REVIEW ARTICLE

Mealtime: A circadian disruptor and determinant of energy balance?

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Abstract

Circadian rhythms play a critical role in the physiological processes involved in energy metabolism and energy balance (EB). A large array of metabolic processes, including the expression of many energy-regulating endocrine hormones, display temporal rhythms that are driven by both the circadian clock and food intake. Mealtime has been shown to be a compelling zeitgeber in peripheral tissue rhythms. Inconsistent signalling to the periphery, because of mismatched input from the central clock vs time of eating, results in circadian disruption in which central and/or peripheral rhythms are asynchronously time shifted or their amplitudes reduced. A growing body of evidence supports the negative health effects of circadian disruption, with strong evidence in murine models that mealtime-induced circadian disruption results in various metabolic consequences, including energy imbalance and weight gain. Increased weight gain has been reported to occur even without differences in energy intake, indicating an effect of circadian disruption on energy expenditure. However, the translation of these findings to humans is not well established because the ability to undertake rigorously controlled dietary studies that explore the chronic effects on energy regulation is challenging. Establishing the neuroendocrine changes in response to both acute and chronic variations in mealtime, along with observations in populations with routinely abnormal mealtimes, may provide greater insight into underlying mechanisms that influence long-term weight management under different meal patterns. Human studies should explore mechanisms through relevant biomarkers; for example, cortisol, leptin, ghrelin and other energy-regulating neuroendocrine factors. Mistiming between aggregate hormonal signals, or between hormones with their receptors, may cause reduced signalling intensity and hormonal resistance. Understanding how mealtimes may impact on the coordination of endocrine factors is essential for untangling the complex regulation of EB. Here a review is provided on current evidence of the impacts of mealtime on energy metabolism and the underlying neuroendocrine mechanisms, with a specific focus on human research.

KEYWORDS
chrononutrition, circadian disruption, circadian rhythms, energy balance, energy expenditure

1 | INTRODUCTION

The influence of circadian rhythms on energy balance (EB) has become a topic of increasing interest with a new-found pursuit to identify whether meal timing or energy distribution across the day can impact on weight management and metabolic health. Life on earth is characterised by continuous rhythms arising from evolutionary adaptations to earth's natural 24-hour light/dark cycle. As humans, we have evolved an active light phase primarily designed for energy replenishment, reproduction and activity, and an inactive dark phase in which to sleep, recover and regenerate. To achieve these daily cycles, input is required to inform the body of the time of day, and outputs are required to relay this information between central and peripheral tissues.[1,2]

New research in murine and human models highlights the importance of circadian rhythms with respect to regulating energy metabolism, and the metabolic health consequences that may occur from disruption of these rhythms. How time of eating results in changes in clock genes and then impacts on metabolic health is currently not well defined. Specifically, the effect of meal timing on energy expenditure (EE) and EB remains controversial. Figure 1 illustrates the complex regulation of EB, with temporal input from the central clock (in the brain), activity and feeding, as required to synchronise the temporal excretion of neuroendocrine hormones, which in turn regulate energy intake (EI) and EE. Here, we review current evidence regarding the influence of circadian rhythm disruption, and specifically differences in mealtime, on EE with a focus on underlying endocrine mechanisms involved in energy regulation. Because the term circadian disruption is not clearly defined, we address the effects of potent desynchronisation protocols as circadian disruptors, as well as the more subtle effects of altering mealtime, where the extent of circadian disruption may be less obvious. The first part of the review addresses the effects of circadian disruption on whole body EE. The second part addresses the underlying endocrine changes that may contribute to chronic alterations in energy regulation.

2 | CIRCADIAN RHYTHMS AND THEIR ROLE IN METABOLISM

The suprachiasmatic nucleus (SCN) is located in the hypothalamus within the brain and is the primary regulator of circadian rhythms. The SCN receives photic input from the retina, relaying temporal information to the brain and peripheral tissues. The SCN maintains a self-sustaining 24-hour rhythm with output to peripheral tissues sent via neural (autonomic), hormonal (hypothalamo-pituitary) and behavioural signals to create internal synchrony between central and peripheral clocks of the body (Figure 1). Regulation of the mammalian system, including human rhythms, is driven by two primary feedforward/feedback loops in which transcription factors CLOCK and BMAL1 activate several clock genes (cryptochrome [CRY 1 and CRY2] and period [PER1, PER2, PER3]) and nuclear receptors (RORα and REV-ERBα). These in turn inhibit or further activate CLOCK/

BMAL1 expression and therefore the timing of clock-controlled gene expression required for temporal regulation of local tissue (Figure 2).[3,4] These clock genes have been identified in almost all human organs and tissues and individually regulate the timing of physiological processes within different compartments of the body. Specifically, many of the functions involved in energy metabolism and regulation of EB are under strong circadian control and have been reviewed in detail previously.[5,6] In addition to photic inputs, other factors, such as food (both quality, quantity and timing) and physical activity, can act as entrainment cues (zeitgebers). Although the timing of activity can induce phase-shifts in the master clock,[7,8] feeding time primarily influences peripheral clock timing with little to no effect on the SCN.[9-11] Therefore, in an interactive loop, circadian rhythms can drive EI and regulate energy metabolism, yet energy intake and activity can also influence the timing of clock genes and their local tissue activity (Figure 1).

Regular circadian rhythms help to maintain normal body functions and enable anticipation of events required for survival, including regulation of the timing of sleep, activity, digestive processes and metabolism (both storage and breakdown of fuel sources).[1,2] Both central and peripheral rhythms are evident in many key metabolic processes, including regulation of EB, from the most basic cellular level though to whole body energy metabolism. For example, circadian rhythms can influence genes and gene products involved in rate-limiting steps of cellular metabolism. A good example is the supply of NAD +, which exhibits a daily rhythm as a result of circadian oscillations in nicotinamide phosphoribosyltransferase (NAMPT), which controls a rate-limiting step in the salvage of NAD+.[12,13] Various endocrine signals involved in the regulation of energy metabolism display circadian oscillations[6] and circadian variations in overall whole body EE and macronutrient balance have been observed as a result of oscillations in preferential nutrient uptake and the use of macronutrients at specific times of the day.[5,6] Circadian variation in resting metabolic rate (RMR) has been observed in a number of human studies, with RMR or CO_2 production peaking around 5.00 to 6.00 PM, and with a trough at approximately 5.00 AM.[14,15] The thermic effect of food (TEF) has also been reported to be greater in the morning compared to the evening.[16-19] The reasons for this are not clearly understood, although it was suggested to be the result of many of factors, including insulin resistance in the evening,[20-22] reduced nutrient uptake in the evening resulting in lower energy intensive processes such as hepatic and muscle glycogen synthesis, which both display diurnal variation and peak during the active phase,[23-25] as well as lower rates of futile substrate cycling and/or reduced rates of protein turnover.[16] Following the consumption of identical meals, glucose, insulin and free fatty acid levels are reportedly elevated in the evening compared to the morning, indicating a lower uptake and storage of nutrients.[19] This may in part explain the lower evening TEF measured in some studies. Furthermore, circadian clock gene regulation in peripheral tissues is likely to be responsible for reducing nutrient absorption in the evening, allowing for more readily available fuel to prepare for the onset of fasting.
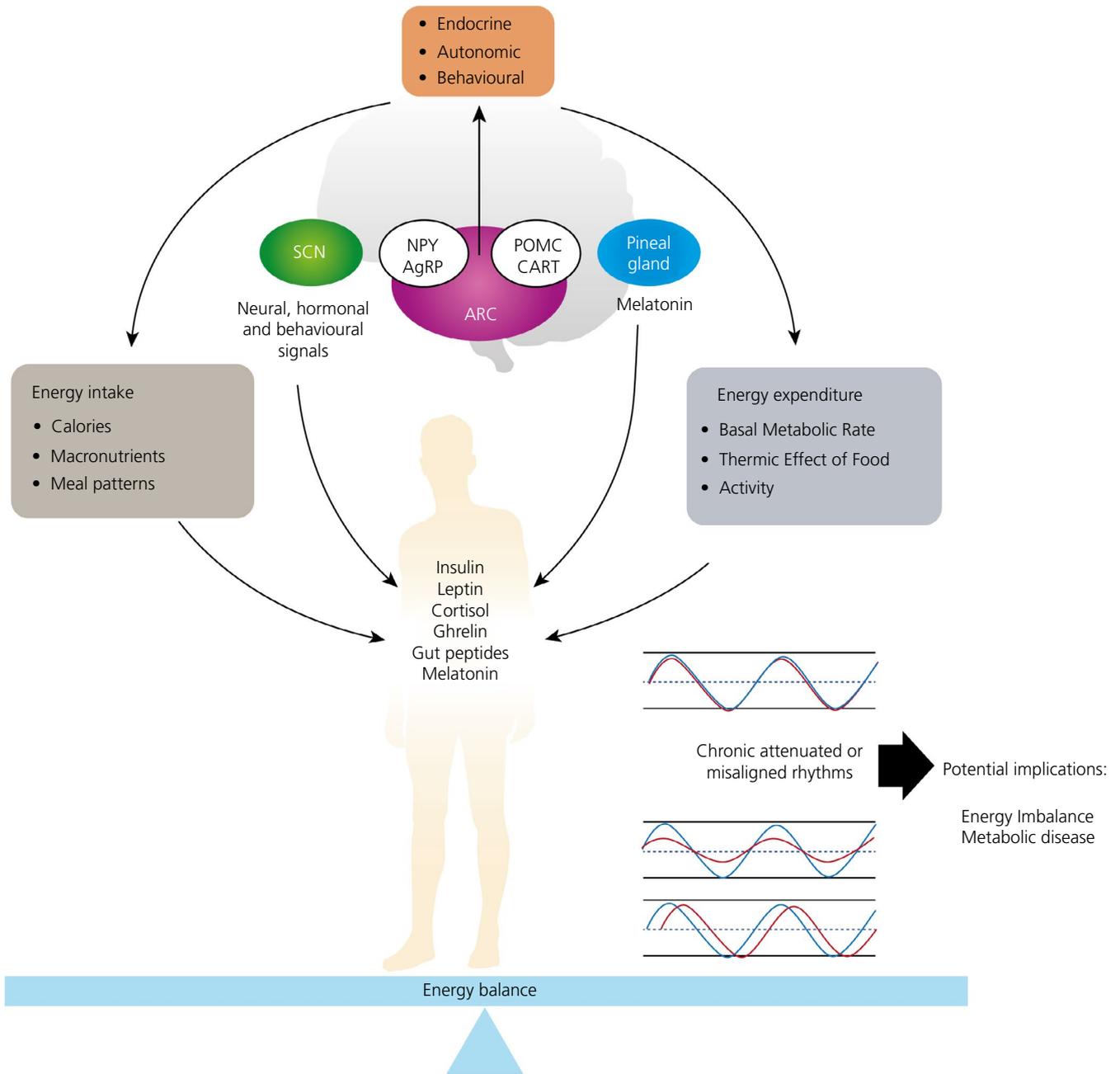
FIGURE 1 Circadian influences in the regulation of energy balance. Neuroendocrine hormones responsible for regulation of energy balance are excreted from multiple peripheral organs at specific times of the day in response to temporal input from neural, hormonal (predominantly melatonin) and behavioural signals from the suprachiasmatic nucleus (SCN). Hormonal signals relay messages within the periphery and to the energy regulatory centres in the arcuate nucleus (ARC) in the hypothalamus where temporal expression of receptors allows for effective signalling. Within the ARC, activation of the neuropeptide Y (NPY)/agouti-related protein (AgRP) and pro-opiomelanocortin (POMC)/cocaine- and amphetamine-related transcript (CART) neurones express their respective neuropeptides to increase or decrease appetite and reduce or increase energy metabolism and energy expenditure respectively. Mealtime and activity can also influence the timing and amplitude of peripheral clock genes and hence timing of hormone secretion. Differential input from energy intake (EI)/energy expenditure (EE) and the SCN may result in circadian desynchrony with either misaligned or attenuated circadian rhythms. Chronic misalignment may result in energy imbalance through dysregulation of peripheral energy metabolism and dysregulated signalling to the brain in relation to EE and EI

Nutrient oxidation also appears to be under circadian control, with higher carbohydrate oxidation in the morning and greater fat oxidation in the evening.[15] These findings are evidence of the robust circadian regulation involved in processes of energy metabolism.

3 | MEALTIME AS A ZEITGEBER

Meal timing is a potent zeitgeber in peripheral clocks. This is based not only on the time of eating, but also nutritional cues. Macronutrients
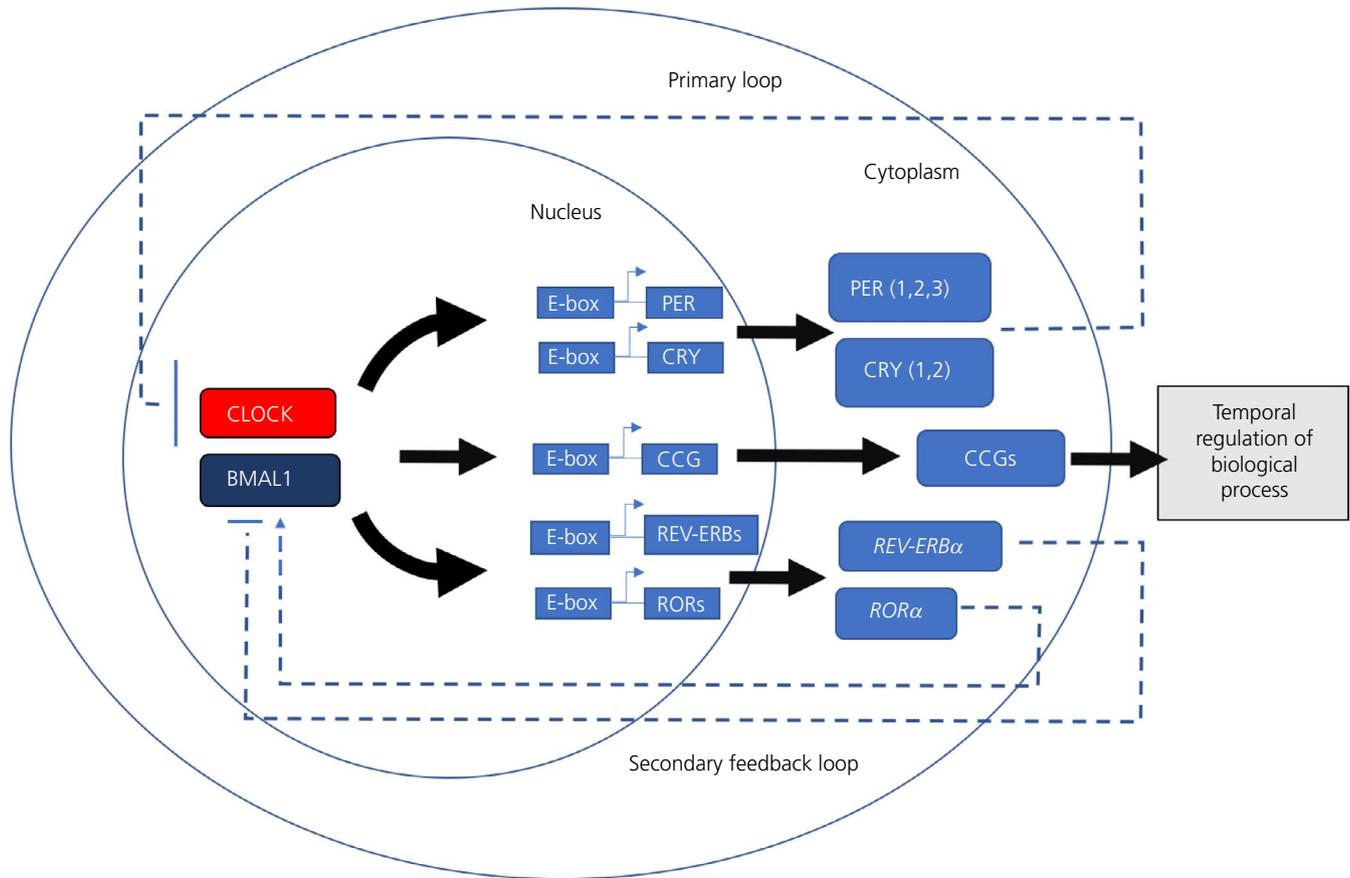
FIGURE 2 Regulation of circadian rhythms by molecular clock components. Two transcription/translation feedback loops work together to generate 24-hour rhythmic gene expression in the mammalian system. Primary transcription factors CLOCK and BMAL1 bind to specific E-box sites to activate the expression of protein genes CRY1 and PER. In a primary negative-feedback loop, CRY and PER proteins inhibit their own transcription by inhibiting CLOCK and BMAL1 activity. In a secondary feedback loop, nuclear receptors RORα and REV-ERBα, are activated by BMAL1 and CLOCK and, in turn, RORα activates and REV-ERBα suppresses BMAL1 transcription. BMAL1, brain and muscle ARNT-like 1; CCG, clock controlled genes; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; PER, period; ROR, retinoic acid receptor-related orphan receptor

and energy sensing enzymes (including PARP-1, SIRT1, AMPK and mTOR),[26,27] all may serve as signals for entraining peripheral clocks to meal timing. Additionally, secretion of food driven hormones from the gut (eg, peptide YY [PYY], oxyntomodulin, cholecystokinin [CCK], gastric leptin and ghrelin),[28-30] peripheral tissues (eg, insulin, glucagon),[31-33] as well as derivatives of gut microbiota, including hydrogen sulphide, certain vitamins and tryptophan, short chain fatty acids and bile acids,[34] all act as signals for entraining peripheral clocks. The ability of mealtime to influence peripheral clock gene expression is evident through the provision of food during the inactive phase in rodent models. Restriction of food to the light phase results in various tissue specific changes in clock gene expression, with a complete inversion of clock gene expression in the liver, partial shifts in brown adipose tissue and arrhythmic expression in skeletal muscle.[9,35] Although the SCN senses food intake, it remains primarily regulated by the light dark cycle. The period required to resynchronise clock genes in peripheral tissues in response to food-induced phase resetting is different between tissues, with faster phase resetting in the liver compared to the heart, kidneys and pancreas, resulting not only in misalignment from the master clock, but also misalignment between peripheral clocks.[9] Similarly, in humans, delaying all meals by 5 hours resulted in a significant delay in the timing of PER2 expression in white adipose tissue; however, there was no significant change in the phase of PER3 or BMAL1 with no change in central clock timing, as assessed by melatonin and cortisol rhythms.[36] This misalignment of rhythms between and within tissues, is suspected to be the cause of the many health implications associated with late night or irregular meal timing.

Delayed meal timing can impose negative effects on health; alternatively, optimal meal timing may improve clock synchrony. It has been observed that the provision of a high-fat diet (HFD) independently of other circadian disrupting factors, can negatively modify the expression of circadian clock genes. Time-restricted feeding (TRF) in mice models, with feeding of a HFD only within an 8-hour window during the active phase in combination with a 16-hour fast, can overcome the large reduction in clock gene expression amplitude in the liver (reduced amplitude in PER2, BMAL1, Rev-erb, Cry1) and amplitude in genes regulating glucose and fatty acid metabolism, as observed during an ad lib. HFD.[37] The translation of such findings to humans is currently limited and likely to be a feature of future research.

4 | PART 1: CIRCADIAN DISRUPTION AND ENERGY EXPENDITURE

4.1 | Effects of circadian disruption on whole body EB and EE

Rodent knockout models provide irrefutable evidence that clock genes influence metabolic physiology and impact on pathways involved in EB. Knockout models result in a large range of health impairments including obesity phenotypes, hyperinsulinaemia, hyperlipidaemia and diabetic phenotypes.[38] However, the more subtle effects of circadian misalignment as opposed to gene knockout models are still being investigated and the effects of larger vs smaller misalignments (eg, shift work vs small changes in meal timing) and chronic vs acute impacts, are as yet incompletely understood. In humans, shift work is associated with an increased risk of obesity,[39] with an increasing number of night shifts per month[40,41] and the duration of shift work,[42,43] both positively correlated with greater body mass index (BMI). This higher BMI has also been reported despite similar EIs, indicating that other factors such as circadian misalignment or lack of sleep, may affect the regulation of EE. In both human and rodent studies, simulated shift work or forced desynchrony protocols have resulted in significantly decreased amplitude, as well as decreased numbers of rhythmic transcripts.[44-47] The effect that this has on energy metabolism is not entirely clear.

Laboratory-based desynchronisation protocols, including the use of altered light/dark cycles to create long or short days, acute phase shifts or a simulated night shift, allow the investigation of the effects of circadian desynchronisation and we are now beginning to understand the underlying mechanisms regulating EB. In rodent studies, restricting food intake to the rest- phase, light at night or forced wheel running in the habitual rest-phase causes rest-phase wakefulness along with feeding and activity out of phase with the master clock. A cumulative number of rodent studies have shown increased body weight, despite similar calorie intake, when rodents are forced into desynchronising behaviours (daytime wakefulness and eating or bright light at night).[48-51] Even dim light at night has been shown to phase shift core body temperature and result in significant decreases in EE and increases in weight gain in mice.[52] However studies reporting no changes[53-56] or decreases in body weight[57,58] are often overlooked and, indeed, there are large variations in energy intake, expenditure and balance between studies in response to desynchronisation protocols and specific outcomes may be species specific. Despite this, most studies do show a level of metabolic disturbance including reduced EE and impaired glucose tolerance.[53,54,57]

In human studies, the effects of circadian desynchrony on EE and EB are also unclear. Imposing desynchrony through long or short days had no effect on total daily EE.[59,60] Gonnissen et al[60] reported a small significant decrease in sleeping metabolic rate after 3 days of phase advance, although this was not reflected in total daily EE and there were no measurable differences in RMR, activity EE or TEF. Buxton et al[61] observed significant decreases

in RMR in a combined sleep restriction plus desynchrony protocol (3 weeks 28-hour days + 5.6-hour sleep/24 hours); however, this may be a result of the restriction of sleep, rather than desynchrony. Certainly, sleep restriction may alter behavioural and physiological mechanisms regulating EB irrespective of circadian misalignment. Leproult et al[62] found significant increases in EI in sleep-restricted individuals under both aligned and misaligned conditions. However, it is important to note that situational cues can easily drive over-consumption in humans. Provision of large ad lib. meals, as was the case in the study by Leproult et al,[62] increased food variety, and simply providing meals in the laboratory compared to eating at home can stimulate increased EI.[63] Furthermore, Leproult et al[62] did not measure EE and therefore the distinction between misalignment and reduced sleep quality/quantity on energy metabolism requires further investigation. In studies of simulated night shift work, reported changes in EE are mixed. McHill et al[64] reported a significant reduction in total daily EE on the second and third days of night shift work and significant reductions in TEF on the first day of shift work, which began to resolve by the third day, suggesting entrainment to the new schedule. By contrast, Morris et al[17] observed no differences in RMR or TEF with misalignment; however, when broken down by gender, females actually showed a significant increase in fasting and postprandial EE during misalignment which was not seen in males.[65] However, in these studies, RMR was only measured at the beginning and end of the day with relatively short and incomplete measures of TEF. Wefers et al[66] have also reported significant increases in sleeping metabolic rate during misalignment, although it is not clear whether this was the result of a change in sleep quality and, in addition, total daily EE was not measured. Assessment of RMR in long-term shift workers indicates that the effects of undergoing large and chronic shifts in time do not alter measured RMR compared to non-shift workers or prediction equations[67,68] and therefore lower RMRs are unlikely to be a causative factor for weight gain in this population. Poorer metabolic health in these individuals may be attributed to other factors, such as changes in appetite, food choice, activity and other behavioural differences. For example, shift workers may have more challenges with respect to coordinating regular mealtimes, balancing sleep, activity and meals around work, and social and family commitments, and may also have higher stress jobs increasing emotional stress and anxiety. Individual variation in coping mechanisms (stress eating, snacking, caffeine, activity avoidance vs activity as an outlet), and the ability to plan and access healthy meals on shift, may differentially influence those at risk of weight gain.[69,70] However, regardless of maintaining EB, metabolic health implications may occur in response to abnormal meal timing and circadian misalignment.

4.2 | Meal timing on EB and EE

Epidemiological studies have contributed to a cumulative body of research showing that disturbances in meal timing including breakfast

skipping, late night eating, and shift work are linked to higher BMIs and elevated risk of metabolic disorders.[71-76] It is now assumed these metabolic disturbances are a result of the effects of meal timing on circadian rhythms. Consistent with this, studies in animal models have highlighted the importance of meal timing in the regulation of EB. Restricted feeding to the dark phase (active phase) in mice has been shown to suppress the normal weight gain that occurs in mice consuming a high-fat ad lib. diet.[37,48,77] Furthermore, day feeding even on chow diet results in weight gain and metabolic impairment, including decreased glucose tolerance and insulin resistance.[54,78-80] Many of these studies show differences in weight gain despite similar calorie intake, indicating that mealtime must alter EB through altered EE. Although the effects of these extreme shifts in the time of feeding found in rodent studies may be extrapolatable to shift workers, there is a need to understand the more subtle effects of shifting meals, such as from earlier to later in the day.[81]

Mealtime studies in rodent models have begun to address these more subtle effects of time of eating and redistribution of energy intake, across the normal wake-phase, on body weight and EB. One study reported that skipping dinner resulted in significantly lower body weight compared to skipping the first meal of the day or having three meals per day.[82] Significantly greater weight gain has been observed in mice that were subjected to a 4-6-hour delay in the onset of wake-phase feeding compared to mice allowed to eat ad lib.[83,84] Yoshida et al[84] confirmed that this weight gain came from greater energy intake compared to mice allowed to eat ad lib. (ad lib. mice consumed 65% of their calories in the first 6 hours of their wake-phase). In a second protocol comparing delayed vs ad libitum feeding, the mice were subjected to energy restriction and matched energy intake. Despite identical intakes, the ad lib. feeding mice lost a greater amount of body weight compared to those in the delayed feeding group. This indicates that later meal timing can contribute to weight gain through reducing EE when energy intake is controlled, as well as through increasing energy intake where food is provided ad lib. Thus, studies in murine models tend to support the idea that eating earlier in the active phase can improve body weight regulation through both energy intake and EE.

In humans, breakfast skipping under EB conditions has regularly been shown to have no effect on RMR or total daily EE compared to consumption of breakfast.[85-87] Although EE is lower in the biological morning, this is compensated for by higher EE later in the day and evening, indicating a redistribution of EE across the day. Indeed, respiratory chamber studies of total daily EE suggest that the lower evening TEF seen with breakfast skipping may be more apparent than real because TEF is actually lower but longer, continuing well into the night and thereby causing an apparently higher sleeping metabolic rate.[87,88] The effects of mealtime appear to be more evident in weight loss studies in which energy distribution is manipulated so that the majority of energy intake is consumed in the morning or consumption of lunch is earlier in the day, resulting in significantly greater weight loss.[89-91] However, even this is not always consistent. Versteeg et al[92] found no differences

in weight loss between individuals consuming 50% of calories at breakfast (15% at dinner) vs 50% at dinner. However, with the exception of the study by Versteeg et al[92] who found no differences in REE with different energy distributions across the day, none of these studies have confirmed whether differential EE could explain their results, rather than the study findings being a result of misreported energy intake.

Although TRF in rodents during the active phase has shown promise by improving markers of glucose metabolism and metabolic health in the absence of weight loss, comparable well-controlled studies to investigate TRF in humans are lacking. So far, most human TRF studies have not controlled or accurately measured energy intake or TEE. Thus, the reports to date suggesting that TRF results in a modest reduction in body weight in humans[80,93-97] of 1%-3% over a period of 2-16 weeks, as linked to improvement in bio-markers of glucose homeostasis, need further investigation and validation. It is not clear whether the apparent improvements in metabolic health are a result of decreased energy intake (negative EB), improved circadian alignment or an increased duration of overnight fasting. Sutton et al[98] reported that, following 5 weeks of early TRF (early eating, 18-hour fast), males showed greater improvements in glucose/insulin metabolism during a morning oral glucose tolerance test, in contrast to the controlled feeding schedule (12 hours of eating and 12 hours of fasting). Interestingly, these improvements were reported in the absence of weight loss, with subjects being weight stable. Furthermore, work by Hutchison et al[99] indicated no effect of TRF on total daily EE or activity. By contrast, Ravussin et al[100] reported elevated post-prandial TEF with early TRF, although this may have been the result of overlapping postprandial EE after meals during the morning feeding period. Additionally, the lower EE during the morning in the control (non TRF) group was made up for by a higher EE overnight and there was no overall difference in total daily EE between feeding regimes. Most recently, Wilkinson et al[97] reported significant improvements in metabolic health, including weight loss, reduced blood glucose, lipids and blood pressure, when individuals adopted a TRF schedule that reduced food intake from 15 hours down to 11 hours per day. These effects were likely the result of a reduced energy intake and elongated overnight fast, with no changes in physical activity and no measures of resting or daily EE. However, similar to animal studies,[37,101] metabolic flexibility, which is the capacity to switch between carbohydrate and fat oxidation, is amplified in TRF in humans with greater lipid oxidation during the prolonged overnight fast.[100] Further to this, Kelly et al[102] found that shifting an eating window to later in the day (from 8.00 AM to 5.45 PM to 12.30 PM to 22.00 PM) resulted in a higher RER, from higher CHO oxidation into the evening and delayed transition into lipid oxidation. This occurred despite the same duration of fasting and no differences in EE. This lack of overnight lipid oxidation may overtime promote lipid storage and adiposity. Further studies with controlled energy intake may be necessary to specifically determine the effects of TRF on human EE and EB.

5 | PART 2: CIRCADIAN DISRUPTION AND ENDOCRINE FACTORS

5.1 | The effects of circadian disruption on energy-regulating endocrine factors

Endocrine factors play an essential role in communication between organs (eg between the central nervous system and peripheral tissues) and provide a fundamental communication pathway involved in clock synchrony, as well as in the regulation of EB. Many of the endocrine factors involved in the regulation of energy metabolism and EB also display diurnal oscillations. However, many are also highly responsive to food intake and other behavioural factors including activity and sleep (Table 1). Clock genes and nutritional signals regulate not only the synthesis and secretion of endocrine factors, but also the abundance/availability and or sensitivity of receptors, as well as the activity of post receptor signalling.[6] Regulation of EE requires complex coordination of multiple hormones acting together in synergistic and additive relationships, as well as synchronised regulation of receptor expression and sensitivity. This necessitates temporal synchrony between all tissues involved in neuroendocrine regulation of metabolism and EB and coordinated temporal input from the central clock and food derived factors. The potential for misaligned temporal hormones to influence energy regulation is shown in the study by Roelfsema and Pijl,[103] in which a wider gap between an individual's cortisol and prolactin acrophase was associated with a higher BMI. Although only comprising an association study, this agrees with research in various species in which the timing of the acrophase of cortisol and prolactin vary across the seasons with an increasing gap during spring/summer linked to fat gain and a shorter gap in autumn/winter linked to fat loss.[104] Furthermore, manipulation of the timing of the prolactin acrophase in hamsters and rats can result in weight gain or loss without changes in energy intake.[105,106] Understanding the circadian nature of energy-regulating endocrine hormones, as well as how they respond to and influence circadian disruption, may provide a means to understand the impacts of desynchrony on metabolic health and EB. Table 1 illustrates the roles and rhythmicity of several key hormones involved in EB regulation. Below we discuss the impacts of circadian disruption on endocrine regulation of EB.

Forced desynchrony protocols are a potent circadian disruptor that we can draw on to assess the effects of circadian disruption on endocrine hormones. Currently, the effect of circadian disruption on the expression of endocrine signals is inconsistent. One example is cortisol. In some cases, the cortisol pattern has tracked the changes in timing of the new behavioural cycle without any negative changes in the amplitude, profile or overall mean concentration.[59,61] However, one study found flattened rhythms with phase advanced protocols and suppression of mean concentrations with phase delay protocols.[60] Other hormones have also been reported on with varied results. Gonnissen et al[60] reported significantly higher mean insulin concentrations during a phase advance protocol (21-hour days) compared to control 24-hour days, although no differences in daily mean leptin, glucagon-like peptide (GLP)-1, ghrelin and glucose concentrations. However, with a phase delay protocol (27-hour days), there were significantly higher glucose and lower GLP-1 levels and a tendency for reduced leptin concentration, although no differences in mean ghrelin or insulin concentration. Scheer et al[59] also reported a 17% lower leptin across the entire behavioural cycle with the implementation of 28-hour days with significant increases in insulin (22% increase) and glucose (6% higher), which was predominantly from exaggerated postprandial responses as opposed to changes in fasting glucose. Receptor sensitivity may also be negatively affected by circadian disruption; however, the evidence currently stems from rodent models. Arcuate nucleus (ARC) leptin sensitivity displays a 24-hour rhythm,[164] with chronic jet lag in mouse models shown to impair leptin signalling, through dampening signal transducer and activator of transcription 3-pro-opiomelanocortin signalling in the ARC, resulting in leptin resistance from desensitisation of LEPR-B-expressing ARC neurones.[144] These changes in leptin signalling were also coupled with reduced and arrhythmic EE. Similarly, chronic jet lag has been found to alter insulin signalling pathways at various levels within the ARC. The actual implications of this are currently inconclusive, with chronic jet lag found to negatively impact on insulin sensitivity at the insulin receptor substrate level, yet to increase sensitivity at the phospho Akt level.[165] Therefore, coupling of central and peripheral clocks regulating leptin and insulin are necessary for functional homeostatic feedback loops. Further research is necessary to comprehensively establish the circadian disruption-induced neuroendocrine changes that may contribute to changes in acute and chronic EB.

5.2 | The effects of mealtime on endocrine factors

Compared to forced desynchrony protocols, it is less clear to what extent meal timing causes circadian disruption and negative changes in the circadian regulation of EB. Night eating syndrome (NES) provides a model for understanding possible implications of meal timing. NES is defined as consuming ≥ 25% of daily energy intake after the evening meal and/or ≥ 2 nocturnal ingestions (waking up at night to eat) per week.[166] Individuals with NES often display increased cortisol levels and decreased or delayed melatonin levels, often with no delay in the time of sleep relative to those with regular food consumption. In these individuals, both leptin and ghrelin may be lower, not different or phase shifted, and insulin and glucose are often increased with generally a degree of phase shift and loss of synchrony between glucose and insulin.[167] In a study by Goel et al,[168] NES patients displayed a significant delay in the phase of melatonin (1 hour 6 minutes delay) with a smaller yet non-significant decrease in amplitude (15.3% lower). Even ignoring melatonin disruptions, a large cohort study found eating a greater percentage of calories closer to the personal relative melatonin onset, irrespective of clock time, was associated with increased body weight.[169] Goel[168] also reported individuals with NES had a significant decrease in cortisol amplitude (25.6% lower), although

there was no significant delay in the phase (42 minute delay). This was accompanied by significant differences in the profiles of ghrelin (49.6% lower amplitude, 5 hour 18 minutes phase advance), leptin (1-hour phase delay), and insulin (57.7% lower amplitude, 2 hour 48 minutes phase delay). In rodent models, simply suppressing the amplitude of glucocorticoids, without significantly changing their mean concentrations, results in substantially greater weight gain compared to controls. This occurred despite no differences in energy intake.[170] Hence, flattening of the cortisol rhythm may affect EB through alterations in EE and may account for the higher BMI in those with NES. Interestingly, in the study by Wehrens et al,[36] a 5-hour delay in meal timing (33% of energy intake within the half-hour before bed), resulted in no alterations in the phase or amplitude of plasma cortisol. It is possible that changes in cortisol rhythm may take longer than the 6 days of delayed meals, as was undertaken in the study by Wehrens et al,[36] or other factors, such as disrupted sleep or awakening to eat, may account for cortisol amplitude suppression in NES.

Ramadan is characterised by daylight fasting and night-time feasting and provides another regular and convenient model of assessing the effects of irregular meal timing. The majority of calories are consumed shortly after sunset, with snacks often consumed throughout the night and all food intake ceased at dawn. By the end of Ramadan, a number of studies have shown a tendency for postponed endogenous circadian rhythms by as much as 2-3 hours[171,172] reduced amplitude and 24-hour mean melatonin[173] and significant flattening of cortisol rhythms.[174] By contrast to the anticipated negative ramifications, Ramadan often results in small improvements in many markers of cardiometabolic health as a result of the typically observed transient weight loss likely from prolonged fasting.[175,176] However, increased morning and evening insulin levels have been noted.[174] Few studies have looked at the effects of Ramadan on energy-regulating neuroendocrine hormones. In one study, there were no changes in the acrophase or amplitude of leptin and ghrelin; however ghrelin was modestly higher at 11.00 AM and leptin significantly lower at 10.00 PM.[177] Despite a trend to lower daytime EE likely as a result of lower activity, the small number of studies which have assessed EE have observed no evidence of metabolic adaptation, with no change in RMR or 24-hour EE.[177,178]

Breakfast skipping, tends to push meal intake later into the day and has been proposed to have a negative impact on EB mechanisms. The Bath Breakfast Study compared 6 weeks of breakfast eating to skipping and observed no differences in fasting measures of glucose, insulin, T3 and T4, leptin, ghrelin, PYY, GLP-1 or adiponectin. This was the case for both lean and obese individuals. Test day postprandial measures of leptin, ghrelin, PYY, insulin and glucose, as assessed for 3 hours post breakfast and lunch, were also indifferent between breakfast conditions.[179] GLP-1 and adiponectin were the only hormones to show a tendency for a difference. Plasma GLP-1 increased in the breakfast group and decreased in the fasting group, whereas adiponectin showed no change in the breakfast group compared to increasing

in the fasting group. Farshchi et al[180] reported that skipping breakfast resulted in significant increases in postprandial insulin area under the curve (AUC), although this did not have any effect on postprandial EE. Delaying the timing of lunch may even be sufficient to alter endocrine regulation, with Bandin et al[181] finding a suppression of morning cortisol after 2 weeks of late lunch eating (16.30 PM) vs early lunch eating (1.00 PM). However, this is in contrast to the lack of any differences in 24-hour cortisol values and profiles in the study by Nas et al[88] comparing habitual three meals, breakfast skipping and dinner skipping. Despite the larger weight loss in the earlier lunch eaters in the study by Garaulet et al,[89] there were no notable differences in leptin, ghrelin or insulin. However, all of these measures were undertaken fasting and there may have been differences across the day or in the postprandial state (ie, the circadian rhythm in these markers was not captured). Changing the energy distribution across the day so that majority of calories are consumed in the morning vs the evening may also affect EB through neuroendocrine changes. Jakubowicz et al[90] noted significantly higher insulin levels and ghrelin levels in individuals consuming 45% of their calories in the evening. Versteeg et al[92] reported that 50% of calories consumed at breakfast vs dinner during weight loss resulted in differential effects on fasting cortisol and glucagon, with an increase in fasting cortisol in the breakfast group compared to a decrease in the dinner group and a significant decrease in glucagon only in the breakfast group.[92] However, they found no differences in fasting ghrelin, leptin, glucose or insulin between the groups.[182] Interestingly, they also looked specifically at neuronal circuits that regulate energy homeostasis and found significant increases in dopamine transporter in the striatum and serotonin transporter in the thalamus with early feeding and decreases with late feeding. They hypothesise that morning predominant calorie intake may impact on EB through positively reinforcing brain reward circuitries involved in the hedonic aspects related to food.[182] These findings could theoretically reduce overconsumption, improve dietary compliance and improve satiety. If true, these findings could display a more measurable impact on body weight regulation under ad lib. feeding conditions, where they could improve EB through mechanisms regulating EI more so than EE. Further research is required to understand how endocrine differences resulting from breakfast skipping and energy distribution may contribute to differential EB.

Time-restricted feeding has become a novel approach to potentially improve EB. Although, in humans, the negative EB and weight loss currently appear to be related to reduced energy intake, alterations in endocrine regulation may result in long-term changes in mechanisms controlling both energy intake and EE. Often, no differences are noted in fasting measures of ghrelin, leptin, adiponectin glucagon and insulin[98,99,183]; however, mixed results have been reported for PYY and GLP-1. One study demonstrated a reduced fasting GLP-1 with early TRF and no change in PYY,[99] whereas another found a decreased morning PYY yet no change in GLP-1 in the morning.[98] Hutchison et al[99] also reported a lower postprandial glucose incremental AUC and trend to a

TABLE 1 Overview of the roles and rhythms in energy-regulating endocrine hormones

Hormone (references)	Role in energy balance	Circadian/diurnal or food related rhythm	Role in regulation of other endocrine signals
Melatonin[107-114]	Influences insulin sensitivity and induces nocturnal insulin resistance. Stimulates lipolysis via: • Activating the SNS • Stimulating intramuscular adipocyte lipolysis May enhance intramuscular adipocyte thermogenesis via: • Increased mitochondrial biogenesis • Increased mitochondrial respiration Supports reduction in food intake via: • Stimulation of POMC mRNA in the hypothalamus and pituitary Possible role in leptin signalling: • Absence of melatonin can result in impaired leptin signalling and leptin resistance in the hypothalamus and subsequent increases in orexigenic neuropeptides AgRP and NPY	Robust circadian pattern Secreted from the pineal gland via activations of noradrenergic (sympathetic) afferents in response to direct input from the SCN Onset in the evening, night-time peak and decreases in the morning	Potent regulator of peripheral rhythms Primary hormone acting as an internal synchronizer for peripheral tissues through either direct or downstream effects Feeds back to the master clock itself Essential for maintaining rhythmic leptin secretion, maintaining the phase of cortisol secretion and may also adjust the phase of insulin release
Cortisol (glucocorticoids)[115-122]	Essential for mobilising fuels in response to other hormonal signals (eg insulin and glucagon) Catabolic in nature. Enhances readily available energy in the body via: • Reducing uptake of nutrients from the blood (partially by reducing insulin sensitivity) • Maintaining adequate concentrations of enzymes required for macronutrient breakdown • Stimulating the breakdown of nutrient reserves (increased lipolysis, proteolysis and glycolysis) • Converting energy to readily available forms (gluconeogenesis)	Robust circadian pattern Peak in the early hours of the wake phase and a nadir in the evening/early night Regulated by circadian variation in ACTH release as well as circadian regulation of tissue specific sensitivity to ACTH in the adrenal gland Acute stressors and meals can stimulate ACTH and cortisol release. This response is generally superimposed above the 24-hour endogenous cycle without an overall effect on the phase or amplitude Highly regulated by the sleep/wake cycle. Decreases at the onset of sleep even during the day and higher cortisol at night during nocturnal awakenings	Glucocorticoid receptors are located on various tissues indicating a role of cortisol as a messenger to peripheral tissues Receptors identified in the liver, muscle, pancreatic β-cells, white adipose and gut tissue Direct impact of glucocorticoids or dexamethasone, (a potent synthetic glucocorticoid) have been shown in synchronising, shifting or reducing the amplitude of local clock genes in the liver, skeletal muscle and white adipose tissue
Insulin[123-132]	Primary role is to regulate blood glucose levels. Peripherally, insulin is highly anabolic: • Attaches to receptor sites on target cells to enable the uptake of glucose from the blood stream • Enhances synthetic processes (fatty acid and triacylglycerol synthesis, protein synthesis, glycogenesis) • Suppressed catabolic processes (lipolysis, proteolysis, gluconeogenesis and glycogenolysis) Centrally, insulin acts as a deterrent to weight gain. Readily crosses the blood-brain barrier and binds to receptors in the ARC in the hypothalamus to repress food intake via: • Decreasing the expression of the orexigenic neuropeptides NPY and AgRP • Increasing the expression of anorexigenic neuropeptides POMC and CART	Primarily released in response to glucose intake However, its secretion and receptor sensitivity show diurnal variation. In healthy individuals, β-cell responsiveness to glucose and whole-body insulin sensitivity are impaired later in the day In obese individuals, rhythms in insulin sensitivity are attenuated, phase delayed or even absent, with inverted or absent rhythms reported in individuals with type 2 diabetes	

TABLE 1 (Continued)

Hormone (references)	Role in energy balance	Circadian/diurnal or food related rhythm	Role in regulation of other endocrine signals
Glucagon[160-163]	Primarily known for its role in glucose regulation. Increases energy availability through processes in hepatocytes: • Increases glycogenolysis and gluconeogenesis • Decreases glycolysis and glycogenesis. • Increases fatty acid breakdown in the liver and decreases lipogenesis. • Promotes amino acid breakdown • Therefore, may reduce hepatic lipid accumulation May stimulate lipolysis in adipocytes in humans however only if insulin levels are low. Possible roles in satiety • May modulate satiety – has been shown to reduce food intake and inhibit hunger, likely through brain – liver axis • Although somewhat counterintuitive, it may be due to cross-reactivity with GLP-1 receptors. • It may arise from hepatic metabolic changes or from glucagon working directly in the CNSPossible capacity to increase energy expenditure: Infused glucagon shown to increase EE in some human studies however the Effects of endogenous glucagon on EE remain unclear	Secreted primarily in response to nutrient availability in the body. Eg hypoglycaemia, prolonged fasting, exercise and protein rich meals. Additional mechanism governed by by cell-autonomous islet clocks Daily oscillation in pancreatic alpha cells section in vitro (mice and human cells) Correspondingly, glucagon secretion is also circadian as assessed in vivo (rodents) and in vitro (mice and human cells). The acrophase of the glucagon rhythm is slightly phase delayed compared to insulin. (about 2 h delay in the peak) Type 2 diabetes α- and β-cells exhibit significant phase delays and wider phase distribution indicating less synchronization among the endocrine cells within islets	Glucagon signalling increases the secretion of fibroblast growth factor 21 (FGF-21), also known to be involved in regulating energy balance. Glucagon may regulate its own secretion indirectly via stimulating beta cells to secrete insulin.
Leptin[133-144].	Central leptin acts in hypothalamus to suppress food intake and stimulate EE via: • Activation of anorexigenic neuropeptides POMC/CART • Inhibition of orexigenic AgRP/NPY • Opposing ghrelin signalling and synergising with insulin signalling • Effecting the mesolimbic dopaminergic reward/motivation system which in turn regulates locomotor activity Peripheral leptin: • Alters intestinal absorption (alters nutrient uptake from the gut) • Increases insulin sensitivity • Reduces gluconeogenesis in the liver • Increases thermogenesis in adipocytes • Increases uncoupling proteins and fatty acid oxidation in adipocytes, muscle and pancreas • Effects fat and carbohydrate oxidation	Diurnal rhythm. Predominantly regulated by food intake though also dependent on the circadian clock Circadian amplitude reportedly 10% of the overall diurnal profile Nadir in the early morning though to middle of the active phase, increases throughout the day and peaks during sleep at night Maintains this diurnal pattern regardless of standard meal intake, continuous enteral nutrition or prolonged wakefulness Restriction of food to the rest phase can completely invert leptin rhythms indicating external food cues are the primary regulator Receptiveness of circulating leptin in the CNS is also circadian, with the SCN rhythmically potentiating the response of ARC neurones to circulating leptin	Increases insulin sensitivity Opposes ghrelin signalling and synergizes with insulin signalling Can decreases cortisol levels Influenced by glucocorticoids and insulin which increase leptin secretion and by catecholamines, T3/T4 and androgens which reduce leptin section

(Continues)

TABLE 1 (Continued)

Hormone (references)	Role in energy balance	Circadian/diurnal or food related rhythm	Role in regulation of other endocrine signals
Ghrelin[145-155]	Primary recognised for its effects in inducing hunger Centrally elicits hunger and food intake via: • Activating GHS-Rs in the hypothalamus which express NPY/AgRP and orexin Peripherally: • Stimulates gut motility and gastric acid secretion • Suppresses fat thermogenesis and protects against muscle atrophy • Decreases insulin secretion and sensitivity • Increases glucagon secretion, hepatic gluconeogenesis and lipogenesis as well as lipogenesis and adipogenesis in adipose tissue May impact on EE: Ablation of the ghrelin receptor GHS-R increases EE by: • Increasing thermogenesis in brown adipose tissue • Increasing uncoupling oxidative phosphorylation • Can reduce thermogenesis through reducing SNS activity	Predominantly regulated by feeding/fasting cycles with clear pre-prandial rises and postprandial decreases Ghrelin levels continue to show small peaks and troughs around meals times even under fasting conditions Although predominantly affected by meal timing, both fasting and postprandial acylated ghrelin was reported to be significantly higher in the biological evening compared to the morning	Activates growth hormone secretagogue receptors (GHS-R) in the pituitary which subsequently leads to growth hormone secretion. Decreases insulin secretion and sensitivity Increases glucagon secretion
Other gut peptides[156-159]	Satiety peptides from the stomach and intestine include PYY, pancreatic polypeptide, GLP-1, oxyntomodulin, and CCK. Predominantly • Indirect signals to the hypothalamus through stimulation of the vagus nerve and the solitary tract nucleus of the brain stem Secondary roles involve promoting digestion via: • Altering gastric emptying • Stimulating/decreasing pancreatic enzyme secretion • Stimulating gall bladder contraction • Increasing the absorption of fluids and electrolytes from the ileum	Predominantly secreted in response to meals in relation to the size, energy content and macronutrient composition. Their response to any given meal may show a degree of circadian variation. Large lack of research on circadian rhythms in gut peptides under gold standard measures. Current findings: • Rhythmic expression of clock genes in human L cells has been identified in vitro GLP1: • Diurnal rhythm in secretion under both basal and postprandial conditions. • Fasting GLP-1 secretion highest at 06:00 and lower at 11:00 and 23:00 • Postprandial secretion varying results: • First 30 min excretion - lower at 11.00 AM compared to 11.00 PM Trend to higher postprandial GLP-1 in the morning vs evening after identical meals GIP: • Postprandial GIP secretion significantly higher in the evening CCK and Gastrin: • Reports of rhythmic secretion	

Abbreviations: ACTH, adrenocorticotrophic hormone; AgRP, agouti-related peptide; ARC, arcuate nucleus; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CNS, central nervous system; EE, energy expenditure; GHS-R, growth hormone secretagogue receptor; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; mRNA, messenger RNA (ribonucleic acid); NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, pancreatic peptide YY; SCN, suprachiasmatic nucleus; SNS, sympathetic nervous system; T3, triiodothyronine; T4, thyroxine.

lower insulin incremental AUC with early vs late TRF. Moro et al[184] found that, after 8 weeks of restricting intake to between 1.00 PM to 9.00 PM compared to 8.00 AM to 9.00 PM, there was a significant reduction in inflammatory markers and increased adiponectin. Adiponectin has anti-inflammatory functions, interacts with AMPK and stimulates peroxisome proliferator-activated receptor gamma coactivator 1α) protein expression and mitochondrial biogenesis. It can also act in the brain to increase EE and hence may have contributed to differential weight loss in the TRF group. However, Sutton et al,[98] reported that early TRF for 5 weeks had no effect on inflammatory markers high-sensitivity C-reactive protein and interleukin-6, as well as no changes in cortisol. They also note a significant increase in 8-isoprostane (a marker of oxidative stress) in the control group which was not detected in the early TRF group. Therefore, early TRF may have been preventative against the effects of the diet provided. TRF may improve energy metabolism through decreased inflammation and subsequently improved insulin, leptin and other endocrine sensitivity. Further research aiming to understand differences in meal timing is necessary, including more longitudinal measures and accurate 24-hour assessments of EI, expenditure and neuroendocrine regulatory factors.

6 | FURTHER CONSIDERATIONS AND SPECULATIONS

The effects of mealtime on circadian rhythms and metabolic health are highly complex and current research has only scratched the surface of this new topic. Many studies are complicated by the fact that any negative effects of eating at the wrong time of day may be at least partially compensated for by extended periods of daily fasting, which is the case in many animal studies, as well as in the examples of Ramadan, breakfast skipping and TRF. Further to this, the majority of human TRF trials have only compared TRF (generally using an early window) to regular eating durations, with only one study specifically comparing early vs late TRF.[99] In rodent studies, early compared to late TRF may improve circadian alignment,[83] reduce insulin resistance[185] and reduce weight gain.[83,185] However, the only human study to date found no differences in weight change as a result of the feeding window. There were also only small improvements in fasting glucose in early TRF compared to baseline and no differences in fasting glucose between early and late TRF. Therefore, the time window for which TRF may have its greatest impacts has not currently been verified in humans. In addition to the current findings, the role of macronutrient intake at different times of the day and an individual's genetic predisposition to the negative effects of late-night feeding need to be considered. For example, one study reported that, when a high carbohydrate meal (75% carbohydrate, 1600 kcal) was served at breakfast (8.30 AM) for three consecutive days, it resulted in a 1-hour phase advance in core body temperature. By contrast, the same meal served at night (9.00 PM) had no

effect on body temperature, although it did shorten or attenuate the melatonin rhythm.[186] It is not clear whether this was the result of the carbohydrate content or energy content of the meal and whether similar macronutrients would have similar effects. The time in which dietary fat is consumed has also been suggested to influence cardiometabolic health. In rodents, a HFD consumed at the end of the active phase resulted in significant weight gain, increased adiposity, hyperinsulinaemia and hyperleptinemia, relative to a HFD consumed at the start of the active phase.[187] The order of carbohydrate and fat intake throughout a day may also impact on endocrine signals. In humans, starting the day with a high carbohydrate diet and finishing with a HFD led to higher daily leptin levels compared to starting the day with high fat and finishing with high carbohydrate. However, these results need to be advocated.[188]

Many sleep and circadian behaviours have been established to be trait like and reproducible within individuals, including responses to sleep deprivation, hormonal responses to awakening,[189] awakenings in response to environmental stimuli,[190] weight gain, increased EI, late-night eating and fat intake in response to insufficient sleep,[191] and phase shifting responses to caffeine or light.[192] Research has observed that specific genotypes predispose individuals to developing more negative responses to circadian disruptive behaviours. Carriers of specific genetic variants in the circadian gene CLOCK (rs3749474, rs1801260, rs4580704), as well as carriers of a common variant in Melatonin Receptor 1B gene, are more likely to be obese, have greater difficulties in regulating body weight, display worse dietary weight loss treatment outcomes and show greater impairments in glucose regulation with late meals.[193-197] This emphasises the need to consider individual responses to meal timing and circadian desynchrony and to focus on methods that will identify those most at risk of negative health consequences. This advocates a precision nutrition approach that current studies and healthcare models do not yet address. Furthermore, the effects of chronodisruption from late feeding may be a secondary effect of poor quantity and quality of sleep. Sleep loss can induce hypercortisolemia, elevated C-reactive protein, increased secretion of pro-inflammatory cytokines,[198-200] and reduced circulating levels or leptin and increase ghrelin.[201,202] In addition, the central and peripheral administration of certain neuropeptides (including insulin, CCK, ghrelin and leptin) can impact on the timing and quality of sleep.[203,204] Thus, food at night may increase circulating appetite-related hormones in the evening, subsequently impacting on sleep. This, in turn, could result in increased inflammation and circulating neuroendocrine hormones, which drive appetite and reduce EE.

7 | CONCLUSIONS

The evidence regarding the capacity of meal timing to cause circadian disruption, altered EB, and subsequent weight gain and metabolic disorders in human studies is inconclusive. Current findings suggest that differential mealtime can alter the excretion of many energy-regulating endocrine hormones through altering their

temporal phase and amplitude or by suppression of entire rhythms. Theoretically, this could contribute to desynchrony between synergistic hormones and their receptors, leading to reduced signalling and apparent hormone resistance. Presently, however, there is minimal evidence that these alterations in endocrine signalling are directly linked to any alteration in EE in human studies. Small reductions in TEF that have been reported with later meals appear to be balanced out by the redistribution of EE and no differences in total daily EE. There is no clear evidence of any effect of mealtime induced circadian disruption on EE in humans. However, the technical assessment of EE in humans is challenging and a lack of sensitive measures, changes in habits under laboratory and research settings, and individual human phenotypes contribute to the challenges in measuring such small effects. Despite this, some studies have reported greater weight loss with earlier eating and TRF protocols. Further well controlled research is necessary that aims to understand whether meal timing (and the extent of mealtime differences) causes changes in mechanisms regulating EI and/or EE and whether there is further interplay between mealtime, macronutrient intake and specific populations.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY

Data sharing is not applicable to this article because no new data were created or analysed in this review.

PEER REVIEW

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