



Chrononutrition and Melatonin – A Comprehensive Review

Gargi Bose*

Department of Nutrition, Ramananda College, Bishnupur, Bankura, West Bengal, India

***Corresponding Author:** Gargi Bose, Department of Nutrition, Ramananda College, Bishnupur, Bankura, West Bengal, India.

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Abstract

Chrononutrition primarily investigates how meal timing influences the human circadian clock. The central circadian clock, as well as the peripheral clocks, regulate the sleep-wake cycle, metabolic processes and energy balance in human body. Melatonin, the pineal hormone is responsible for the maintenance of the circadian clock and plays a crucial role in human metabolism. Disruption of chronobiological regulation of metabolism can potentially give rise to serious consequences and plethora of non-communicable diseases (NCDs). This paper explores the intricate interplay between chrononutrition and melatonin and its implications for circadian rhythm regulation and metabolic health.

Keywords: Chrononutrition; Melatonin; Circadian Rhythm; Chronodisruption; Circadian Entrainment

Introduction

Chrononutrition is a relatively new concept in the field of food science and nutrition. Chrononutrition is emerging as a field that correlate the meal timing with the circadian rhythm of the human body and analyse the effects thereof. It mainly focuses on the influence of the timing of food intake on different physiological processes, including metabolism, energy balance, and sleep-wake cycles. Melatonin a hormone, is responsible for the maintenance of the human biological clock, is secreted only during dark phase of the human circadian cycle. Melatonin is suggested to play a crucial role in the circadian health and metabolic effects in health and diseases [1-6]. Therefore, it may be implicated in chrononutrition. This paper explores the intricate interplay between chrononutrition and melatonin, and consequently, the circadian rhythm and metabolic health.

Biological clock and circadian rhythm

The word “circadian” derives from the Latin words “circum”, meaning around, and “diem”, meaning day. Therefore, circadian rhythm refers to the natural process that regulates the sleep-wake cycle and repeats every 24 hours. This rhythm controls a myriad of physiological and behavioural functions and regulates the sleep cycle, body temperature, metabolic activities, secretion of hormones, and the diurnal variations in their levels in blood. The circadian rhythm is not unique to humans; however, it is a fundamental aspect of human biology that helps the being adapt to the changes in its environment. The central circadian clock of humans is located in the hypothalamus in the suprachiasmatic nucleus (SCN). There are peripheral clocks located in other organs, such as the liver, heart, pancreas, and gut. These peripheral clocks are synchronized with the SCN to maintain the circadian rhythm [7-11]. Genes as well as nutrition play an important role in regulating

the functions of these body clocks. However, melatonin, a hormone, secreted from the pineal gland only during the dark phase of the light-dark cycle, is also an established regulatory factor for the circadian clock [12,13].

Significance of circadian rhythm and chrononutrition

The circadian rhythm regulates a plethora of physiological functions in the human body. Regulating the sleep-wake cycle is the most obvious function of the biological clock. Melatonin, the sleep-inducing hormone, is directly related to the functioning of circadian rhythms. On the other hand, cortisol, another hormone related to the wakefulness and stress response of the organism, also shows similar relationships. However, apart from these specific hormones, various other chemicals of the body exhibit diurnal variation and a circadian pattern. Most important among them are the hormones regulating hunger and satiety, such as ghrelin, leptin, and insulin. These hormones that control the feeding behaviour and subsequent metabolism in the organism show time-dependent variations in secretions and levels in blood and other tissues. It has long been observed that well-regulated eating habits are a prerequisite for good overall health. The SCN is sensitive to exposure to natural light through the retina. So, any disturbances or interference can disrupt the circadian rhythm. This phenomenon, also known as chronodisruption, can occur due to shift work, jet lag, irregularities in sleep, or excessive exposure to artificial light at night, etc. The circadian rhythm indicates that usually the body is not ready for digestion or metabolism of heavy meals at certain times, linking metabolic health to the chronology of nutrient intake [14-16]. Therefore, with the advent of time, chrononutrition has gained importance in human health. However, chronodisruption can have far-fetched effects such as impaired glucose tolerance, insulin resistance, and overall impairment of metabolism leading to complex disease conditions including obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) [17-21].

Circadian regulation of metabolism and melatonin

The circadian clock is regulated by a transcriptional-translational feedback loop mechanism. The positive feedback elements of this transcriptional loop involve CLOCK and BMAL1, while three PERIOD (PER1, PER2, and PER3) proteins put negative feedback on the activity of the CLOCK-BMAL1 dimer [22,23].

The time of day when meals are taken trains the peripheral clocks, and therefore, directly affects obesity and metabolic disease.

Studies show that nocturnal mice fed on a high-fat diet during their resting phase, i.e., daytime, gained significant weight as compared to those fed on the same diet during the active phase. Thus, it can be proposed that alignment of meal times with the circadian clock can result in better utilisation and storage of nutrients and metabolites and can emerge as an effective strategy to prevent metabolic disorders [24,25].

The hormone melatonin plays a pivotal role in the regulation of circadian rhythm and has been shown to regulate the downstream regulation of metabolites in the cellular environment according to the light/dark cycle [5].

N-acetyl-5-methoxytryptamine or melatonin is a highly evolutionarily conserved molecule secreted by the cells of the pineal gland only during the dark phase of the light/dark cycle. This hormone is synthesized from tryptophan. The regulatory enzyme of the melatonin synthesis pathway, arylalkylamine N-acetyltransferase (AA-NAT), is upregulated by the release of norepinephrine at night, and, therefore, synthesis and secretion of melatonin exhibit a strong circadian pattern, peaking typically between 2:00am and 4:00am in humans [26]. Light from any source on the retina during night halts norepinephrine release and consequently disrupts the synthesis and secretion of melatonin. The SCN, which governs the circadian clock, regulates the rhythm of melatonin production. The “clock genes” in the SCN, namely, CLOCK, BMAL1, PER, and CRY drive the AA-NAT transcription, stimulating melatonin synthesis. Melatonin enters a feedback loop whereby it provides a positive signal to the peripheral clocks and even re-enters the SCN to reinforce circadian phase. Melatonin, therefore, acts as a chronobiotic (circadian clock marker) which is capable of shifting biological rhythms [12,13].

Chrononutrition: Meal timing and circadian entrainment

Chrononutrition recognizes that feeding is a powerful tool for the entrainment of the peripheral biological clocks. Eating at the wrong times can misalign the biological clock and the metabolic hormones. Food intake during night, which is the natural dark phase of humans, has been found to decrease glucose tolerance even if the total calorie intake remains the same. Evolutionarily, the nocturnal melatonin surge coincides with fasting, and eating late at night disrupts this. Alternatively, bright light at night suppresses melatonin and causes alterations in leptin and ghrelin metabolisms such that hunger is favoured [27-29]. Studies have

found that exogenous melatonin administration before the evening meal can increase circulating leptin and reduce hunger in humans, suggesting that melatonin plays a pivotal role in signalling satiety during overnight fasting. The loss of this signal can contribute to unregulated eating and adiposity [30-35].

Animal studies have reported that external melatonin administration during the dark phase exerts a positive effect on body weight regulation and fat homeostasis. It has been found that high-fat diet (HFD) fed mice treated with nightly melatonin doses accumulated less visceral fat and body weight as compared to their counterparts only fed on a high-fat diet. This goes on to prove that melatonin is effective irrespective of dietary preferences in regulating fat accumulation, improving insulin sensitivity, and protecting from hepatic steatosis [36-38].

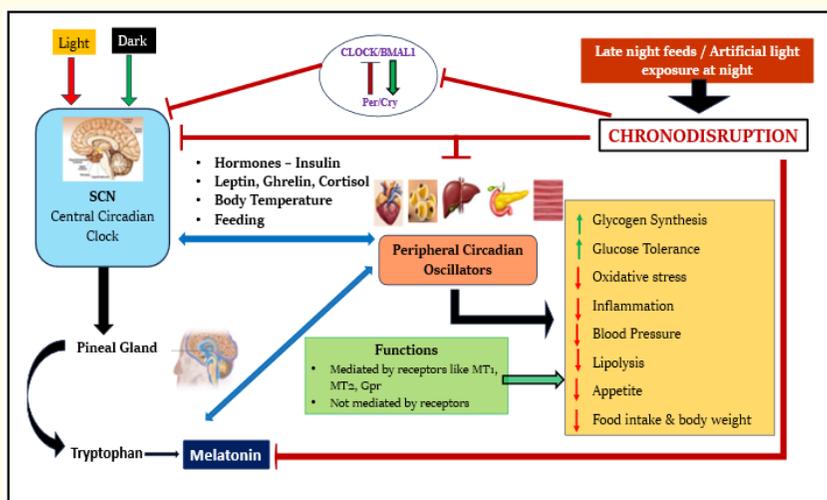


Figure 1: The regulation of Central Circadian Clock situated in suprachiasmatic nucleus (SCN) and the peripheral circadian clocks by the pineal hormone melatonin, its effects on cellular metabolism and dysregulations due to factors of chronodisruption.

Melatonin exerts its effects through the high-affinity G-protein-coupled receptors MT1 and MT2, which, in turn, activate many intracellular cascades of metabolism. These receptors are expressed in the SCN in the hypothalamus and also in peripheral tissues. The thermogenic effects of melatonin have been found to primarily depend on increased fat oxidation via elevated levels of FGF21 and AMPK phosphorylation. However, many studies have also reported that it stimulates adiponectin and UCP1 expression, enhancing brown fat thermogenesis [39-42].

Misalignment of circadian rhythm can be manifested in pinealectomized rodents, which have no endogenous melatonin. It has been found in a study using such animals that the nocturnal feeding rhythm is lost and, due to improper metabolic regulation,

the rodents become obese if food is available ad libitum, while exogenous melatonin treatment successfully reversed the phenotype [43]. Other studies have reported that forced feeding during the rest phase aggravated metabolic syndrome while increasing the chances of adiposity and NAFLD in studied animals.

Recently, the research in human chrononutrition is increasing, and the involvement of melatonin is being evaluated. Epidemiological data already support that disruption of the day-night cycle in humans due to shift-work, lifestyle choices, and light pollution are contributing to growing rates of obesity and insulin resistance, ultimately resulting in metabolic syndrome. Melatonin, as a potential regulator for controlling appetite in humans, is currently being investigated. Few studies have reported

that melatonin supplementation at night led to better metabolic regulation and modest weight loss. However, supplementation of melatonin in overweight night shift workers chronically exposed to light during the rest phase failed to produce any desirable changes. A recent meta-analysis of available data showed that melatonin administration caused a significant reduction in body weight in adults as compared to placebo, while variable results were observed for BMI and waist circumference. Overall, it is found from different studies that melatonin can be potentially used to improve lipid profile, insulin sensitivity, and hepatic steatosis in humans with metabolic syndrome [44-47].

Conclusion

Research in this field is in a nascent stage and all the results may not be consistent as per timing, dosage and/or formulation of melatonin. A more curated approach integrating regular meal timings, managing exposure to light during biological night and melatonin supplementation as a chronobiotic may improve circadian realignment and provide a positive direction in controlling glucose regulation and weight gain in future.

Declaration of Conflict of Interest

The author reports no conflict of interest.

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