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Circadian rhythm disruption, Shift work and its Metabolic impact

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Abstract. Shift work has an irreplaceable role in many companies and posts, however the negative health impacts are ineluctable, so it is worthy to clarify the possible influence that can post on the metabolism and therefore causing dangerous disorders. The relationship between the shift work and circadian rhythm including the master clock (SCN) and peripheral clock in the tissue and the external environment is researched, in the meantime the various effects are also mentioned. The main focus was on the metabolism, contending that glucose and lipid metabolism has affected by the changes of the circadian rhythm and potential consequences like diabetes and obesity might emerge. Additionally, insulin sensitivity drops as the circadian phases' shifts, with accompanied by the risk of type 2 diabetes. Other effects like influences on the hormone secretion and functioning does also shows relationships with metabolic rhythms, for instance the melatonin reduction can leads several diseases. With the clear understanding of these relationships further clinical studies show be able to utilize the mechanisms and produce therapeutic interventions.

Keywords: Shift work, circadian disturbance, metabolic impact.

1. Introduction

The cyclical rotation of the Earth has led to the alternating periods of sunrise and sunset, creating a converging trend for the organisms to develop a 'clock' inside them to determine their activities according to the light-dark cycle. This clock take part in the suprachiasmatic nucleus (SCN) located in the hypothalamus, which help synchronize the body's internal clock with the environment. Mammals' transcriptional autoregulatory feedback loop, which is made up of the transcriptional activators CLOCK and BMAL1 as well as their target genes Period and Cryptochrome, produces cell autonomous circadian clocks. These elements accumulate rhythmically to form a repressor complex, which then interacts with CLOCK-BMAL1 to inhibit their own transcription.

The importance of maintaining a normal circadian rhythm on metabolism is well-documented in several scientific studies, especially in various metabolic processes including the insulin activity, fat storage and appetite. It is evident that insulin activity is highly adjusted according to the circadian rhythm, for instance during the day time when the body is activated and requires more energy the insulin sensitivity is relatively high, while vice versa [1].Moreover, the time for consuming food in a day is particular important in maintaining metabolic health, since late time eating is associated with higher blood glucose level [2].

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While in today's modern society, shift workers are highly demanded, especially in the hospitality, manufacturing, transport and policing industries. Approximately 20% of workers in the world are engaged in shift work in some form [3], it is design to ensure the services and production processed to work around the clock.

Night shift works can direct lead to circadian rhythm disturbance including changes in the sleep wake schedule caused by artificial light entrainment, consumption of food at inappropriate times etc. A mismatch could emerge between the center and peripheral clocks contributed to disorders include metabolic disease, fatigue and sleep disturbance [4]. In molecular level, studies in human transcriptome demonstrates that night shift works would affects the majority of transcripts into chaotic rhythms instead of adapting to the night shift schedule [5]. While early research utilizing forced desynchrony technique showed comparable outcomes, circadian disruption resulted in a 6-fold drop in circadian transcripts when compared to sleeping in phase with the melatonin rhythm. [4].

Shift workers are required to change their schedules abruptly due to various rotating shift and non-standard hours. So, adipocyte hypertrophy, fatty liver, abnormal lipid profile, hypoinsulinaemia, hyperglycaemia and obesity are the metabolic syndromes that shown in the experiments in the rodents which have disrupted circadian clock genes [6]. Alike studies were established on humans with circadian disruption, a straightforward causal relationship between circadian disruption and the metabolic syndrome has been confirmed such that low levels of melatonin secretion—caused by circadian disruption, is linked with the reduction of insulin sensitivity, type 2 diabetes mellitus and obesity [7]. Additionally, when sleeping duration in workdays is far less than in free days is considered as another category of jet lag which is widely observed on students named 'social jet leg'. It contributes to higher risks of cardiovascular disorder and adverse endocrine [8]. So, it is valuable to get fully understand of the influences due to the disrupted circadian rhythm on the metabolome, and address the possible clinical implications.

2. Impact of Shift Work on Circadian Rhythms

Our endogenous circadian timing system influences every section in our body, which includes our biological behaviours, molecular processes and physiological parameters. So, shift work might influence a person in every facet via the circadian clock.

2.1. Disruption of the Master Clock

Light is significantly crucial to the entrainment of the central clock. With the absence of the environmental light-dark signals, the center clock can function approximately identical with the collection of clock gene, produce and sustain the circadian rhythm. The transcriptional auto-regulated feedback loops make up the molecular clockwork's core. It is easier to synchronize tissue activities and behaviors with the day/night cycles when using the most potent circadian rhythm modulator, the retinal ganglion cell, which detects photonic inputs and transduces them to the SCN. In an experiment of studying phase shift on the fruit flies shown that when expose to 600 lux of light during the midnight (around 11p.m in the subjective circadian time), the phase response curve(PRC) have witness a maximum 4 hour delay on the circadian rhythm; whereas when receiving similar amount of light at early morning approximately 4 hours of advancements might emerge [9]. This data demonstrates that shift-workers who often expose to both artificial light and natural sunlight can lead to chaos in their circadian phase shift.

2.2. Desynchronization of Peripheral Clocks

The peripheral clocks are not as durable as the centre clocks to maintain, after a few days in vitro, the oscillations seen in peripheral tissues often subside at the tissue level, albeit not always at the level of individual cells [10- 11].However, some rhythmic activities oscillate on cycles of feeding and fasting other than the light-dark cycle, which are the nutrient-sensitive hormones. Meanwhile, desynchrony occurred between most of the peripheral clocks, for instance in at least 12 hours sampling of the shift

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work model studies, scalp hair follicle cells have a 2 h delay, oral mucosa cells encountered a 11h delay, peripheral blood mononuclear cells were appeared to have a 3.17h postpone and etc [4].

2.3. Misalignment between master and peripheral clocks

Studies demonstrates that misalignment not merely emerge between the circadian clock and the environment, also this relationship bridged between the centre and peripheral clocks. The findings of Boivin DB et al illustrates that after three days on a night-oriented schedule, the expression of the PER1, PER2, PER3, and BMAL1 clock genes desynchronized from the sleep-wake cycle and from each other in a controlled laboratory setting [4]. The misalignments decreased the rhythmically expressed transcripts and the amplitude of hormones to secrete [4].

2.4. Acute vs. Chronic Effects of shift work

Obviously, various affects were posted on the night-shift workers, some are straightforward while others might be chronical. Sleep disturbance, cognition impairment and mood change are acute impacts that can be observed on the people who has circadian disorder. Night shift workers, in particular, may lose up to 4 hours of sleep per day compared to those on a regular schedule which is caused by excessive daytime sleepiness and difficulty maintaining alertness during work hours. Besides, degrade of cognitive function, including impaired decision-making and slower reaction times would show up. By contrast, the chronic effects consist of altering glucose metabolism and manifesting of the diabetogenic state in humans. The disrupted system of shown more significant postprandial glucose rise after the same meal, caused by the decrease of the insulin sensitivity. Nonetheless, chronic effects also manifests on the psychological level, surveys in South Koreans have compared the people who have major depressive disorder(MDD) among the night shift-workers and within the normal workers, in around 4000 workers the prevalence of the normal daytime employees was significantly lower than the night shift workers [12]. Symptoms of circadian disruption and MDD are alike as both include non-rhythmic sleep-wake cycle (decreased latency to rapid eye movement sleep, concurrent with increased rapid eye movement sleep and reduced slow wave sleep), alternations of body temperature, changes of hormone rhythms and social rhythms [13]. Clinical studies have illustrated relationships between the severity of MDD and the degree of circadian misalignment to be highly correlated [14].

2.5. Other effect

The disrupted sleep and circadian rhythms are related to anxiety, bipolar disorders, and schizophrenia. For the relationship between anxiety, mood change is associated sleep disturbances instead of the circadian rhythm, with research supported [15]. While rapid switching from normal rhythm to rotate shift work have no indication of their correlations in nurses [16]. Additionally, the relationships of the other 2 mental disorders are either weak or with unclear nature.

3. Metabolic Impact of Circadian Rhythm Disruption in Shift Work

As the demand for shift work continues to rise in modern society, increasing research attention has been focused on the adverse health effects associated with night shifts. Shift work can cause a disruption in the circadian rhythm, which can have a significant impact on metabolic processes and increase the risk of metabolic disorders and related diseases. Examining the health effects of shift work requires an understanding of the connection between metabolism and the biological clock.

3.1. Circadian Regulation of Metabolic Processes

As the demand for shift work continues to rise in modern society, increasing research attention has been focused on the adverse health effects associated with night shifts. Disruption of the natural circadian rhythm due to shift work can have profound effects on metabolic processes, heightening the risk of metabolic disorders and related diseases. Understanding the relationship between the biological clock and metabolism is crucial for exploring the health implications of shift work. When the master clock is entrained, the central rhythm synchronizes with the peripheral clocks in various body cells, including

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those in organs like liver and pancreas. While desynchronization often emerge in the night-shift workers according to the previous finding, so reasonable assumptions may state that shift-work can be one of the possible ethology that contributes to the metabolic disorders and metabolite syndrome [17].

3.1.1. Glucose metabolism

Meta-analysis and large databases have demonstrated a significant correlation between obesity rates and shiftwork, shift workers had a higher possibility of developing abdominal obesity than other obesity types [18]. And researchers have found clear evidence linking type 2 diabetes to sleep disorders [19-20], This is supported by findings that night shift work is associated with poorer glycemic control in the people with type 2 diabetes with the measurements of haemoglobin A1c level in their blood samples [21].

The specific mechanism of how the glucose level is altered and affected by the clock gene misalignments is further explained with the introduction of insulin resistance and glucose tolerance, the insulin sensitivity is discussed later. For glucose tolerability, findings shows that healthy adults have blood glucose level peak at morning while the nadir is at around 19:00 when glycemic control is at its weakest. In obese and diabetic individuals, circadian rhythms are attenuated or phase-delayed, suggesting that altered circadian rhythms may be both a cause and a consequence of various metabolic diseases. [22].

Metabolic disturbances are not solely caused by the misalignment of circadian rhythm but partially rely on the duration and quality of sleep. As previously mentioned, sleep deprivation has found to be a factor that contributes to the extra consumption of calories. However, this is not the merely effect that sleep has, the variation of glucose tolerance does hinges to the sleep-wake cycle, since brain is the major site that demanded on numerous of glucose for energy. During sleeping even though fasting, the glucose level remains or decrease with a minor amount, thus, indicated that there is a mechanism to maintain the plasma glucose concentration in order to prevent a similar occurrence of decrease of glucose level in the wake state. Meanwhile, the drop of glucose utility during the night causes a likewise fall in the glucose tolerance but its level retrieved at the morning. These effects shows that sleep loss have detrimental consequences to our endocrine systems and metabolic functions [23].

3.1.2. Lipid metabolism

Many rodent studies have demonstrated that lipid metabolism is regulated by the circadian rhythm, while minor studies show this relationship in human. Studies is divided due to the different category of lipid it is examined—diurnal findings of cholesterol and its subcomponents have discovered controversial results; agreements have reached on the diurnal rhythm of the triglycerides despite the stages of the rhythm [24- 25]. Other species of lipids are also researched on their rhythms, the circadian rhythm may be one of the driving force of the lipid transportation, absorption, and division, since it is not confirmed on human (only with animal protocol [26]). On the other hand, besides the diurnal studies, circadian studies explained a greater proportion of the lipids having a rhythm compared to other metabolites. Brown SA.'s paper illustrates that the majority of the plasma metabolites which expressed rhythmically are lipids, while peaking at the period during the late morning to noon [27]. Besides, a research obtained from young adults' blood sample shows around one eight of the lipid species observed with rhythmic oscillation in the whole, however, several distinctions within individual emerge on the amplitude of the and the phase of the lipid rhythms [28].Circadian rhythm is apparently to be the most effective factor in regulating the lipid metabolites among others whereas a few contract results have been also obtained. It is now known that circadian disruption has a pathogenic role in metabolic illnesses, such as obesity, type 2 diabetes, and metabolic syndrome.

3.1.3. Insulin sensitivity

Likewise with the glucose tolerance level, the insulin sensitivity reaches its crest at morning and falls to nadir at night, with strong diurnal variations in insulin-mediated inhibition of endogenous glucose production. In studies of mice that has lesioned SCN, the primary cause of the modified insulin

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sensitivity is endogenous glucose production rather than blood glucose clearance, yet data interpretation may be hampered by the greater body weight of SCN-lesioned mice. Meanwhile, clarified causal relationship has been found that continuous light entrainment disrupts the SCN neural firing rhythm which subsequently effects the insulin sensitivity [1]. The sensitivity of insulin is also affected by a neurotoxin, which is the tetrodotoxin, via injection; however, injection at paraventricular nucleus (PVN) has shown ineffectiveness, indicating that the insulin sensitivity's diurnal cycle is explained by PVN-independent processes. The rhythmic insulin sensitivity is abolished without the BMAL1 gene on mice, so it is heavily related to the circadian rhythm [29]. The natural rhythm of the insulin sensitive tissue can be disturbed to cause insulin resistance and obesity [29].

3.2. Circadian Regulation of Hormone

Our body secretes numerous numbers of hormones in order to regulate, adjust and supervise the biological reactions and processes which are essential to us. To be specific, melatonin and cortisol are 2 hormones made by the pineal gland and heavily involved in forming circadian rhythms and influencing our energy metabolism.

3.2.1. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a crucial factor to regulate the diabetogenic syndrome which consists of glucose tolerance and insulin sensitivity throughout the body. It emphasizes the role of melatonin in the therapy of circadian disruptions, supportive findings proved when knocking off the melatonin receptors (MT1 and MT2), metabolic syndromes appeared. The glucose tolerance and insulin resistance are associated with melatonin on a molecular level—pathways and related gene expressions, additionally, highlighting the functional synergy between melatonin and insulin, it was demonstrated that melatonin activates the β-subunit of the insulin receptor's tyrosine kinase and induces rapid tyrosine phosphorylation, as well as activating several intracellular transduction steps of the insulin-signalling pathway [30- 31]. The first direct relationship demonstrated was about 3 decades ago, done by Lima FB et al. Parkinson's disease and Alzheimer's disease are two pathologic conditions involving the nervous system that have been linked to dysfunction in melatonin release or synthesis. Decreased melatonin has also been linked to several malignancies, depression, myocardial infarction, atopic dermatitis, and other dermatological, mental, cardiovascular, and genitourinary conditions.

3.2.2. Leptin and Ghrelin

Leptin and ghrelin are 2 antagonist hormones, responsible for altering the appetite via boosting and retraining hunger respectively. Prior to regular mealtimes, ghrelin levels rise, and then it falls. Reports discovered that ghrelin level become inertia when experiencing sleep deprivation; also, in a study with a 28 hour per day protocol, the measurement made on the plasma leptin level witnessed a 17% decrease in its circadian phase [32- 33]. Which indicates that circadian rhythm does affects the scale of appetite and the appearing time. To be exact, when only sleep for 4 hours, participant exhibits an 18% decrease in leptin, 24% increase in ghrelin, 24% increase in hunger, and 23% increase in appetite [34]. These figures suggest that more energy is consumed when experiencing sleep deprivations.

4. Conclusion

Shift work has found to have numerous effects on the circadian rhythm by alternating the sleep quality and duration, including the acute mood influence and chronic metabolic and mental impacts. The most severe consequences occupied by metabolism dysfunction which consist of the type 2 diabetes, obesity, insulin resistance and associated metabolic syndromes. Glucose and lipid metabolic pathways are heavily hinges on the circadian oscillation in the cell, plus the type 2 diabetes correlated to insulin sensitivity that is related to SCN neural firing rhythms while hormone secretion indirectly changes the metabolism. Future research should focus on practical clinical applications, aiming to mitigate the adverse effects of shift work through optimized schedules and early detection of metabolic disorders.

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