secretion [27, 28]. Studies have additionally demonstrated that diabetes influences basic qualities, which direct the circadian rhythm, such as, "clock", "bmal1" and "period" [29]. The lack of a functioning pancreatic circadian rhythm prompts adjusted insulin secretion by the beta cells of the islets of Langerhans, which are basic for glucose homeostasis [30]. One of the most notable approaches to research a circadian rhythm is through analysing the sleep wake cycle. Physiological and behavioral alteration have been recorded in mice and people who experience a disrupted sleep cycle. Annoyances to this cycle lead to an increase in appetite, weight gain and increased chances of developing type 2 diabetes [31].

Circadian Rhythms and Type II Diabetes

Role of circadian clock in diabetes is whether disruption of CLOCK or BMAL1 directly prompts metabolic imperfections or whether the cause is indirect related to clock function [32,33]. Disruption of the clock genes or clock system is directly associated with the development of diabetes. In addition to unusual patterns of sleep, unusual eating behavior, for example, skipping breakfast and late-night eating related with shift work or other way of life-style interruptions of the day-night cycle [34].

Circadian Disruption and Insulin Resistance

Circadian disruption and insulin resistance can be explained by Epidemiological studies & Experimental studies in humans, shown in Table no: 1.

Molecular Level

Clock Gene Polymorphisms

All cells in the body are directed by clock gene system as per the day-night cycle. Disruption of clock gene influences both locomotor action and feeding behavior and might indirectly change metabolism. Human mutations in a few clock genes add to the genetic susceptibility to obesity and type II diabetes. Observational investigations have indicated relationship between single nucleotide polymorphisms in ARNTL1 [35], CLOCK, BMAL-1, CRY2 development of diabetes. A few examiners investigated a gene behavior interaction and indicated that interaction between diet and clock gene mutation influence fasting glucose [51], insulin resistance, body weight [52].

Behaviorual level

Effects of light

Light gives the principle contribution to the SCN, and streamlining of day by day light presentation can therefore increase circadian synchrony [53]. Our modern lifestyle is characterized by diminished light exposure during the day and increase light exposure during the night. These way of lifestyle changes have significant impact on the arrangement of our circadian timing system to the solar day. In animal models, show that dim light around night time disturbs diurnal rhythms of nourishment consumption and locomotor behavior, causing obesity and decreased glucose tolerance in mice. Observational studies in humans shows exposure to light around night with obesity and type II diabetes mellitus.

MELATONIN

Melatonin is a tryptophan-derived indoleamine which is essentially secreted by the pineal gland, with contributions from various different tissues including the retina, bone marrow, gastrointestinal tract, skin, ovary and placenta [54,55].The extra-pineal contribution to melatonin production is little when compared with secretion from the pineal organ; with suggestions that it is just activated by some particular impulses[56]. Melatonin secretion is regulated by the central circadian clock, as well as by seasonal variations in length of daylight. The maximum plasma concentration peak around 2AM, with very low concentration during the day. role of melatonin signalling in the pathophysiology of type II diabetes, decreased melatonin levels and polymorphisms in melatonin receptor (MTNR1B) have been related with diabetes risk. Increased pancreatic beta cell melatonin signalling may reduce insulin secretion in human.

Melatonin receptors (MT1 and MT2) have been seen to be available in rat [57-59] and human [60,61] pancreatic islets. The expression of these receptors likewise differs with the circadian rhythm and feeding status [62]. In people, a few hereditary examinations have related MT2 receptor polymorphisms with an increased risk of developing T2DM [63]. Associations between single nucleotide polymorphisms that are arranged near (or inside) the gene that encodes MT2 (MTNR1B), and an increased risk of developing T2DM [64], diminished B-cell function [65] and impaired glycemic control [66,67] have all been accounted for in companions of various districts and ethnicities. Studies have likewise exhibited an increase in the expression of MT1 and MT2 receptors in the pancreases of diabetic rodents and in subjects with T2DM[68].In rodents, melatonin has been appeared to manage blood glucose concentration through its capacity to bind directly to melatonin receptors on hepatocytes[69] and regulate the uptake of glucose in adipocytes, by adjusting the expression of the glucose take-up transporter[70].Low melatonin secretion is also independently connected with a higher risk of developing T2DM; an association that further builds up the role of melatonin in glucose metabolism and insulin sensitivity [71].

Table 1. Circadian disruption and insulin resistance

Epidemiological studies in Humans	Experimental studies in Humans
Clock gene polymorphisms {ARNTL [35], CLOCK [36], CRY2}	Diet-Clock gene mutation interaction [44-46]
Light at night [37],	Ambient light [47]
Reduced or Increased Melatonin signalling	Melatonin [48]
Short or long sleep [38,39]	Sleep restriction & Sleep disruption [49]
Evening Chronotype [40]	Circadian misalignment [50]
Social jet lag [41,42]	
Shift work [43]	

Table 2. Blood glucose level regulating hormones

Hormones increasing the blood glucose Level	Hormones decreasing the blood glucose level
Growth hormone	Insulin
Catecholamines	Glucose dependent insulinotropic polypeptide
Glucagon	Glucagon like peptide-1
Glucocorticosteroids	
Thyroid hormones (T3, T4)	
Pancreatic peptide	

Table 3. Comparison between Dawn & Somogyi Phenomenon

Comparison	Dawn phenomenon	Somogyi phenomenon
Definition	Recurring early hyperglycemia	Early morning hyperglycemia due to treatment with excessive amount of exogenous insulin
Causes	Decrease of insulin secretion between 3AM-5AM, Increase of Insulin antagonistic hormones	Nocturnal hypoglycemia due to excessive dose of insulin, Next early morning hyperglycemia due to increase of Insulin antagonistic hormones

Figure:1 The circadian timing system

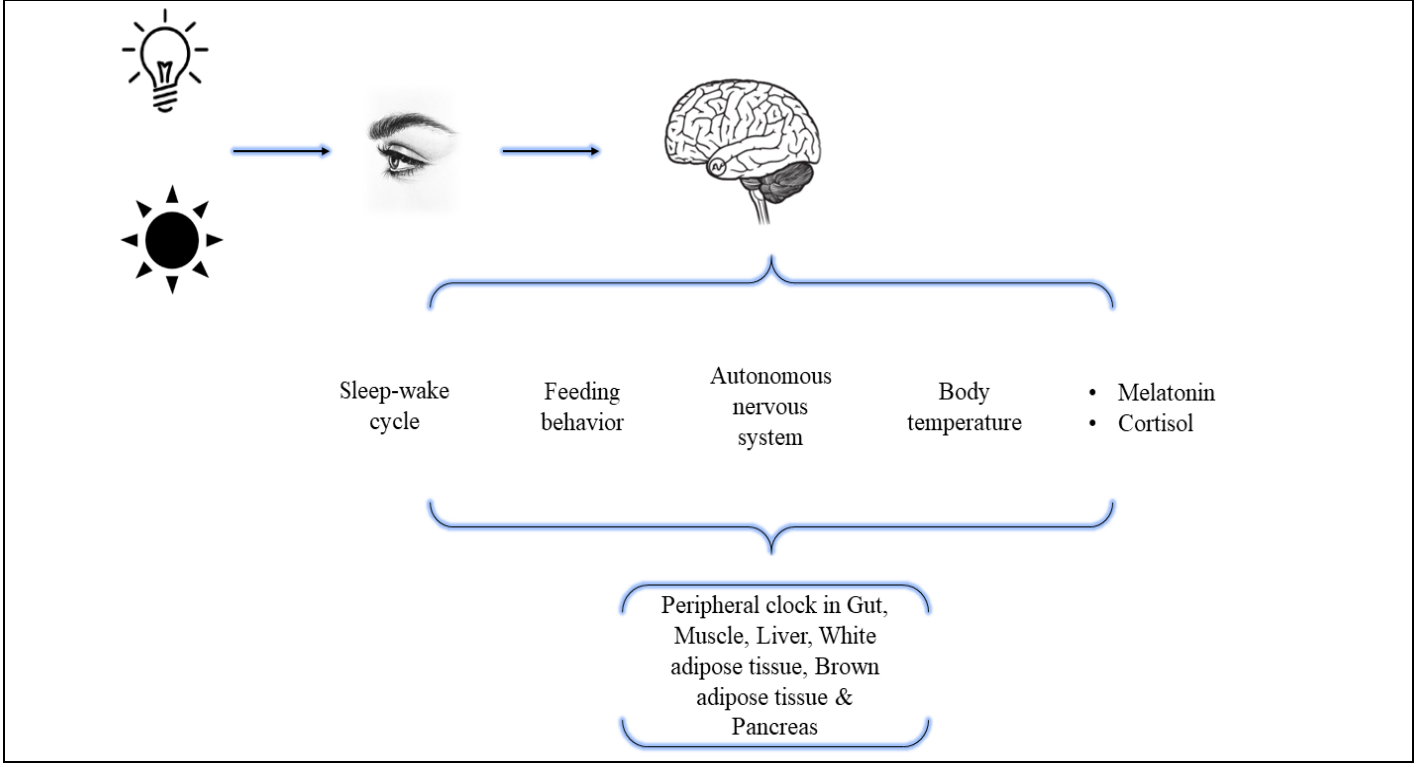


Figure 2: Simplified representation of the transcription cycle

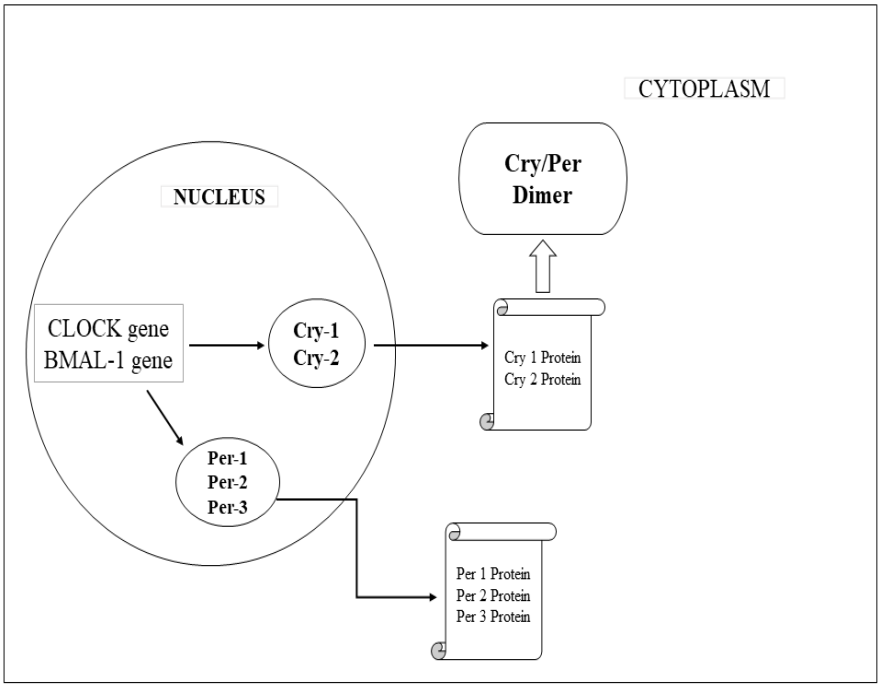


Figure: 3 Pathophysiology of type II diabetes mellitus

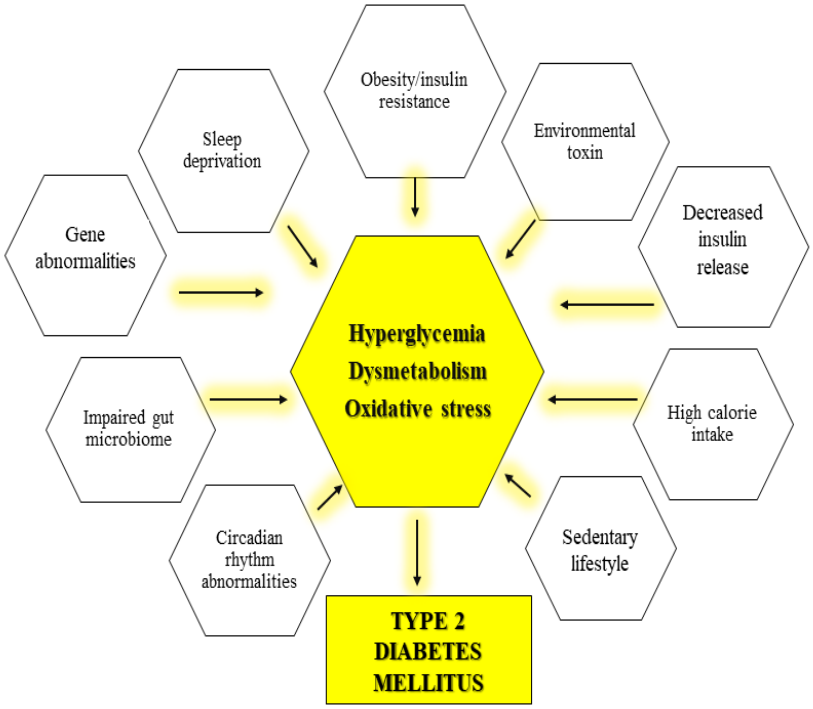


Figure: 4 The pancreas clock. In the pancreas, CLOCK and BMAL-1 activate the transcription of genes involved in insulin biosynthesis, insulin transport and glucose-stimulated insulin secretion. All depicted processes show circadian rhythmicity. GLUT-Glucose transporter, VOCC- Voltage-dependent calcium channel

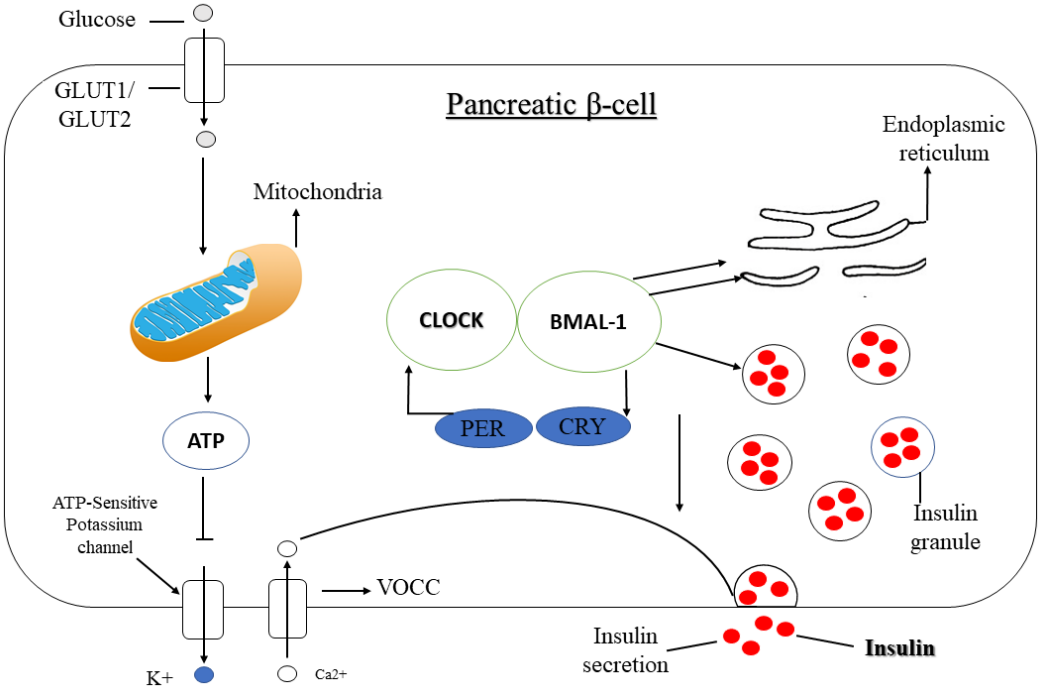


Figure: 5 Molecular, Physiological & Behavioral factors that may affect the development of type 2 diabetes mellitus

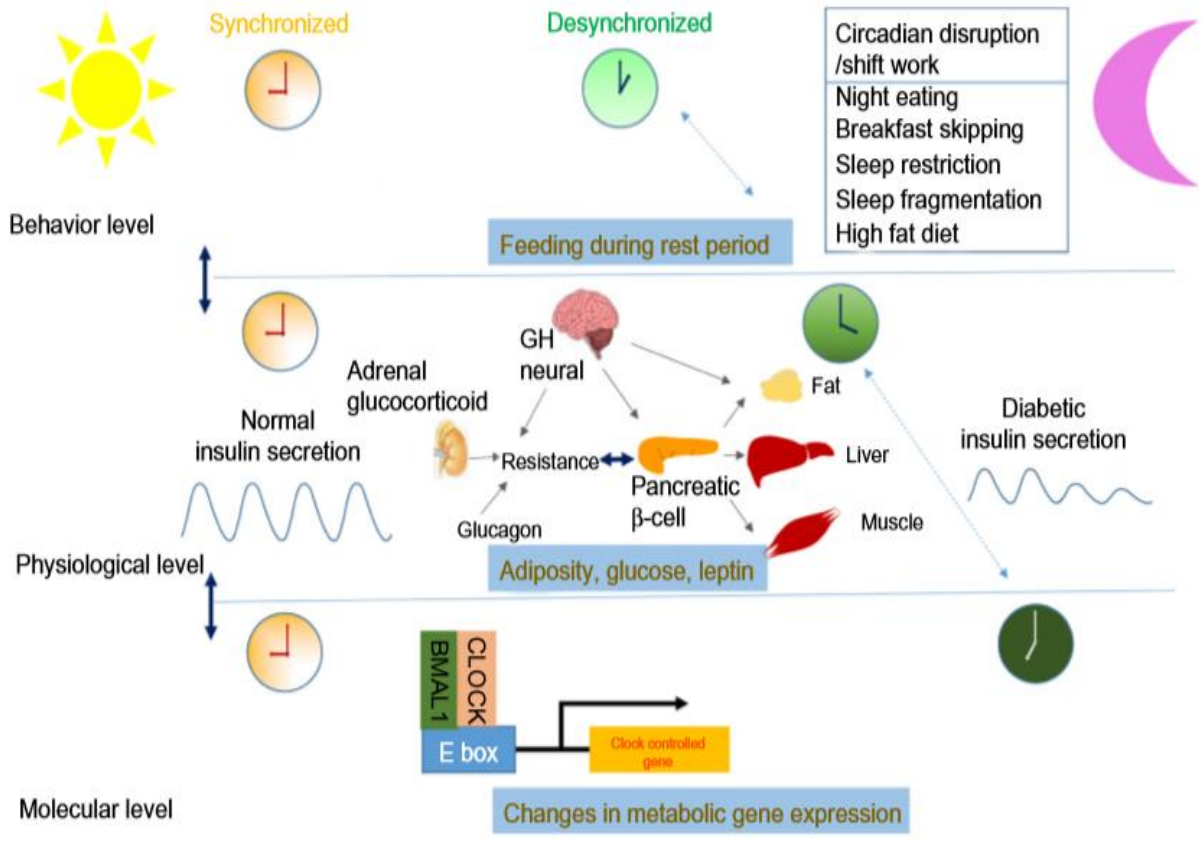


Figure: 6 The role of Melatonin in the development of type 2 diabetes

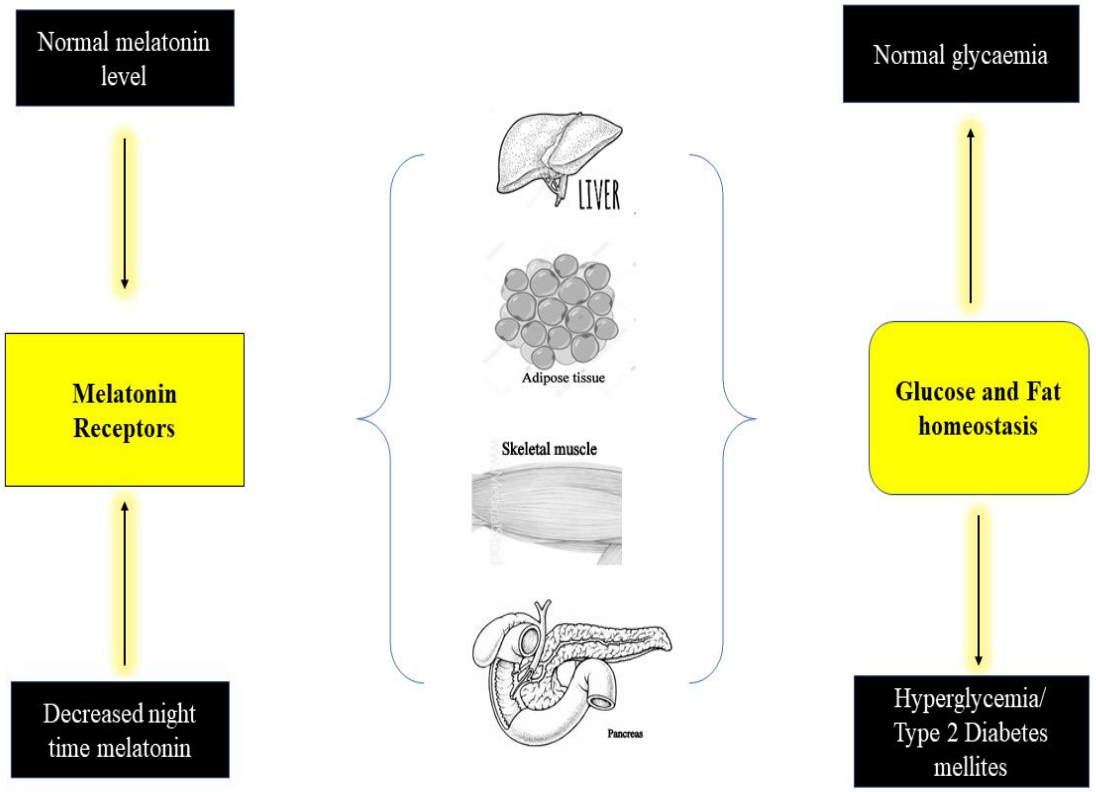


Figure: 7 Insulin and glucose daily biorhythm

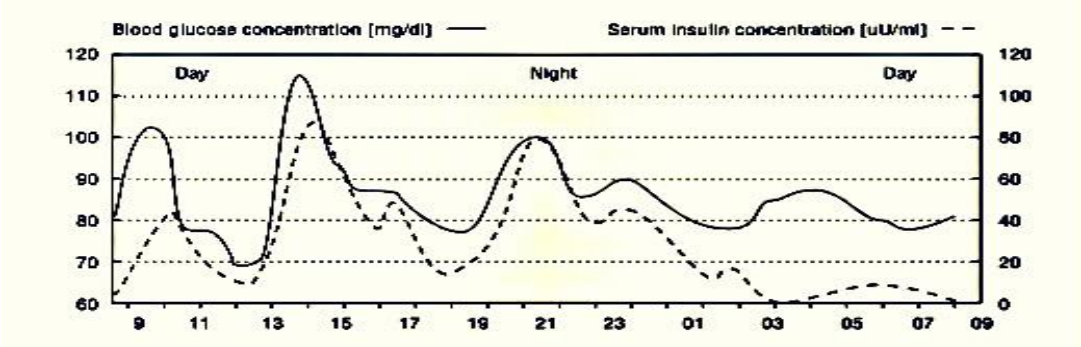
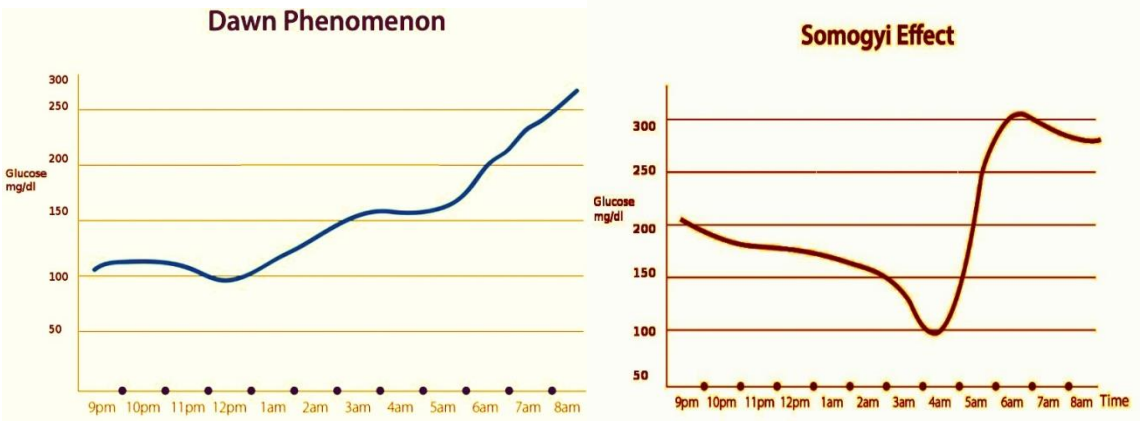


Figure: 8 Comparison between Dawn & Somogyi Phenomenon



Sleep-Wake Rhythms

The significance of an appropriate sleep cycle is fundamental for glucose homeostasis, since sleep permits the body to re-establish proper metabolic and hormonal (i.e., insulin) forms. Sleep disorder (short duration/poor quality sleep) impact on the development type II diabetes and obesity. Disturbed sleep-wake cycle is regularly connected with a light stage. In human that the molecular clock is connected with sleep [72, 73], in familial advanced sleep phase disorder. This abnormal disorder is characterized by early sleep time and early morning arousing [74] Recent examination on sleep restriction, with significant sleepiness, impairment of psychomotor performance, and increased secretion of proinflammatory cytokines, for example, interleukin (IL-6) and tumour necrosis factor alpha (TNF-alpha) which induce insulin resistance [75]**.** Proof from both epidemiological and experimental studies shows that behavioral sleep-wake rhythms influence the risk of developing insulin resistance. Studies shows that people who rest for short periods and the individuals who rest for long period are at increased risk of developing type II diabetes. General understanding that poor sleep quality increases the risk of obesity and type II diabetes [76]. People with obstructive sleep apnoea are at increased risk of developing type II diabetes, which could be mediated by increased food admission and decreased physical activity among different components ups mechanism disturbed sleep [77]. Experimental studies under controlled condition affirmed diminished liver, fat, entire body insulin sensitivity because of sleep restriction to 4-6hrs per night [78]. Impact of sleep restriction and sleep disturbance influence on insulin sensitivity incorporate a changed sympatho-vagal balance and increased circulating levels of catecholamines or cortisol.

Chronotype & Social Jet Lag

Chronotype is characterized by biological markers, for example, sleep-wake cycle, body temperature, cortisol and melatonin. Two kind of chronotype MT, ET, [79]. Evening chronotypes are at increased risk of developing type II diabetes compared with morning chronotypes. Evening chronotype who are working normal daytime hours are at increased risk of social jet lack. Social jet lack is the impact of fighting your body's regular circadian rhythms by sleeping short nights during the week and sleeping late on the end of the week which is related with the development of type II diabetes [80].

Shift Work

Most examinations group shift laborers as those who consistently work outside the usual daytime shift hours [81]. Shift work is thought to be related with a few health problems, for example, metabolic disorder, diabetes mellitus and result of impaired biological circadian rhythms [82]. Shift laborers are at increased risk of developing type II diabetes. Risk of type II diabetes may be mediated by a mix of acute and chronic effects. Experimental circadian misalignment under carefully controlled condition acutely diminishes glucose tolerance and insulin sensitivity both in non-shift laborers and chronic shift laborers. Animal studies shows that repeated phase shifts cause increased food consumption, increased body weight and disturbed glucose metabolism [83]. Night shift laborers additionally have essentially diminished melatonin levels band raised cortisol levels, which have been shown to increase and suppress leptin, respectively. Several examines exhibit that sleep restriction in healthy people brings about changed circulating levels of leptin, and it is believed that loss of neurohormonal control of hunger and energy balance could be a contributing factor to the weight gain (though only partially due to overeating) related with circadian disturbance and shift work.

Eating Behaviours [84]

In a population-based investigation of teenagers and their parents, breakfast skipping was essentially connected with high BMI, in young people as well as in their parents. Breakfast skipping is unequivocally connected with obesity and risk for type II diabetes. Other eating disorder, for example, late evening eating condition is additionally firmly connected with obesity, which emphatically influences the clinical result of type II diabetes and increasingly diabetic complications. Night eating behavior is related with obesity, higher glycated haemoglobin, and progressively diabetic complications.

Physiological Level

In typical people, blood glucose and insulin levels in response to an oral glucose load vary over 24 h, with lower glucose response and higher insulin levels occurring in the morning, regardless of fasting duration, bringing about increased glucose tolerance in the morning compared to evening [85,86]. The theoretical reasons for this variety incorporate diminished night time glucose usage, low late-day insulin secretion, and neurohormonal control of cortisol and other regulatory hormones [87]. Obese patients with type 2 diabetes were appeared to have an altered rhythm of glucose tolerance and insulin sensitivity, with increased sensitivity in the evening and night compared to morning [88,89]. An extra outcome of type 2 diabetes is known as the " dawn phenomenon ", whereby typical early morning release of counterregulatory hormones (for example, cortisol, growth hormone and epinephrine that capacity to oppose insulin and mobilize glucose) may cause increased blood glucose levels just before waking [90,91].The reversed rhythm of insulin sensitivity in these patients might be the reason for the raised fasting blood glucose levels saw in the dawn phenomenon. Further investigation of the detrimental impacts of glucose and insulin intolerance on normal functional peripheral rhythms will be important to give better treatments to type 2 diabetes. The main hormone which diminishes the plasma glucose level is

the pancreatic beta cells product, insulin. Insulin synthesis and release is affected by high plasma glucose levels, which are the strongest stimulus for insulin secretion.

Hyperglycemia may also result from insulin resistance, despite hyperinsulinemia and increased levels of insulin-antagonistic hormones, normally counteracted by proper insulin secretion in type 2 diabetes. Bowen and Moorhouse Fasting hyperglycemia is a phenomenon observed in almost all individuals with diabetes, and may be caused by a dysregulation of the normal circadian hormonal patterns resulting in increased hepatic glucose output. Morning hyperglycemia can have three causes the dawn phenomenon, the Somogyi effect, and insufficient insulin supply.

Dawn Phenomenon [92]

Repeating abnormally high plasma glucose levels in morning before breakfast are generally called the dawn phenomenon. As indicated by the everyday insulin discharge profile set out in **Figure 7**. The dawn phenomenon can be separated into two types: physiological and pathological. The two types happen simultaneously of the day for example between 3 a.m. and, 5 a.m., however vary in the estimation of plasma glucose levels. The physiological dawn phenomenon is related with a natural decrease of insulin secretion between 3 a.m. also, 5 a.m. combined with elevation of blood glucose level staying up to standard. This diminishing of insulin secretion unblocks the secretion of insulin-antagonistic hormones with hyperglycemic properties, especially GH. The morning plasma glucose level development in non-diabetic individuals with undisturbed insulin secretion is remunerated by a burst of insulin. Thus, diabetic patients may encounter the pathological dawn phenomenon, where the morning plasma glucose level is anomalous high because of insulin secretion disturbance and impacts of night time GH secretion. The dawn phenomenon is a combination of an initial decrease in insulin requirements among 3 a.m, followed by an increase in the insulin needs between around 5 a.m. furthermore, 8 a.m. In this way, the dawn phenomenon can happen among the two individuals with type 1 and type 2 diabetes mellitus with deterioration of beta cells work and without insulin treatment. The decrease of endogenous insulin causes the absence of adequate restraint of insulin-antagonist hormones secretion, for the most part GH, cortisol and catecholamines and prompts hyperglycemia. Because of impaired function of pancreas beta cells, there is additionally a lacking insulin secretion response to hyperglycemia which causes long-acting hyperglycemia, recognized by patients subsequent awakening as the dawn phenomenon.

Somogyi Phaenomenon

The Somogyi effect, otherwise called the " chronic Somogyi rebound," or "post hypoglycemic hyperglycemia," was a hypothesis proposed during the 1930s by Dr. Michael Somogyi, who was a Hungarian-conceived educator at Washington University, St. Louis, MO, United States [92]. He described the paradoxical tendency of the body to respond to hypoglycemia by producing hyperglycemia. Somogyi proposed, that when blood glucose levels drop excessively low during the late evening, initiation of counterregulatory hormones, for example, adrenaline, corticosteroids, growth hormone, and glucagon may be observed, prompting activation of gluconeogenesis and resultant hyperglycemia in the early morning [93]. The Somogyi phenomenon expresses that early morning hyperglycemia happens because of a rebound effect from late-night hypoglycemia.

CONCLUSION

In the current review, we attempted to gain insight into pathophysiological mechanism underlying the predisposition to Type 2 DM following exposure to circadian misalignment. At the point when circadian systems are disrupted by different environmental or genetic defects, dysfunction of different physiological process can occur. A common reason of human circadian disorder is misalignment between the environmental rhythm (e.g., light–night cycle) and the endogenous circadian oscillators. As appeared above, evidence that gives new understanding into clock function and the pathophysiology of type 2 diabetes. Disruption of circadian rhythms, by molecular, physiological and behavior levels prompts different metabolic disorders, for example, obesity and type 2 diabetes mellitus. Since the extent of these impacts in the current increase found in the development of type 2 diabetes is obscure, progressively exact mechanism and the general significance of these variables in the development of type 2 diabetes ought to be investigated. To accomplish this objective, it will be important to set up techniques to quantify parameters of circadian system in feeding and glucose and lipid metabolism. Furthermore, it is additionally important to analyse the contribution of circadian gene variations in the development of type 2 diabetes. According to the currently available information, diabetes patients ought to be warned about breakfast skipping and late-night eating disorder in their diabetes training. In spite of the fact that it is extremely hard to control these behaviors for each individual patient with type 2 diabetes, a socio-economical methodology, for example, suggestions in regards to the work environment may also be significant. Despite the fact that there is presently insufficient evidence to assess the effect of these chronophysiological disruptions on the progression or pathophysiology of diabetes absolutely, future concentrated research on these issues can respond to these inquiries.

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