Interaction between Mealtime and Circadian Hormones

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Achieving synchronization between the central and peripheral body clocks is essential for ensuring optimal metabolic function. Meal timing is an emerging field of research that investigates the influence of eating patterns on our circadian rhythm, metabolism, and overall health.

Keywords: dawn ; melatonin ; clock genes ; metabolic health ; glucose control ; dinner ; cortisol

1. Introduction

Metabolic disorders have a substantial impact on a large population worldwide, leading to decreased quality of life, increased healthcare utilization, and shortened life expectancy [1]. Numerous risk factors contribute to an increased susceptibility to metabolic diseases, necessitating a systematic approach to comprehend these factors. The timing of fasting/feeding, mealtimes, circadian rhythm, and sleep, as well as the complex interplay between these elements, may exert influence on the circadian rhythms of various organs and cells within the body, particularly when food intake occurs at inappropriate intervals relative to the body's circadian clock [2].

In humans and mammals, the internal circadian timing system synchronizes with the 24-h light–dark cycle by receiving light signals that reach a central clock in the hypothalamus [3]. The circadian rhythm, an endogenous timekeeping system, is crucial in regulating various physiological processes in the human body. This biological clock is responsible for maintaining a 24-h cycle that influences the timing of sleep, metabolism, body temperature, and hormone secretion, and the internal clock was for centuries synchronized with mealtimes at specific periods. Moreover, the circadian rhythm and meal timing mutually interact; virtually all mouse models with diet-induced dysmetabolism exhibit disrupted feeding patterns, frequently marked by the absence of specific mealtimes and the dispersion of caloric consumption across both day and night [4].

The widespread availability of electrical lighting has increased nocturnal activities and granted humans the ability to personally select their light–dark cycles and prolong wakefulness activities well into the night [5]. This ability to modify the timing of wakefulness can lead to a misalignment between the external (environmental) and internal circadian physiology [6]. Disharmony in circadian rhythms can compromise the functioning of these organs and impact the overall metabolic systems in the body [7] and has been correlated with adverse health outcomes, including diminished energy metabolism [8], impaired glucose metabolism [9], and heightened risk of cardiovascular disease [10].

Furthermore, consuming meals during nighttime hours can disrupt sleep latency, duration, and quality [7]. Insufficient sleep duration and poor sleep quality are established risk factors for metabolic diseases [7]. Additionally, emerging evidence has indicated a connection between eating patterns, mealtimes, and metabolic health in humans [11]. Current evidence from animal studies [12] and human research [13] suggests that consuming food during periods typically allocated for sleep can lead to increased weight and detrimental metabolic health. Groups prone to shifting their activities to later hours, like night or rotating shift workers, or some young people, such as teenagers and college students who stay awake at night, also exhibit a higher prevalence of weight gain and obesity [14]. Numerous circadian events occurring at dawn have been observed in humans, including changes in blood glucose, insulin sensitivity, and hormone levels (such as cortisol), as well as heightened activity in the autonomic nervous system [15][16], which could be linked to early morning meals.

2. A Brief History of Meal Timings

Meal timing has witnessed changes in different cultures over time [17][18][19][20]. Moreover, religion may have an impact as well on mealtimes. The timing of meals during the Middle Ages was shaped by the presence of daylight. In a time without electricity, people would rise earlier to utilize natural light for a range of tasks, including meal preparation and eating [21]. Due to the absence of electricity, the option to cook dinner in the evening was not available. Peasants had their main meal around midday, although it was a considerably simpler and less extravagant event [21]. Ancient traditional Chinese

Medicine, practiced for over 2500 years, suggests that the ideal time for carbohydrate-rich meals is between 0700 and 1100, with smaller meals recommended later in the day during the transition from an active phase (“yang”) to a resting phase (“yin”) [17][22]. This practice is rooted in the belief that consuming energy-dense meals in the evening can disrupt sleep and various bodily functions. In medieval England, dinner, the main meal of the day, was consumed around noon or 01:00 p.m., while supper, a smaller meal, was closer to sunset, typically between 04:00 p.m. and 06:00 p.m. [17][23]. Religion also impacts mealtime; for example, during Islamic fasting inside or outside the month of Ramadan, followers refrain from eating and drinking between dawn and sunset for a month and are requested to eat an early pre-dawn meal called Suhur before fasting, which has a religious dimension [24]. Also, during ordinary days, Muslims were historically required to wake up every day for the dawn prayer, where they eat a meal after the prayer and start their day [24]. The advent of artificial lighting, such as oil lamps, led to a shift in dinner and other activities to later times. By the late eighteenth century, dinner had moved to around 04:00 p.m. or 05:00 p.m., and the introduction of lunch was a response to extended fasting periods between breakfast and dinner. The Industrial Revolution also contributed to later dinner times among working-class men who split the workday with a quick noon meal [17][23]. In the USA, an examination of data derived from the National Health and Nutrition Examination Survey (NHANES) demonstrated that snacks consumed after dinner constituted the largest share of calories, providing nearly 45% of overall calorie consumption [25]. Over 40 years, from 1971–1974 to 2007–2010, the timing of breakfast and lunch generally shifted to later times, while dinner timing remained stable [25]. In the most recent NHANES analysis involving 15,341 adults from the 2009 to 2014 cycle, the average dinner time was 6:24 p.m., with the average time of the last eating episode being 8:18 p.m. [25]. In fact, contrary to the commonly held belief that humans follow a strict three-meal pattern, it is currently evident that calorie intake occurs sporadically and over an extensive timeframe throughout the 24-h cycle [26]. Hence, limiting food intake to predetermined time windows may present a readily implementable behavioral intervention with the potential to enhance outcomes in patients with metabolic syndrome.

3. Regulation and Control of the Circadian Body Clocks

Every organ, tissue, and cell in the body functions according to a biological clock that adheres to a circadian rhythm. Biological clocks can be classified into central and peripheral clocks depending on where they are located anatomically [27]. The primary biological clock is situated within the hypothalamus, precisely within the suprachiasmatic nucleus (SCN), while peripheral clocks exist in all cells throughout the body [28]. These clocks help maintain normal tissue function by regulating the activity of tissue-specific genes [28]. The body’s internal clocks, known as circadian rhythms, rely on independent oscillators within cells to regulate gene expression; circadian clocks are intrinsic biological oscillators that exhibit a periodicity of approximately 24 h [29], even without external cues [30]. To achieve external and internal synchrony, the body’s biological clocks must be entrained daily.

Circadian clocks are intrinsic biological oscillators that exhibit a periodicity of approximately 24 h [29]. Found in a wide range of light-sensitive organisms, these clocks play a vital role in coordinating rhythmic activities in accordance with the natural daily cycles [31]. In order to stay synchronized with the external environment, circadian clocks rely on external signals called zeitgebers or timing cues to undergo phase resetting [29][31]. The retinohypothalamic tract primarily entrains the SCN through exposure to external light, whereas neurohormonal factors exert an influence on peripheral clocks and mealtimes [32][33], and peripheral tissues can be moderately affected by nonphotic signals, such as food intake and glucocorticoids [34][35]. The nervous and endocrine systems both regulate the peripheral clocks in vivo. One example is the secretion pattern of glucocorticoids, which is regulated by the SCN and helps synchronize peripheral clocks [35][36]. Exposure to intense light during nighttime can disrupt the secondary clocks and rhythms that are controlled by the central clock situated in the SCN; similarly, eating meals during the night can also disrupt the peripheral clocks.

External or internal circadian system desynchrony has been associated with diverse metabolic dysfunctions, including compromised glucose tolerance and diminished insulin sensitivity, elevated susceptibility to complications related to reduced insulin sensitivity, such as non-alcoholic fatty liver disease (NAFLD), heightened levels of proinflammatory cytokines, elevated arterial blood pressure, and decreased energy expenditure, leading to obesity [37][38][39]. Moreover, epidemiological data support the connection between circadian misalignment and elevated susceptibility to metabolic disorders, diabetes, disorders affecting the cardiovascular system, and NAFLD [40][41][42][43].

Laboratory-controlled studies suggest that acute circadian rhythm misalignment increases the risk of developing metabolic disorders [11]. However, more research is needed in the general population as well as long-term studies to investigate the potential for adaptation to long-term disruption of the circadian rhythm [44].

4. Clock Genes and Circadian Rhythms

Clock genes are central to circadian rhythms, profoundly influencing behavior and human physiology [45]. These genes, discovered in fruit flies and mammals like mice, form networks that display a 24-h oscillation [46][47]. These networks not only govern physiological and behavioral rhythms but extend their influence to other cellular functions [48]. Mammalian circadian rhythms arise from a feedback loop involving transcriptional activators and repressors [49]. Key proteins, BMAL1 and CLOCK, stimulate the transcription of Cry and Per genes. When repressor proteins CRY and PER reach a specific concentration, they interfere with the CLOCK-BMAL1, starting a new transcription cycle [30]. Current studies underline the significance of circadian rhythm in health disorders and its synchronization for optimal cellular functioning [50]. Moreover, there is a documented interplay between clock genes and feeding times, with feeding rapidly impacting circadian clock gene expression in animals [51][52]. For nocturnal rodents, daylight feeding alters circadian clock phases in peripheral tissues but not in the central timekeeper [53]. The relationship between human feeding times and clocks is an emerging field, suggesting that timed feeding could have clinical benefits [54].

5. Mealtime and Cardiometabolic Risk

Emerging evidence highlights the significant role of mealtime in controlling metabolic processes and its close interaction with the biological clock [11][55]. Chrononutrition, a new discipline, addresses the interplay between mealtime, circadian rhythm, and metabolic regulation [56]. Current research indicates that meal timing influences the circadian cycle, metabolic regulation, and body weight [57]. Consuming meals during inappropriate time periods can cause misalignment between peripheral biological clocks and the central biological clock in the SCN, increasing the potential for developing metabolic disorders [7][33][55]. Studies in both nocturnal species and humans have shown comparable results, wherein consuming meals at inappropriate hours (dark hours, “inactive phase” for humans) is linked to an increased likelihood of experiencing metabolic impairment [58]. In shift workers, night eating has been linked to metabolic disturbances [59][60]. Research has also shown that confining the timing of food intake to either daytime or nighttime can influence the risk of metabolic disorders [26][61][62][63]. However, it is essential to acknowledge that studying the intricate interplay between mealtime, circadian rhythm, and metabolism poses challenges due to the influence of multiple interacting factors. Factors including individual chronotype, lifestyle elements like shift work, sleep disruptions and sleep patterns, dietary composition and portion sizes, physical activity levels, environmental factors including nighttime light exposure, age, and genetic factors can interact with these rhythms, with some evidence suggesting that high-fat meals eaten late at night may be particularly disruptive [55][64][65].

In addition to caloric intake control, maintaining a consistent meal schedule is crucial as it aids in the effective management of energy balance. Consuming meals at set times from sunrise to sunset (between dawn and dusk rather than continuously throughout the day) enhances circadian rhythmicity and promotes a beneficial cycle for optimal metabolic health [17]. In experiments conducted on Wistar rats, it was observed that providing a daily serving of chocolate during the period of activity (breakfast) facilitated the adjustment of the SCN activity to the new schedule in a model of jet lag, leading to faster re-entrainment [66]. Additionally, in a model using rats simulating shift work, having a daily serving of chocolate coinciding with the start of the active phase (breakfast time) prevented disruption of the body’s internal clock by increasing the strength of the day–night activation in the SCN, specifically involving c-Fos (c-Fos is a helpful physiological marker of neural activation, which proved to be successfully utilized in the SCN) [66][67]. In contrast, chocolate consumed during dinner hindered re-synchronization in the jet lag condition and fostered disruption of circadian coordination in shift work models [66]. Furthermore, rats consuming chocolate during breakfast showed lower weight gain, while those having chocolate during dinner exhibited increased body weight [66]. These findings emphasize the importance of meal timing in regulating circadian synchrony and metabolic function, particularly for a high-calorie and appetizing meal like chocolate.

The favorable impacts of morning meal (breakfast) consumption on body weight and cardiometabolic well-being have not been consistently reported in all studies [68][69]. A consensus statement from the American Heart Association concluded that while epidemiological evidence indicates a potential adverse impact of consuming meals late in the day on cardiometabolic hazard, the scope of clinical intervention studies addressing this issue has been scant and lacks the specific focus to draw definitive conclusions or formulate recommendations [33]. The statement also emphasized that mealtime and frequency are not the sole determining factors; the length of time between meals and caloric intake are also crucial considerations [33].

6. The Interaction between Mealtime and Circadian Hormones

The classical rodent circadian system simulation proposed by Pittendrigh and Daan (1976) [70] is also suggested to apply to humans. This model, along with its expansion by Illnerova and Vanecek (1982) [71], describes two distinct rhythmic

components in the circadian timing system. One oscillator is aligned with dusk, regulating evening movement patterns and the onset of melatonin production in nocturnal rodents. The second oscillator is aligned with dawn, controlling morning locomotor activity and the cessation of melatonin secretion.

In a human study, clear patterns of wakefulness, internal body temperature, and hormone release were observed throughout the 24-h cycle [72]. These patterns demonstrate distinct diurnal and nocturnal states, with noticeable transitions resembling biological “dawn” and “dusk” [72].

In humans, the complex circadian pacemaker components synchronized with dusk and dawn play a role in regulating transitions in hormone secretion, such as melatonin and cortisol, during the evening and morning. These components also help adjust the timing of these transitions based on seasonal variations in daylight duration. Hormones like melatonin and glucocorticoids, tightly regulated by the master clock in the suprachiasmatic nucleus (SCN), influence the timing of secondary clocks expressing their respective receptors [73]. Peripheral clocks, even without a functional master clock, can maintain a daily rhythm under a light–dark cycle [74].

6.1. Cortisol

The circadian pattern of corticosteroids in diurnal and nocturnal mammals follows opposite patterns in accordance with the cycle of light and darkness, specifically aligning with dawn and dusk, respectively. However, it functions in both groups to anticipate the beginning of the daily period of wakefulness and activity, aiding in the activation of energy reserves and the stimulation of appetite [75][76]. Glucocorticoids play a crucial role as essential timing signals for numerous peripheral oscillators, facilitating their appropriate synchronization and adjustment to the light–dark (LD) cycle [35][77][78]. Furthermore, it has been suggested that they contribute to preventing sudden shifts in the timing of peripheral clocks within the circadian rhythm. This is particularly important when peripheral clocks become disconnected as a result of consecutive days of fasting and subsequent refeeding cycles [79]. Research has shown that individuals who fast from dawn to dusk exhibit two peaks (acrophases) of cortisol during dawn and dusk, compared with those who do not fast and individuals with a single peak (acrophase) [80]. These findings suggest that when meals are timed immediately before and after a fasting period that spans from dawn to dusk, the fasting-induced biphasic cortisol circadian rhythm synchronizes the peripheral clocks with the central clock, ensuring their phase alignment and thereby preventing phase shifts between the central and peripheral clocks.

Extensive research has focused on investigating the role of glucocorticoids, which have been linked to the central clock situated in the SCN [81][82]. The secretion of adrenocorticotropin hormone (ATCH) from the anterior pituitary gland is regulated by the SCN [83]. Consequently, this endocrine hormone plays a pivotal role in modulating the release of glucocorticoid hormones from the adrenal glands, which subsequently coordinate the functioning of peripheral tissue circadian clocks.

Studies have provided evidence showing that the regulation of clock gene expression and dietary rhythmicity involves the influence of glucocorticoid receptors [35]. Therefore, considering this relationship, it is plausible to suggest a potential connection between clock genes, the hypothalamic–pituitary–adrenal (HPA) axis, and metabolism [84].

Glucocorticoids, through the glucocorticoid receptor (GR), have been observed to exert a broad impact on gene expression [85]. Upon activation, the inactive complexed state of cytoplasmic GR experiences structural modifications and moves into the nucleus after dimerization. In the nucleus, the binding of GR to glucocorticoid response elements (GREs) facilitates the transcription of genes targeted by glucocorticoids [86]. These GREs are responsible for regulating the expression of several genes, including core clock genes such as Per1, Per2, Npas2, and Rev-erbß [87][88]. Both in laboratory settings (in vitro) and living organisms (in vivo), glucocorticoids have shown the capability to alter the circadian rhythms of peripheral clocks [35]. The synthetic glucocorticoid analog dexamethasone, for example, has been observed to stimulate the expression of clock genes and genes influenced by the circadian clock in rat fibroblasts [35]. Additionally, depending on the timing of administration to mice, dexamethasone was observed to either postpone or accelerate the timing of clock gene expression in the liver, kidney, and heart [35]. More recently, there is evidence suggesting that glucocorticoids can influence the human adipose tissue’s biological rhythms as well [89].

The association between meal timing and diurnal fluctuations in cortisol levels has been documented, highlighting the possibility of both adrenal and extra-adrenal regulatory influences [90]. Glucocorticoid levels are affected by meals and mealtime; it is suggested that when meals are timed immediately before and after dawn and dusk, the dual-phase cortisol circadian rhythm during periods of fasting aligns the timing of peripheral clocks with the central clock, promoting synchronization and preventing disruptions or transitions between the central and peripheral clocks [91].

In summary, the circadian pattern of corticosteroids aligns with dawn and dusk, following opposite patterns in diurnal and nocturnal mammals. Further research is needed to understand the impact of meal timing on cortisol regulation and metabolic health. Comprehensive multi-omics analyses in randomized-controlled trials can provide valuable insights into this relationship. Studies need to encompass circadian gene expression profiling, metabolomics, and proteomics to investigate the impact of meals around dawn and dusk in individuals suffering from chronic metabolic conditions and metabolic syndrome.

6.2. Melatonin

Melatonin levels follow a circadian pattern, reaching their highest point during sleep, decreasing toward the early morning hours, and remaining low until nighttime [92]. At night, melatonin levels begin to rise again in preparation for sleep. Apart from its function in regulating the sleep–wake cycle, melatonin also possesses antioxidant and anti-inflammatory properties and plays a role in controlling glucose and lipid metabolism and the pathophysiology of cardiovascular diseases [93][94]. Reduced levels of melatonin and its major metabolite, 6-sulphatoxymelatonin, have been reported in various cardiovascular diseases, including myocardial infarcts, coronary heart disease, congestive heart failure, and nocturnal hypertension [95][96]. Furthermore, melatonin deficiency caused by factors such as shift work, aging, and exposure to illuminated environments at night can result in glucose intolerance, insulin resistance, metabolic circadian disorganization, and sleep disturbance, all of which pose a threat to health conditions [97].

The timing of meals may also interact with melatonin to affect circadian rhythm and metabolism. Consuming a meal during nighttime when melatonin levels are elevated, particularly during night shifts, has been suggested as a potential mechanism for an elevated risk of heart disease and diabetes. A study conducted with 40 overweight/obese women of European ancestry who were habitual late eaters revealed that taking melatonin (5 mg) had a negative effect on glucose tolerance [98]. Specifically, the participants who had dinner within 2.5 h of their usual bedtime and had high levels of natural melatonin experienced a decrease in glucose tolerance. This suggests that when meal timing coincides with elevated melatonin levels, it impairs glucose tolerance. It is important to note that melatonin levels typically rise about 30 min before bedtime [99]. Another study utilized a mobile phone application with time-stamped pictures to track participants' food intake over seven consecutive days, while also evaluating their body composition and the timing of melatonin release in a laboratory setting [14]. The findings revealed that individuals with higher body fat, known as non-lean individuals, consumed most of their calories approximately 1.1 h closer to the onset of melatonin release, which signifies the start of the biological night, compared with individuals with lower body fat, known as lean individuals [14]. These results provide additional evidence that the timing of meal intake throughout the circadian evening and/or night, independent of more conventional risk factors such as the quantity or content of consumed food and activity level, plays a vital role in determining body composition [14].

Therefore, in countries where dinner is served early, such as Sweden and Germany, the chances of food intake aligning with elevated melatonin levels are low [100]. However, in Spain, where dinner is usually around 10 p.m., melatonin levels at dinner time are approximately three times higher, especially among young individuals who have higher natural melatonin levels than older individuals [100]; this situation increases the likelihood of metabolic changes related to glucose [101]. In a randomized crossover study involving a Spanish population, researchers investigated the impact of late eating and elevated melatonin levels on glucose control, particularly in individuals carrying the G allele in the MTNR1B gene associated with type 2 diabetes [102]. The study found that late dinner timing resulted in significantly higher melatonin levels and impaired glucose tolerance, with lower insulin response and higher glucose levels. These effects were more pronounced in individuals carrying the G allele, suggesting that the combination of high melatonin and carbohydrate intake during late eating can lead to insulin secretion defects and impaired glucose control [102].

Therefore, it is advisable to have dinner early, around dusk, and refrain from consuming meals, particularly those with high glycemic content, in close proximity to exogenous melatonin intake or during nighttime when endogenous melatonin levels are typically elevated.

6.3. Other Mechanisms

In rodents, under the natural circadian setting, the light phase is associated with continuous suppression of feeding compared with the dark phase [103]. It has been consistently observed that food intake in normal rodents is significantly suppressed during the light phase compared with the dark phase [35][46]. This light-induced feeding inhibition is not simply due to the suppression of locomotor activity but is associated with the activation of anorexigenic neurons [104].

Oxytocin expression in the brain exhibits a circadian pattern synchrony with the light–dark cycle, with higher levels during the light phase in rodents [103][105][106][107]. Experimental evidence supports the role of nesfatin-1, derived from

nucleobindin-2 (NUCB2) and expressed in the paraventricular nucleus (PVN), as a physiological anorexigenic peptide [103][108][109]. Nesfatin-1 attenuates food intake during the light phase in rodents through its action on oxytocin neurons in the PVN [103][108][110]. Light exposure, mediated via the SCN, activates the PVN oxytocin pathway, leading to the termination of feeding in mice [111]. The anorexigenic effect of oxytocin-induced suppression of food intake is related to nesfatin-1, as oxytocin administration increases the number of activated NUCB2/nesfatin-1 neurons in various brain regions, and this effect can be attenuated by inhibiting nesfatin-1 [112]. Altered levels of NUCB2/nesfatin-1 have been observed in obesity-related conditions in the rodent hypothalamus and human blood [103]. Furthermore, nesfatin-1, expressed in endocrine cells in the pancreas, has recently emerged as an important player in the regulation of glucose homeostasis through its insulinotropic action [103][112]. Based on these findings and the independent anorexigenic effect of nesfatin-1 from leptin, it is worth exploring its potential as a target for further research aimed at evaluating its efficacy as a treatment for obesity and type 2 diabetes mellitus [103][112][113].

Further research is required to investigate the link between nighttime light exposure in humans and the interplay among nesfatin-1, NUCB2, and oxytocin neurons in the paraventricular nucleus (PVN). Understanding this association can provide valuable insights into its impact on human appetite and metabolism

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