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When should I eat: A circadian view on food intake and metabolic regulation

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Abstract

The circadian clock is a hierarchical timing system regulating most physiological and behavioral functions with a period of approximately 24 h in humans and other mammalian species. The circadian clock drives daily eating rhythms that, in turn, reinforce the circadian clock network itself to anticipate and orchestrate metabolic responses to food intake. Eating is tightly interconnected with the circadian clock and recent evidence shows that the timing of meals is crucial for the control of appetite and metabolic regulation. Obesity results from combined long-term dysregulation in food intake (homeostatic and hedonic circuits), energy expenditure, and energy storage. Increasing evidence supports that the loss of synchrony of daily rhythms significantly impairs metabolic homeostasis and is associated with obesity. This review presents an overview of mechanisms regulating food intake (homeostatic/hedonic) and focuses on the crucial role of the circadian clock on the metabolic response to eating, thus providing a fundamental research axis to maintain a healthy eating behavior.

KEYWORDS

circadian misalignment, homeostatic/hedonic food intake, mammalian circadian clock, metabolism, obesity

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1 | INTRODUCTION

The high prevalence of non-communicable metabolic diseases, such as type 2 diabetes (T2D), hypertension, and obesity, continues to be a current challenge for public health systems worldwide.[1,2] These diseases are among the leading causes of death globally, and obesity is a common underlying factor for several metabolic disorders.[3–5] So far, the most successful steps to tackle obesity include energy restriction, increased physical activity, and psychological support.[2] Still, current interventions have not effectively reduced the overwhelming obesity pandemic.[6]

Obesity is a complex disease resulting from a positive energy balance sustained over time. Therefore, studying the factors that regulate energy intake and expenditure is essential to understanding obesity.[7] Food intake regulation is influenced – among others – by homeostatic, hedonic, and social factors, all of which contribute to the habitual eating pattern.[8] Circadian rhythms, i.e., endogenous self-sustained rhythms with ~24 h duration, expressed in every cell of living organisms, also influence eating and metabolic responses to food intake. Most physiological and nutrition-related processes are under circadian control.[9,10] These rhythms, driven by the hypothalamic suprachiasmatic nucleus (SCN), synchronize physiological processes in a 24-h temporal context.[11] Food intake and macronutrient metabolism,[12] hunger/appetite feelings,[13] and hormones with a critical role in energy balance such as insulin,[14] leptin,[15] ghrelin,[16] adrenocorticotropic hormone, and cortisol,[17] are all under circadian regulation.

Recent evidence has also shown that a timed and stable (healthy) eating pattern can positively influence circadian and metabolic regulation. Current research highlights the role of diet as a critical synchronizing factor of the circadian system, particularly for peripheral tissue clocks.[18] It has been reported that the timing of food intake plays a crucial role in maintaining metabolic health or treating impaired metabolic processes in pathological conditions.[9,19,20] In humans, for instance, decreasing caloric intake from morning to afternoon hours could be a valuable strategy for weight-loss success in adults with obesity.[21,22] However, the time of day has only been taken into consideration more recently in the context of dietary interventions, as most nutritional strategies have focused on restricting total energy intake (i.e., continuous caloric restriction) or the manipulation of the diet's macronutrient composition.

In this narrative review, we focuse on the role of the time of eating on the metabolic response to food intake. After describing the mammalian oscillator, food intake regulation is reviewed with a particular focus on the role of food as a critical factor for the circadian system. After that, the relevance of the timing of food intake for body weight and metabolic regulation is highlighted.

1.1 | Introduction into chronobiology and circadian rhythms

Due to the Earth's rotation around its axis, organisms are subject to daily environmental changes. As an evolutionary response to these variations, most species have developed a timing system called the circadian clock (from the Latin circa *diem*: about a day) to anticipate and adapt to their environment. In 1960, Pittendrigh[10] defined circadian rhythms as about 24-h oscillations that are ubiquitous, innate, endogenous, and self-sustained. They are almost independent from temperature, light intensity dependent, and entrainable by external cues called *Zeitgeber* (German for *time giver*), light being one of the major *Zeitgeber*. Over the years, an increasing number of studies revealed evidence of its crucial role in regulating metabolism, physiology and behavior.[23]

While present virtually in every cell of the organism,[24] in mammals, the circadian clock is hierarchically organized.[25,26] The central pacemaker, located in the SCN of the hypothalamus, is a structure composed of about 20 000 neurons in mice,[27] and its clock autonomously exhibits 24-h oscillations that are daily synchronized by light input via the retino-hypothalamic tract. Indeed, the light signal is transmitted as photic information to the retina, where specific receptors called intrinsically photosensitive retinal ganglion cells (ipRGCs) can relay the photic information via the photopigment melanopsin (OPN4) to the SCN.[28,29] The SCN clock orchestrates the clocks of peripheral tissues, such as in the liver, adipose tissues, and muscles, through neuronal signals,[30] hormones,[24] eating/fasting states,[31] and metabolite signals.[32,33] The circadian rhythm in mammals results from interconnected and aligned clocks together synchronized by the light through the fine-tuned orchestration by the SCN (Figure 1).[25,34]

The molecular circadian clock is highly conserved throughout evolution. The mechanism generating the 24-h rhythmicity in mammals consists of a transcription-translation feedback loop (TTFL)[35] (Figure 2). BMAL1 (brain and muscle ARNT-like 1) associates with CLOCK (circadian locomotor output cycles kaput) or NPAS2 (neuronal PAS domain protein 2) to form the activator complex. In the nucleus, this complex can play its role of a transcription factor by binding to E-boxes, specific DNA sequences (motif CACGT[G/T]) found in the promoters of its target genes, such as *Per* (period) 1–3 and *Cry* (cryptochrome) 1–2. PERs and CRYs heterodimerize in the cytoplasm and translocate into the nucleus to inhibit the actions of the activator complex.[36] Proteasomal actions on

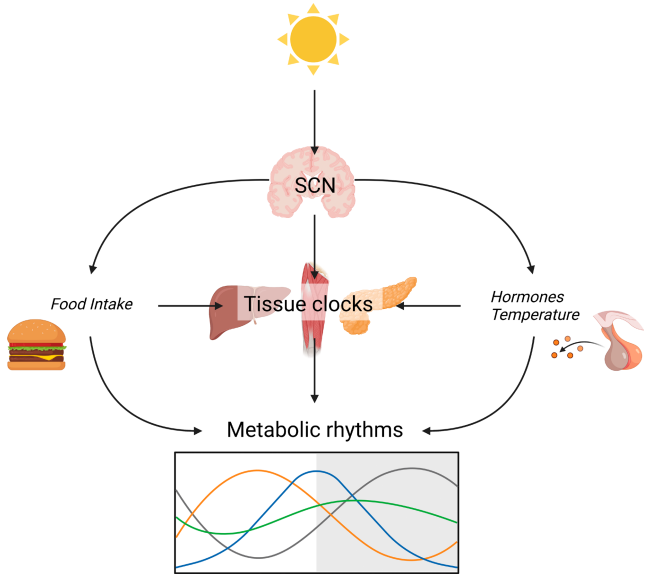

FIGURE 1 Circadian clocks regulate daily energy metabolism. The circadian pacemaker in the suprachiasmatic nucleus (SCN) is reset by the light/dark cycle. Via various routes, it resets clocks in central and peripheral tissues. SCN-derived systemic and local tissue clock-directed signals together drive daily rhythms of metabolic functions.

PER[37] and CRY,[38] due to post-translational modifications, lead to their degradation allowing the BMAL1 complex to activate again the transcription of gene expression.

An accessory loop, also known as a stabilization loop, allows a fine-tuned regulation of the circadian clock machinery. It consists of BMAL1/CLOCK complex activating the expression of REV-ERBα, and REV-ERBβ (reverse erythroblastosis virus α and β, encoded by the genes *Nr1d1* and *Nr1d2*, respectively) and RORα, β, and γ (retinoic acid-related orphan receptors α, β, and γ, encoded by the genes *Rora*, *Rorb*, and *Rorc*, respectively) proteins. In return, REV-ERBs and RORs negatively and positively regulate *Bmal1* transcription, respectively, by competing for binding to ROR responsive elements (*RREs*) present in the promoter of *Bmal1*.[39,40]

In addition, the circadian clock regulates rhythmic expression of a subset of so-called clock-controlled genes (CCGs). CCGs represent 5–10% of expressed genes in any tissue, and are partly under the direct control of BMAL1/CLOCK.[41,42] These genes can express proteins that modulate the circadian clock in return, such as DEC1 and DEC2 (differentially expressed in chondrocytes 1 and 2 or BHLHE40 and BHLHE41)[43] or the PARbZIP transcription factors DBP (D-site of albumin promoter binding protein), HLF (hepatic leukemia factor) and TEF (thyrotroph embryonic factor),[44] that modulate the rhythm of metabolism. CCGs are partly specific to each tissue[45,46] and are involved in mammals' rhythmic orchestration of physiology.

1.2 | The regulation of eating and food intake

The control of food intake is tightly regulated by the central nervous system (CNS). The CNS integrates several inputs and drives effects on at least three levels: behavior (eating, physical activity, sleep), the autonomic nervous system response (therefore, regulating energy expenditure and metabolic processes), and neuroendocrine signals (regulating food intake and energy expenditure).[47] Food intake, one of the critical components modulating energy balance, is controlled by different factors. Whether we eat a particular type of food is a decision modulated by external and internal cues. Among the former, food availability and food palatability are relevant to eating behavior. Internal factors include metabolic, neural, and endocrine signals.[47] The control of food intake is currently recognized as a complex and highly interactive process involving homeostatic and hedonic systems, cognition, and emotional regulation.[48]

The homeostatic control of energy balance relies upon the adequate functioning of brain structures (e.g., the hypothalamus) integrating peripheral signals such as nutrients (i.e., glucose, amino acids, fatty acids) and neuroendocrine signals like peripheral hormones signaling orexigenic (i.e., ghrelin) and anorexigenic (i.e., leptin, insulin, peptide YY (PYY), glucagon-like peptide-1) effects.[49] The ultimate goal is to preserve the stability of energy stores.[50] It has been proposed that, in obesity, the brain mechanisms involved in the homeostatic regulation of food intake could be impaired, including impaired central action of ghrelin,[51] leptin,[52,53] and insulin,[54] all contributing to the worsening of obesity itself and obesity-related metabolic alterations.

The hedonic control of food intake is mediated by several brain circuits involved in the reward response to food stimuli, including dopaminergic circuits (ventral tegmental area (VTA), *nucleus accumbens*, *substantia nigra*), and the opioid and endocannabinoid systems.[50,55] The relevance of the hedonic drive to eat for energy balance regulation has been highlighted, as the rewarding nature of foods is one of the most potent drives for eating in humans.[55] The homeostatic and the hedonic circuits interact and regulate food intake and body weight based on internal and external (environmental) factors.[48] The hedonic value of a food item can be different when that food is given in a state of satiety compared to when subjects are willing to eat and hungry, illustrating the interaction between the two processes.[56] The role of peripheral (homeostatic) signals in modulating food reward has also been shown in animals. Leptin can modulate the hedonic value of the sweet taste[23] and attenuate self-stimulation behavior in response to lateral hypothalamic

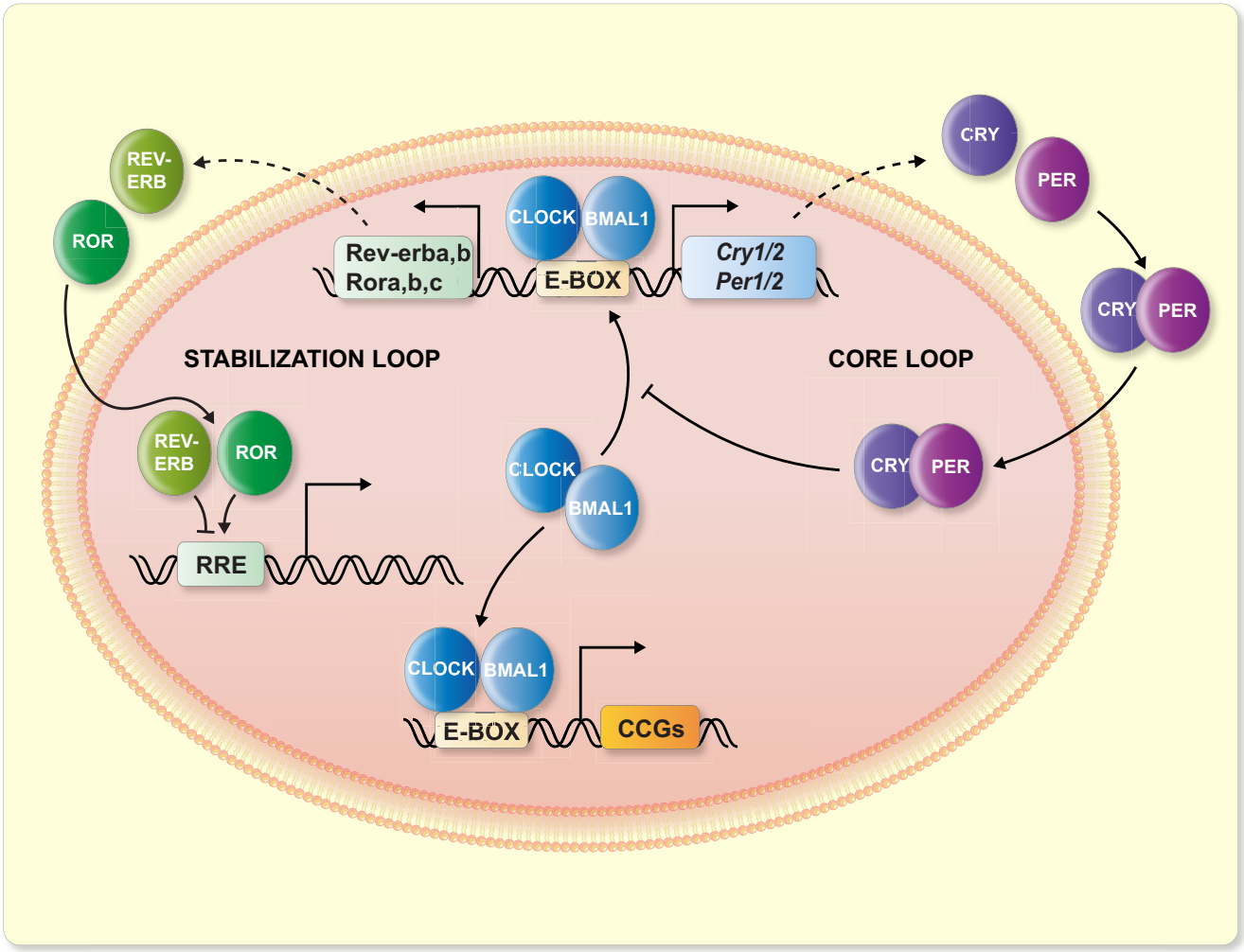

FIGURE 2 The molecular circadian clock in mammals. It is constituted by a core loop with the BMAL1/CLOCK complex activating the expression of PERs and CRYs that forms a homodimer repressing the actions of BMAL1/CLOCK. In an accessory loop, BMAL1/CLOCK activates the expression of REV-ERB and ROR transcription factors that repress or activate, respectively, the expression of *Bmal1*. In addition, BMAL1/CLOCK regulates the expression of clock-controlled genes (CCGs) involved in metabolic control.

stimulation after chronic food restriction in rats.[57] Ghrelin, in turn, can also modulate the reward system.[58] Ghrelin increases reward-driven food motivation in hypothalamic and extra-hypothalamic areas,[59] and ghrelin signaling in the VTA increases the consumption of palatable food in mice.[60] Moreover, the involvement of other gut hormones and peptides in modulating food reward is an exciting area of current research. The role of cholecystokinin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, PYY, and other molecules in food reward mechanisms deepens and broadens our understanding of the interplay between homeostatic and hedonic regulation of food intake.[61]

It has been proposed that the hedonic control of appetite can be separated into two interconnected components of the reward system, *liking* (sensory pleasure experience) and *wanting* (incentive salience). These two processes interact in modulating reward for foods and, thus, regulate food intake even when homeostatic needs are fulfilled.[62,63] The impairment of mechanisms regulating *liking* and *wanting* for food has been proposed in obesity and other eating disorders, suggesting an excessive desire for highly palatable foods (incentive-sensitization theory).[64,65] Interestingly, there is evidence for a diurnal variation in the reward system in humans, showing increased *wanting* in the afternoon hours.[66] Accordingly, Scheer et al. demonstrated a circadian rhythm in hunger and appetite for specific foods (i.e., sweets, salty, and starchy food, among others) and for food overall, showing higher hunger levels in the biological evening (around 8 p.m.) in young healthy adults.[13] More recently, we also reported a *time-of-day* effect regarding food reward in normal-weight adults, who reported increased wanting for high-caloric foods in the afternoon and evening hours.[67]

The role of circadian rhythms has also been shown regarding both the homeostatic and hedonic components

of appetite control, even though it has been less emphasized.[12] The temporal context of eating and remarkable diurnal rhythms in hormone profiles and the metabolic response to food intake demonstrate the role of the circadian system in regulating the homeostatic control of food intake.[68] Notably, the circadian system also regulates food reward (the hedonic control of appetite).[69,70] The circadian influence on normal metabolic responses is also highlighted by data showing that diurnal rhythms of clock and metabolic genes and endocrine factors can be impaired in metabolic diseases such as obesity.[71]

1.3 | Chronobiological impact on eating behavior and metabolism

The circadian system plays a key role in influencing eating behavior, and food itself impinges on the clock as a potent *Zeitgeber*. Several studies in rodents have shown that the timing of food intake strongly influences the expression of clock genes in peripheral tissues.[72,73] It has been demonstrated[31] that restricting food availability to the diurnal period (normal sleep period) for 9 days in mice inverted the phase of clock gene expression (up to 12 h) of peripheral oscillators (liver, kidney, pancreas, and heart) but did not modify the expression phase in the SCN. These data show that in mice, temporal restriction of food intake to daytime exerts a powerful effect on the alignment of peripheral circadian oscillators, inverting the phase of circadian expression of clock-genes and clock-controlled genes in peripheral tissues.[31]

Similarly, the so-called *food-anticipatory activity* (FAA) illustrates the role of the circadian system in modulating eating behavior.[74] This phenomenon described decades ago in rodents kept in a 24-h context, refers to behavioral and physiological changes that anticipate the arrival of food when it is restricted. The circadian influence is well recognized in FAA since it is evident even in constant environmental conditions and disappears if meals are delivered in intervals longer than 24 h.[75] Still, the commanding center (or oscillator) of the FAA has not yet been identified and FAA persists in animals without a functional SCN.[76] Recent data add to this phenomenon, showing that when food is presented at fixed times of the day, rats can anticipate up to 4 meals/day; when food is offered at varying times, however, recurring at 24–26-h intervals, animals can anticipate a maximum of 2 meals. In addition, the SCN is not required for these multiple anticipation bouts, and the authors propose a multiple-entrained oscillator model of FAA.[77]

Another approach to studying the effect of the timing of food intake as a critical factor influencing weight gain and metabolic health comes from studies that have modified (and restricted) the time of food availability and evaluated its metabolic and physiological effects. Arble et al.[78] showed that rats fed exclusively during their usual resting period (daytime) show rapid and excessive weight gain starting after just 2 weeks of treatment compared with animals fed during the active period (nighttime), despite having similar caloric intake and physical activity.[78] Others have shown that mice receiving only one meal/day towards the end of the active period show increased weight gain, impaired glucose tolerance, and dyslipidemia, data supporting the relevance of the time-of-day of food intake for energy homeostasis.[79]

The restriction of the time of food availability (i.e., time-restricted feeding or time-restricted eating (TRE) in humans) has been shown to benefit the circadian system and metabolic functioning. Time-restricted feeding in mice shows improved metabolic regulation in light and dark periods compared to those with ad-libitum access to food.[80] Interestingly, other animal studies have shown that, under a high-fat diet, restricting food access to 8 h/day exclusively during the dark period prevents excessive weight gain, hyperinsulinemia, hepatic steatosis, and changes in liver clock gene expression.[73] More recent evidence in humans supports the metabolic benefits of the temporal restriction of food intake for bodyweight management and the treatment of obesity-related metabolic diseases (see below).

1.4 | Mechanistic concepts linking chronobiology & eating behavior

As mentioned previously, the SCN, synchronized every day by the light cycle, regulates rhythms in physiology via its orchestration of peripheral clocks. This mechanism, called circadian alignment, appears to be fundamental for regulating health. Desynchrony of the clock with the environment (also known as circadian misalignment) such as caused by irregular or abnormal eating patterns promotes a dampening in the rhythmic physiology and can lead to disorders such as metabolic, cardiovascular diseases, inflammation, depressive disorder, and cancer progression.[81,82] It has been suggested that this misalignment is often observed in our modern lifestyle due to night shift work, sleep disorders, social jetlag, irregular eating patterns,[82,83] and a lack of physical activity[84]; this is why the understanding of mechanisms promoting the synchrony of clocks remains of high interest (Figure 3).

Eating behavior constitutes a strong external *Zeitgeber* for the synchronization of peripheral clocks[31] and can drive rhythmic gene expression in peripheral organs, as shown in the liver.[85] In addition to temperature that has been shown to modulate circadian periods in fibroblasts[86] and being involved in the synchronization of peripheral oscillators,[87,88] hormones constitute an essential component of

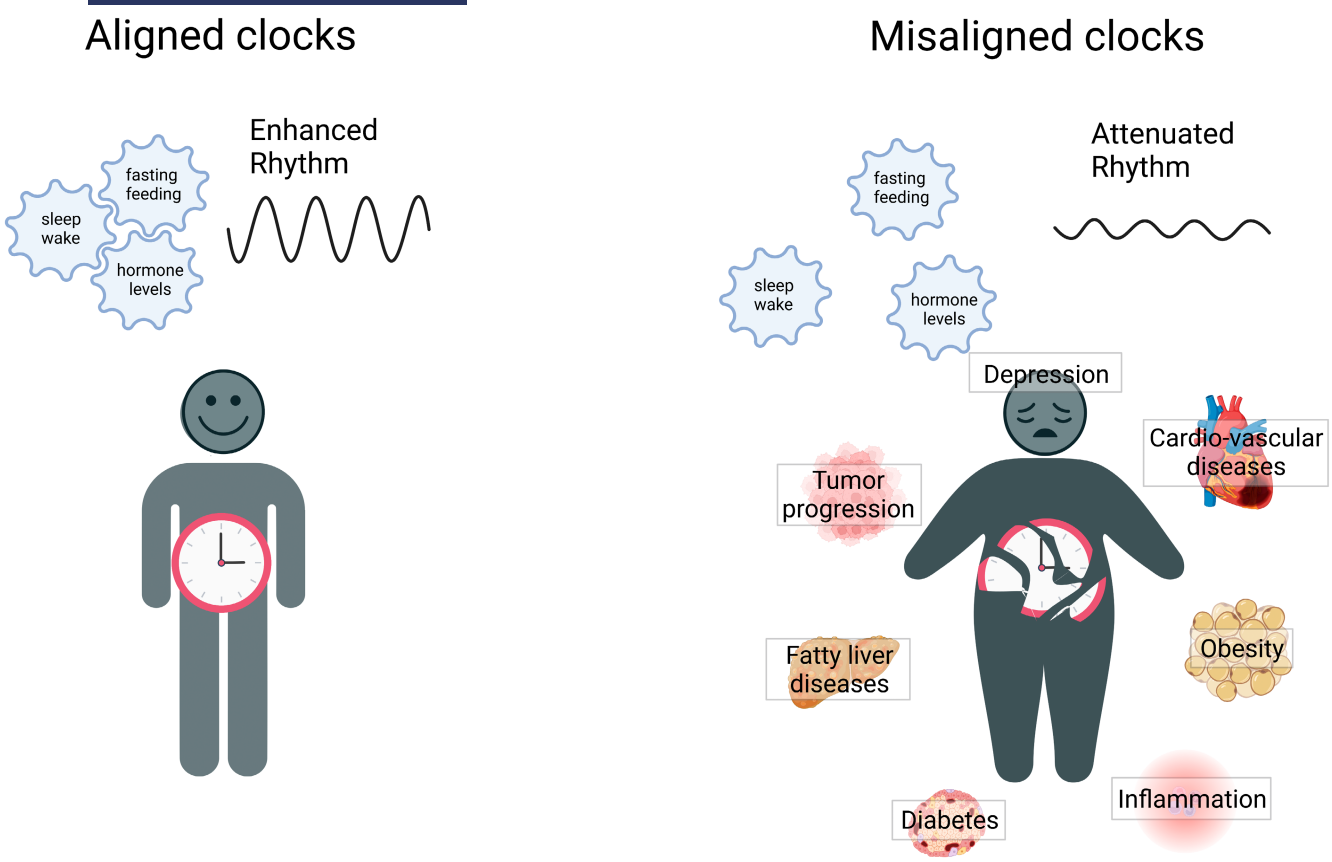

FIGURE 3 Crucial synchronization of body clocks. Circadian alignment (i.e., by maintaining eating/fasting, sleep/wake, and endocrine rhythms in line with body clocks) is fundamental for regulating health. Circadian misalignment, as caused, for example, by irregular or abnormal eating/fasting patterns, can have a broad range of health consequences in humans.

the regulation of the metabolism by the circadian clock, one example being the glucocorticoids. Glucocorticoids (GCs, corticosterone in mice, cortisol in humans) are steroid hormones synthesized in the adrenals after a cascade of hormone stimulations through the hypothalamus-pituitary–adrenal (HPA) axis.[89] Indeed, stress stimulates the release of corticotropin-releasing hormone (CRH) in the hypothalamus, promoting the release of adrenocorticotropic hormone (ACTH) in the pituitary gland, activating then the secretion of GCs in the adrenals. Once released, GCs exert negative feedback on the HPA axis targeting the hypothalamus and the pituitary.[90] While this secretion under stress stimulus is pulsatile, the SCN controls a diurnal rhythmic secretion of GCs in a light-dependent manner.[91] This leads to a peak of GCs at ZT0 (early in the morning) for humans or ZT12 (early in the night) for nocturnal animals (mice), anticipating the beginning of the active/feeding period.[91]

GCs regulate many aspects of mammalian physiology through glucocorticoid receptor (GR)-mediated actions.[92] GR is a transcription factor belonging to the nuclear hormone receptor superfamily. Interestingly, GR directly regulates the expression of several clock genes in positive (*Per1*[92] and *Per2*[93]) or negative (*Rev-erba*[94]) ways. Moreover, CRY1 and CRY2 proteins can physically interact with GR in a ligand-dependent manner, leading to the repression of GC/GR signaling.[95]

In addition to the aforementioned molecular data, several studies have shown physiological evidence for the impact of GCs on the circadian clock. Balsalobre and colleagues presented their first findings that a serum shock is sufficient to impose rhythmic expression of the circadian genes *Per1* and *Per2* in rat fibroblasts.[24] It appeared later that dexamethasone, a synthetic GC analog, can reset the circadian clock in peripheral tissues.[96] Moreover, adrenalectomized mice exhibit a circadian phase-shift in peripheral organs (liver, kidney) faster than sham mice upon time-restricted feeding conditions.[97] In addition, daytime feeding has been shown to alter the rhythmic secretion of corticosterone in mice. Thus, GCs constitute one strong example of circadian clock synchronization by hormones.

1.5 | Transfer into treatment of obesity: the timing of meals and early/late time-restricted eating

The human eating pattern is diurnal and characterized by uninterrupted eating (meals) and fasting episodes.

In addition to meal composition (energy and nutrients) and the social context in which eating occurs (at home, with company, etc.), temporal dietary characteristics are relevant for clinical practice. These can include the number of meals (food frequency), type of meals (main meals, snacks), regularity (omission of meals), the timing of meals, eating window duration (the elapsed time between the first and last meal of the day), and nighttime fasting duration. These have been proposed to be critical dietary variables for weight control and metabolic regulation.[98]

Besides quantitative changes in our diet,[99] how we eat has changed quickly in recent decades. The three main meals (typically breakfast, lunch, and dinner) have been described as healthy eating pattern and being maintained over time in several populations.[100] This, together with the fact that this pattern is also evident in humans isolated from environmental stimuli, suggests a circadian influence on this pattern.[100] However, data from US show that the percentage of adults who eat 3 meals/day regularly has significantly decreased (by nearly 60% in both sexes in 2010) while the proportion of energy from snacks has increased by almost 25%.[101] Gill et al.[102] confirmed that a large part (>35%) of caloric intake over the day occurs after 6:00 pm. Also, high variability is seen in meal types, which are organized dispersedly (not in 3 main meals/day). Also, an extended eating window has been observed in several populations (>14 h/day).[102,103] These data suggest erratic meal timing throughout the 24 h and reduced overnight fasting duration. It has been described that late sleepers (those whose midpoint of sleep occurs after 05:30 am) show higher caloric intake (>50% of total calories/day) after 08:00 pm and poorer dietary quality.[104] Also, a higher obesity risk has been shown in school children (6 to 11 years) and adults (21 to 69 years) consuming more than a third of total calories after 04:00 pm.[105] More recently, McHill et al.[106] confirmed that late eating is related to greater adiposity in adults with a high percentage of body fat, regardless of total caloric intake or level of physical activity. These data are relevant since the appetite for palatable foods increases in the afternoon and early evening hours,[100,107] and eating late during the day, increases weight gain.

Other dietary practices, such as breakfast consumption (vs. breakfast skipping) and meal frequency, are associated with health benefits. Several metabolic benefits are associated with the consumption of breakfast,[108] showing, for example, that a daily breakfast (>700 kcal/day) for 6 weeks results in greater physical activity-induced thermogenesis and improved glycemia regulation in the afternoon and evening hours.[109] A recent systematic review and meta-analysis of controlled trials showed that skipping breakfast has a weight reduction effect but slightly increases LDL-cholesterol without affecting body composition or additional metabolic risk factors.[110] Epidemiological studies, however, have shown that skipping breakfast is associated with an increased obesity risk in children[111] and adults,[112] suggesting a role for breakfast as the first meal of the day in managing body weight. Of note, a high regularity of the first meal of the day (breakfast consumption) is associated with better adherence to caloric restriction and weight loss.[113] There is also some evidence to support a beneficial role of breakfast consumption for the regulation of circadian rhythms.[114] Again, daily breakfast consumption of children and adolescents[76,77] and adults[78,79] in the US has significantly decreased over the last decades.

In turn, meal frequency (i.e., the number of meals per day) would also be relevant for regulating metabolism and body weight. It is inversely associated with body weight and overweight.[115] Stote et al.[116] compared the effect of consuming 1 or 3 meals per day for 8 weeks (with identical total caloric intake) and showed an increased feeling of hunger and altered lipid profiles after 1 meal/day, despite not observing changes in body composition.[116] Even when the proposal to increase meal frequency could be seen as desirable to control appetite and reduce body weight, Leidy et al.[117] in a review of experimental controlled eating studies, conclude no (or very slight) effects of increased meal frequency (>3/day) on the regulation of food intake or appetite control.[117] A higher meal frequency could facilitate overconsumption of energy and initiate weight gain,[117] although it could also positively influence weight loss under caloric-restriction settings.[118] Other authors evaluating the irregularity of meals (e.g., consuming 3–9 meals/day vs. 6 fixed meals/day for 2 weeks) report positive effects of meal regularity on lowering fasting total cholesterol and LDL-cholesterol. Fixed meals improve postprandial insulin responses, increase the thermic effects of food in healthy women with obesity,[119] and lead to higher thermic effects of food in healthy lean women.[120]

In sum, although the maintenance of 3 main meals throughout the day has been proposed as an essential part of a healthy diet and as a model at the population level, more recent research suggests following a circadian eating pattern more adjusted to our physiology.[20] In this way, the timing of meals may be similarly important than meal frequency or even total energy intake.[121,122] The metabolic benefits of the restriction of food intake to the daytime period could be achieved with a consumption of 2 or 3 main meals exclusively during the daytime, 3 small meals in the same period, or the alternation of food intake with periods of fasting (intermittent fasting).[20]

1.6 | Modifying eating time to improve health

Studies evaluating the timing of eating have consistently found beneficial weight loss and metabolic effects of early eating times in humans.[123,124] In obese women under caloric restriction (1400 kcal/day) who consumed decreasing caloric intake from morning to evening hours (700, 500, and 200 kcal, at breakfast, lunch, and dinner, respectively), greater weight loss and better glycemic control after 3 months of intervention have been reported,[125] data consistent with those in patients with T2D.[126] A recent report on middle-aged adults with obesity showed no differences in weight-loss or energy expenditure between weight-loss diets, with most energy consumed in the morning vs. evening. However, the authors found reduced feelings of appetite and hunger after the morning-loaded diet.[22]

In addition, there is epidemiological evidence in adults showing that a higher proportion of carbohydrates (and less fat) consumed in the morning (breakfast) and lunchtime is associated with a lower risk of T2D incidence over 10 years,[127] consistent with others who have shown that the consumption of carbohydrates after 8:00 pm is associated with higher body-mass index.[128] In adults under caloric restriction (1500 kcal/day), a protein/carbohydrate-rich breakfast improves weight maintenance after losing weight, promoting weight loss, satiety, and diminishing ghrelin levels.[129] Despite few contradictory reports,[130] a favorable metabolic effect has been found after consuming a higher intake of carbohydrates early in the day on glucose metabolism in patients with impaired glucose tolerance (but without diabetes).[131]

These data emphasize that both meal timing and the distribution of energy and macronutrients have essential roles in metabolic regulation. Even though the mechanisms are not fully understood, it has been proposed that changes in diet-induced thermogenesis and clock gene expression could explain some of the effects.[18,132] In fact, a very recent study in mice showed that animals fed in line with the circadian clock (i.e., time-restricted animals fed during the dark period) had increased thermogenesis, a finding dependent on the adipocyte circadian clock and on the synthesis of creatine (contributing to creatine-induced thermogenesis), showing that eating out of synchrony with the adipocyte circadian rhythms of thermogenesis contributes to metabolic disruption.[133] It is worth mentioning that in humans, however, studies modifying energy intake throughout the day[22] or implementing a TRE protocol[134,135] have reported no significant changes in total energy expenditure.

In line with evidence from animal models,[136] recent human studies support the benefits of TRE in normal-weight subjects and patients with obesity and metabolic diseases.[137,138] TRE, a form of intermittent fasting, imposes a daily eating window restricted mainly to 4–10 h/day.[139] It has been reported that TRE decreases systolic blood pressure, reduces blood glucose levels, lipid profile, blood pressure, fat mass, and increases insulin sensitivity and glucose oxidation in humans.[140] The effects of TRE on metabolic health can arise through modifying the metabolic switch (i.e., changing the use of glucose towards a preferential use of ketone bodies from fatty acids oxidation), decreasing caloric intake, and improving circadian regulation, therefore, has the potential to bring significant benefits for obesity-related metabolic disorders.[141,142]

An interesting aspect of current research is the timing of TRE (Figure 4). An early TRE focuses only on an early onset of the eating window in morning hours (around 8 am) and differs from studies discussed above that modify the timing of eating but also includes modifications to caloric intake throughout the day. As compared to an early TRE, the eating window in a late TRE protocol starts after midday. Both protocols have been shown to improve glucose metabolism, lipid profiles, blood pressure, and oxidative stress markers.[143,144] In a randomized study including a group of men with obesity and at risk for T2D, Hutchison et al. directly compared early (eating window from 8 am to 5 pm) and late TRE (eating window from noon to 9 pm).[145] They found decreased glucose responses 3 h after the first meal of the day in both TRE groups together with lower fasting triglycerides; reduced fasting glucose was only seen in the early TRE group compared with baseline.[145] A recent study also supports the benefits of an early TRE for weight loss in overweight adults under free-living conditions.[124] Here, an eating window from 8 am to 7 pm for 8 weeks led to decreased body weight, improvement in insulin resistance, and reduced trunk-to-leg fat ratio and respiratory quotient compared to a delayed eating window (from 12 pm to 11 pm).

One of the factors associated with the benefits of following an early TRE regimen could be the circadian timing of food intake. The well-known diurnal rhythm of glucose tolerance in humans,[146] with insulin sensitivity decreasing from morning to evening hours,[147] could significantly benefit from an early TRE protocol. Even when early TRE can also reduce hunger feelings[148] and some benefits have been reported by a late TRE,[149] an early TRE could induce better body weight control and improvements in glucose homeostasis, leading to enhanced metabolic health. However, it remains to be elucidated whether the timing of TRE can be more effective than standard caloric restriction, as there are reports of similar body weight loss between an early TRE and caloric restriction in adults with obesity.[122] More research is needed to clarify the role of the timing of TRE on body weight control and

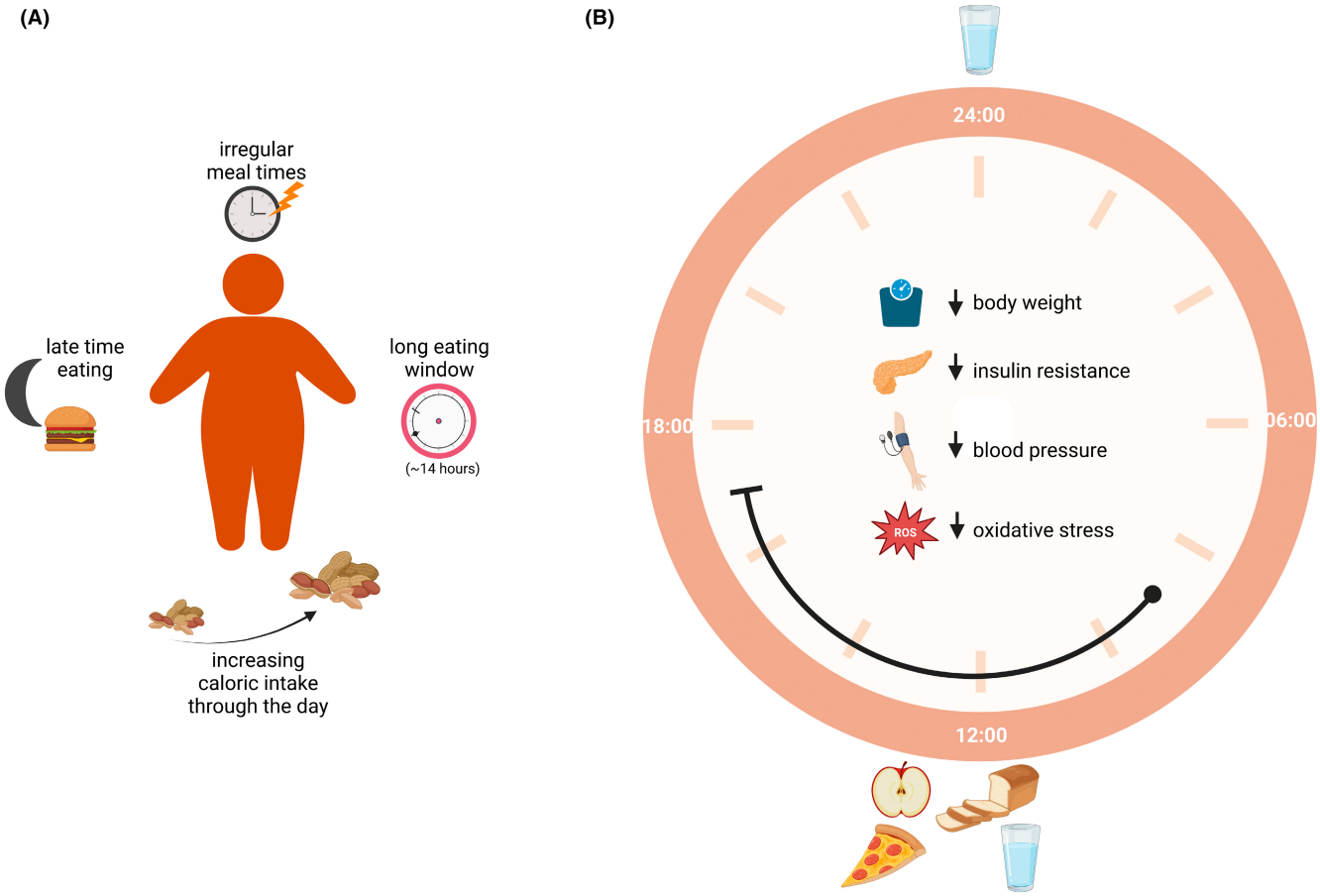

FIGURE 4 An early timing of eating can improve metabolic alterations commonly found in obesity. Alterations of meal timing such as irregular eating times (erratic eating patterns), increasing caloric consumption throughout the day, late time eating (concentrating main meals through late-afternoon and evening hours), and having a long eating window (i.e., the time elapsed between the first and last meal of the day) are commonly found in westernized societies and relates to obesity (A). The restriction of food to a selected eating window ('time restricted eating') can help to counteract metabolic alterations commonly found in obesity (B). An 8-h eating window is depicted (curved black line; from 9 am until 5 pm, as example) a period where food and beverage consumption takes place. No food/beverage intake (containing kilocalories) is permitted outside the eating window except for water. Time-restricted eating has been associated with several metabolic benefits in individuals with and without obesity.

metabolic regulation in humans, as most studies are short-term and sample sizes are small and with high variability in-between studies.

2 | CONCLUSIONS

The circadian clock has a fundamental role in modulating eating behavior and food intake regulation. Data from animal and human studies support that the regular timing of meals and eating in alignment with the circadian clock can enhance metabolic control and prevent metabolic alterations arising from unhealthy eating (energy-rich, high-fat diets) and erratic eating patterns (mistimed food intake). Mounting evidence in humans suggests that eating early during the daytime is associated with improved body weight control and metabolic homeostasis. Undoubtedly, a better understanding of the timing of eating and its metabolic consequences for preventive and eventually therapeutic purposes would be advantageous for treating metabolic diseases such as obesity, and for specific groups exposed to circadian misalignments, such as shift workers.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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