Nutrition and the circadian system

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Abstract

The human circadian system anticipates and adapts to daily environmental changes to optimise behaviour according to time of day and temporally partitions incompatible physiological processes. At the helm of this system is a master clock in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The SCN are primarily synchronised to the 24-h day by the light/dark cycle; however, feeding/fasting cycles are the primary time cues for clocks in peripheral tissues. Aligning feeding/fasting cycles with clock-regulated metabolic changes optimises metabolism, and studies of other animals suggest that feeding at inappropriate times disrupts circadian system organisation, and thereby contributes to adverse metabolic consequences and chronic disease development. 'High-fat diets' (HFD) produce particularly deleterious effects on circadian system organisation in rodents by blunting feeding/fasting cycles. Time-of-day-restricted feeding, where food availability is restricted to a period of several hours, offsets many adverse consequences of HFD in these animals; however, further evidence is required to assess whether the same is true in humans. Several nutritional compounds have robust effects on the circadian system. Caffeine, for example, can speed synchronisation to new time zones after jetlag. An appreciation of the circadian system has many implications for nutritional science and may ultimately help reduce the burden of chronic diseases.

Key words: Chrononutrition: Metabolism: Obesity: Time-restricted feeding

Life is exposed to relatively predictable daily changes in the environment, the most conspicuous of which is the daily light/dark (LD) cycle. Endogenous circadian (approximately 24 h) timing systems have evolved in organisms in response to daily cycles of abiotic (such as temperature cycles) and biotic factors (such as food availability cycles) to generate circadian rhythms in behaviour and physiology to anticipate and adapt to these fluctuations and temporally compartmentalise incompatible biological processes, such as anabolism and catabolism[1]. The circadian system therefore primes organisms to feed at specific times, and restricting food access to times at which feeding is typically low in model organisms produces many deleterious health consequences. Fruit flies fed at the 'wrong' time, for example, produce fewer eggs[2], and mice fed during the light period only – the rest period for these nocturnal rodents – are prone to diabetes, the metabolic syndrome, obesity, and even impaired cognitive function[3–6].

The circadian system comprises networks of molecular clocks throughout body tissues. Although circadian rhythms are autonomous, self-sustaining and temperature compensated, the circadian system has remarkable plasticity, and feeding can modify circadian rhythms from the molecular to behavioural level[7,8]. Indeed, peripheral tissue clocks such as the liver clock are particularly sensitive to the composition and timing of food consumed. Disorganisation of the circadian system and loss of timing relationships between circadian rhythms in particular are thought to contribute to the development of certain chronic diseases[5]. Hence, appropriate nutrition, where energy intake is aligned with energy expenditure and clear feeding/fasting cycles are synchronised with clock-regulated metabolic changes, helps maintain robust behavioural and physiological circadian rhythms and health[9].

Relatively recent environmental changes have predisposed many individuals to circadian system disruption. The advent of artificial lighting, jetlag induced by high-speed trans-meridian travel, shift work and around-the-clock access to energy-dense food are but a few factors that may conspire to disorganise the circadian system, and thereby adversely affect the health of people in modern societies[7,10,11].

The purposes of this review were therefore to introduce the circadian system, highlight its influences on physiological responses to feeding, show how feeding in turn influences the circadian system and to provide implications for nutritionists and directions for future research.

The hierarchical circadian system

Central and peripheral clocks

The paired suprachiasmatic nuclei (SCN) in the anterior hypothalamus orchestrate circadian rhythms throughout body tissues using autonomic, behavioural and humoral mechanisms[12,13]. SCN cells contain cell-autonomous molecular clocks based on negative feedback loops that generate approximately 24-h rhythms in 'clock' gene transcription[14] (Fig. 1). As transcription factors, clock genes temporally segregate incompatible cellular processes by regulating the transcription of myriad clock-controlled genes, many of which are enriched for metabolic functions, and the same molecular clocks present in the SCN regulate rhythmic cellular processes in tissues throughout the body[15]. That over half of protein-coding genes in mice have been shown to exhibit circadian transcription in certain conditions[16], and large proportions of proteins and metabolites follow suit[17,18], exemplifies the importance of clock control in metabolism. Post-transcriptional clock protein regulation confers another level of tissue-specific metabolic control[19–22]. Recently discovered non-transcriptional rhythms in peroxiredoxins, redox-sensitive proteins, are ubiquitous among organisms of all kingdoms, but how these are integrated with clock gene feedback loops is little understood[23].

In the absence of time cues, the human circadian system has a period of approximately 24·2 h[24] and must therefore be re-set (entrained) daily to the 24-h day. The SCN are primarily entrained by light via a monosynaptic pathway from intrinsically photosensitive retinal ganglion cells in the inner retinae to the SCN[25]. In turn, a multisynaptic pathway from the SCN to the pineal gland is a major route by which photoperiodic information is disseminated[26]. During darkness, the pineal gland synthesises melatonin, a hormone that increases sleep propensity and acts on its widely expressed receptors to provide photoperiodic information, and contributes to synchronisation of circadian rhythms in other tissues[27]. Dim light melatonin onset (DLMO) can therefore be used as a proxy for the onset of the biological night in humans, with melatonin offset in the morning corresponding to the start of the biological day.

In addition to melatonin, the SCN help maintain appropriate phase relationships among peripheral clocks by regulation of other humoral factors – for example, the SCN produce their own secretions to support synchronisation of clocks in other tissues[28–30]. Further SCN secretions also contribute to the rhythmic release of hormones such as glucocorticoids by other tissues[31], and glucocorticoids are particularly important entraining agents for many peripheral clocks. The demonstration that glucocorticoid receptor activation restores approximately 60 % of rhythmic gene transcripts in the mouse liver exemplifies this[32]. Another mechanism by which the SCN synchronise clocks throughout tissues is by regulating the circadian body temperature rhythm, as molecular clocks can be entrained by circadian temperature fluctuations by way of the heat shock pathway[33].
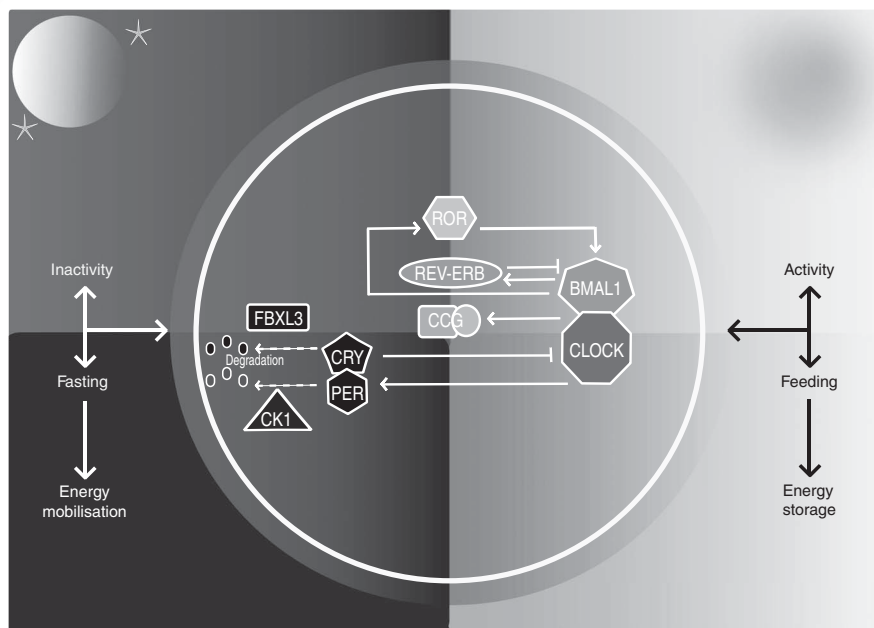

Fig. 1. The mammalian circadian clock. The molecular clock consists of 'clock' genes that form negative-feedback loops. The transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) heterodimerise and activate clock-controlled genes (CCG). On activation by CLOCK-BMAL1, cryptochrome (CRY) 1–2 and period (PER) 1–3 proteins accumulate in the cytosol, multimerise and translocate into the nucleus and form inhibitory complexes, repressing CLOCK-BMAL1 and terminating *CRY1–2* and *PER1–3* transcription during the rest phase. As the rest phase progresses, PER-CRY complexes are degraded by F-box/LRR-repeat protein 3 (FBXL3), casein kinase 1 (CK1) ε and CK1δ. Inhibition of CLOCK-BMAL1 activity ends, completing the negative feedback loop. Auxiliary feedback loops are antiphasic to the core loop and regulate *BMAL1* transcription. The nuclear receptors reverse-erythroblastosis (REV-ERB) α and β repress *BMAL1* transcription, whereas RAR-related orphan receptor (ROR) α activates *BMAL1* transcription. Auxiliary feedback loops add robustness, among other roles.

The circadian system readies for feeding during the active phase

As it does with physical activity, the circadian system readies the body for daytime feeding. Human gastric emptying and gastrointestinal motility rates peak in the morning[34,35], and studies in rodents have shown that clock regulation of bile acids and nutrient transporters optimises digestion during the active phase[36,37]. Furthermore, daily rhythms in the gut microbiota of mice and humans fulfil time-of-day-specific functions, enhancing energy metabolism during the active phase and favouring detoxification during the rest phase[38]. The microbiota and circadian system have a complex bidirectional relationship, as disruption of the molecular clock disorganises rhythmic changes in the gut microbiota[39], and germ-free mice have altered clock gene expression[40]. Related to such changes, there are circadian rhythms in blood concentrations of many nutrients, such as glucose and lipids[41]. An important implication of circadian regulation of the gastrointestinal system is the importance of considering timing of nutritional tests, as exemplified by the recent demonstration that food allergy test results are contingent on the time of day[42].

The circadian system promotes energy substrate storage in appropriate tissues during the day. Insulin sensitivity has a bimodal daily peak during the active phase[43], and appetite for most foods is clock-controlled and lowest in the morning, perhaps to allow consolidated sleep despite diminishing energy availability[44]. Diet-induced thermogenesis too has a circadian rhythm that peaks in the morning[45]. These changes may be of particular relevance to the obesity epidemic, as they suggest that delayed bedtimes increase time for food consumption when appetite is high, and that consuming a higher proportion of dietary energy in the morning might encourage a negative energy balance, the principle determinant of decreasing body mass.

Feeding entrainment of clocks

Although the SCN clocks are primarily entrained by light, time-of-day-restricted feeding (TRF) studies, where food availability is restricted to a period of several hours, have shown that peripheral clocks are predominantly responsive to feeding. Indeed, rest phase TRF inverts gene expression profiles in many peripheral tissues including the heart, kidney, liver, pancreas, adipose tissue and the gastrointestinal tract[7,46–48]. The time course of this entrainment varies depending on the organs in question, with the liver clock responding to feeding particularly rapidly. As a result, peripheral tissue rhythms can be uncoupled from SCN rhythms[7]. Interestingly, feeding shifts the liver clock more rapidly in SCN-lesioned mice, suggesting that the SCN counters internal desynchronisation – the loss of appropriate phase relationships between clocks that is thought to contribute to metabolic aberrations[49]. During *ad libitum* conditions, TRF does not appear to affect the phase of the SCN clock; however, the SCN clock phase may respond somewhat to TRF combined with energy restriction[50]. Although few studies on the effects of TRF on the human circadian system have been published, circadian rhythms in core body temperature and heart rate were advanced after 3 d of morning *v.* evening TRF in healthy young men[51].

Coupling between metabolism and clocks

Feeding entrainment of tissue clocks is predicated on reciprocal relationships between molecular clocks and metabolic sensors and regulators[52]. Feeding/fasting cycles produce changing nutrient availability, and hence periodic phosphorylation of energy sensors such as 5′ AMP-activated protein kinase (AMPK), which promotes ATP production during reduced energy availability, and mechanistic target of rapamycin (mTOR), which promotes anabolic processes during increased energy availability. These regulators are coupled to molecular clock components, which in turn influence myriad metabolic processes integral to nutrient homoeostasis. AMPK, for example, phosphorylates and destabilises cryptochrome (CRY) 1 in peripheral cells[53] and interacts with SIRTUIN (SIRT) 1. In turn, SIRT1 modulates transcription factors including period (PER) 2[54] as well as the ventromedial hypothalamic clock, a brain region that contributes to regulation of the circadian rhythm in feeding behaviour[55]. SIRT1 is one of a family of deacetylase enzymes that have many roles in metabolic regulation, and SIRT1 and SIRT6 appear to be particularly important to temporal partitioning of metabolism by controlling the transcription of distinct sets of genes with circadian expression profiles, with SIRT6 regulating the rhythmic transcription of genes involved in cholesterol and fatty acid (FA) metabolism[56].

Both tissue-specific and whole-body genetic disruption of the molecular clock produce diverse metabolic aberrations[57,58], and the molecular clock partly mediates beneficial effects of some nutritional interventions, such as the longevity-promoting effects of energy restriction[59]. These findings support recent observational studies that have associated SNP in clock genes with various facets of metabolic health. Regarding circadian locomotor output cycles kaput (CLOCK), for example, CLOCK SNP have been associated with non-alcoholic steatohepatitis, the metabolic syndrome, small dense LDL levels, obesity and diabetes[60–64]. Perhaps the most studied of these associations is that of obesity: to date, eight common CLOCK SNP have been linked to obesity and three have been associated with energy intakes[65]. Results of such small, candidate-gene association studies need support from large, unbiased, genome-wide association studies, however.

Food anticipatory activity and food-entrainable oscillators

Coupling between nutrient availability and the circadian system is also evident at the behavioural level. TRF in animals such as rats produces food anticipatory activity (FAA) – food-seeking behaviour at times during which food procurement is most likely. FAA is goal-directed towards places where food is available, and may thus be an adaptive strategy to enhance foraging success[8]. Indeed, FAA is accentuated during energy restriction. As FAA is entrainable and persists

during several days of food deprivation, FAA appears to be a true circadian rhythm.

Interestingly, FAA persists both following SCN ablation[66] and disruption of the positive and negative arms of the molecular clock[67]; therefore, the food-entrainable oscillators thought to underlie FAA must reside elsewhere. Candidate oscillators comprise various brain structures (including the cerebellum, dorsomedial nuclei, and dorsal striatal and mesocorticolimbic circuits[68–70]), neurochemical pathways (including dopaminergic and melanocortinergic signalling[71,72]) and hormonal signals (including ghrelin and orexins[73]).

Eating patterns: feeding/fasting matters

As metabolic rhythms are intertwined with nutrient availability, clear feeding/fasting cycles consolidate robust metabolic and behavioural rhythms. High-fat diets (HFD) blunt feeding/fasting cycles in mice, increasing the proportion of energy consumed during the rest phase, and hence dampen circadian rhythms in clock genes[74,75]. Consistent with this, expression of adipose tissue clock genes such as *PER2* is increased following weight loss in humans[76]. *Ad libitum* access to HFD consistently and rapidly produces obesity in many animals, and endocrine rhythms are similarly blunted in obese humans[77]. Whether obesity precedes dampened circadian rhythms has been contentious, but recent evidence indicates that HFD induce rapid re-organisation of gene transcription rhythms before overt increases in adiposity in mice[78].

Compared with *ad libitum* feeding, TRF offsets HFD-induced blunted feeding rhythms in mice, and the result is superior metabolic health, including reduced adiposity, despite similar energy intakes[75]. Comprehensive recent experiments have shown that, despite similar energy intakes and locomotor activity, various TRF schedules are beneficial during different nutritional 'challenges', such as HFD and high-fructose diets, and that beneficial metabolic effects of TRF are proportional to fasting duration[9]. During HFD feeding, TRF produces nutrient sensor profiles (including AMPK and mTOR) that are more similar to mice fed normal chow[75]. Furthermore, TRF counters HFD-induced reductions in cyclical changes in the gut microbiota, and stool metabolite analyses suggest that this effect of TRF contributes to metabolic health benefits of TRF[79]. These studies used male C57/BL6 mice, animals with a particular susceptibility to diet-induced obesity. As such, it may be premature to extrapolate these findings to humans. Nevertheless, recent research found that eight obese adults with habitual eating periods exceeding 14 h experienced sustained weight loss and improved sleep when consumption of energy-containing foods and drinks was restricted to an 11-h period each day[80]. The latter study was clearly limited by its sample size, however.

In contrast to the beneficial effects of TRF during HFD feeding, TRF may not confer such striking metabolic advantages when mice are fed normal chow[75]. The same may be true among lean humans consuming typical diets. Among fifteen healthy young adults, a cross-over trial found that evening TRF increased fasting glycaemia and impaired glucose tolerance *v.*

an isoenergetic diet comprising three meals throughout the day[81]. Another study of the same design associated TRF with increased hunger, blood pressure and cholesterol[82]. However, findings may have been confounded by circadian variations in these parameters, as measures were taken at different times of the day.

Although not described as TRF studies, breakfast skipping is conceptually akin to TRF. In a larger study of overweight and obese adults, breakfast skipping did not influence responses to weight-loss diets[83], and a careful study in lean young adults found that one of the only effects of 6 weeks of breakfast omission was increased afternoon glycaemic variability[84]. Subsequent research using the same protocol in obese adults also found few differences between groups, although insulin sensitivity was higher in breakfast eaters[85]. It is possible that breakfast omission altered the timing of peak insulin sensitivity, however. Therefore, it appears that TRF may not benefit metabolic health in all contexts. Certainly, further studies with larger sample sizes are needed. Important questions remain unanswered, such as what is the optimal TRF period and meal frequency, and under what circumstances?

Time-of-day-restricted feeding: meal timing matters

One factor that may be relevant to the efficacy of TRF is meal timing. Mice fed HFD during the rest phase tended to gain more fat mass than mice fed HFD during the active phase[4]. Similarly, mice fed normal chow during the rest phase also gained more fat mass than mice fed during the active phase. Rest phase TRF also altered clock and metabolic gene expression profiles in peripheral tissues, blunted corticosterone rhythm amplitudes, reduced energy expenditure despite comparable locomotor activity and reduced lipid oxidation within 9 d[6]. It is possible that deleterious metabolic effects of rest phase TRF are related to misalignment between energy intake and energy expenditure. Clock gene mutations alter circadian rhythm periods in organisms including humans[86], and a transgenic *hPER1* mutation in mice increases obesity risk by advancing peak feeding time relative to peak daily energy expenditure. Subsequently using TRF to synchronise feeding with peak energy expenditure mitigates obesity development in these animals[87].

Ramadan confines eating to the rest phase and modifies circadian rhythms in hormone secretion – for example, the timing of the morning rise in cortisol and night-time melatonin peak are both delayed[88]. Some results of Ramadan studies appear to contradict rodent TRF study findings, however. Meta-analysis of thirty-five observational studies found a mean reduction in body mass of 1·24 kg during Ramadan, with differences between ethnicities and greater reductions in men. No effects on dietary macronutrient proportions were observed, and fasting duration was not associated with body mass changes[89]. It was not possible to evaluate body composition, however, and carefully controlled human TRF experiments are needed to determine whether large differences in TRF timing produce similarly large metabolic changes to those seen in mice.

Time-of-day-restricted feeding: nutrient and energy distribution timing matters

We refer to nutrient intake timing as the timing of ingestion of specific nutrients and the distribution of energy assigned to eating occasions *when the timing of eating occasions is otherwise similar*. Studies of mice show that high-fat meal consumption at the end of the active phase increases adiposity, insulin, leptin, and triacylglycerolaemia *v.* consumption at the beginning of the active phase[90]. Similarly, restricting fructose access to the rest phase increases adiposity and insulin resistance in comparison with restricting access to the active phase[91].

In overweight and obese women matched for energy intakes, those who consumed a larger proportion of daily energy early in the day lost more weight than those consuming more later in the day[92], consistent with other findings that earlier lunch consumption is associated with greater weight loss after 20 weeks[93]. Similar associations have since been reported in severely obese adults following bariatric surgery[94]. As diet-induced thermogenesis peaks in the morning, and breakfast consumption is associated with higher subsequent non-exercise activity thermogenesis, and hence energy expenditure[84], it is plausible that assigning more of daily energy expenditure to earlier meals may encourage a negative energy balance during hypoenergetic diets. Further studies on how meal composition and energy availability affect responses to TRF will be valuable.

Eating patterns: consistency matters

Finally, eating patterns are very inconsistent in some adults[80], and this may be relevant to metabolic health. In mice, fixing TRF to a 12-h period during twice-weekly 6-h LD cycle advances might be expected to uncouple LD cycle-entrained SCN rhythms from feeding-entrained peripheral clock rhythms and produce corresponding metabolic disorder. In these conditions, however, TRF mitigated the obesogenic effects of LD cycle shifts observed in *ad libitum*-fed mice, despite similar energy intakes. Hence, meal regularity and not just its timing relative to activity may be important to metabolic benefits of TRF[95]. The mechanisms by which regular feeding schedules offset obesity in this study are unclear, however, and similar studies in humans are necessary to determine whether these findings are applicable to populations such as shift workers. It will also be interesting to clarify whether TRF needs to be implemented daily to be beneficial; some evidence suggests otherwise[96].

Together, it appears that TRF may be a promising way to improve metabolic health in overweight and obese individuals. Consistent meal patterns and consuming meals shortly after physical activity may help optimise metabolic health. Furthermore, allocating a higher proportion of energy intake to earlier meals may promote a lower energy balance when diets are matched for energy intake. Nevertheless, many questions remain. It is important to determine how effective different TRF schedules are compared to one another and what factors determine inter-individual variability in responses.

Nutrient composition modifies clocks

The compositions of foods have been shown to influence many different circadian rhythms in rodents, from gene expression profiles to behavioural rhythms. HFD have sometimes but not always been found to influence peripheral tissue clock gene expression profiles in mice studies[74,97], and these discrepancies may have resulted from factors including diet composition. In support of this contention, higher-protein, lower-carbohydrate chow advanced expression rhythms of multiple clock genes in the kidneys and livers of mice, and increased mean expressions of brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (*Bmal1*) and *Cry1* in comparison with standard chow[98]. In humans, switching participants from higher-carbohydrate (55 %) and lower-fat (30 %) diets to isoenergetic lower-carbohydrate (40 %) and higher-fat (45 %) diets delayed and increased the amplitude of cortisol rhythms, changed inflammatory and metabolic gene expression profiles and altered *PER* gene expression rhythms in monocytes[99].

In addition to the proportions of dietary energy coming from the macronutrients influencing peripheral clocks, individual nutrients may influence the circadian system, even within certain types of nutrients. Using FA to exemplify this, palmitate, the most abundant SFA in animals, and DHA, a PUFA found plentifully in fish, differentially affected *Bmal1* expression in a murine hypothalamic cell line[100]. Moreover, manipulating dietary DHA and EPA content shifts liver clock gene expression profiles in mice *in vivo*[101].

There are also several non-essential dietary compounds consistently shown to influence the circadian system. Alcohol is widely consumed in many societies and appears to be particularly disruptive to molecular, endocrine and behavioural circadian rhythms in humans and other animals[102–106]. Caffeine, the most-used psychoactive compound worldwide, is present in many foods and beverages and influences the amplitudes and phases of peripheral tissue clock gene expression rhythms in mice[107]. Evening caffeine consumption delays the human circadian system *in vivo* and lengthens clock gene expression periods *in vitro*[108]. Hence, careful use of caffeine can expedite circadian rhythm entrainment following jetlag[109]. However, even if subjective sleepiness is unaffected by its ingestion, caffeine impairs sleep following jetlag[110]. Caffeine has also been studied for efficacy in entraining individuals with chronic circadian system dysfunction. In a small study of blind individuals with non-24-h sleep/wake rhythm disorder, a disorder where light fails to synchronise the circadian system with the 24-h d, 150 mg of morning caffeine was insufficient to entrain circadian rhythms[111]. Dietary polyphenols are another group of compounds consistently shown to influence both molecular and behavioural circadian rhythms in some animals[112,113], and other novel nutritional supplements such as dietary polyamines[114] phase-shift the circadian system in rodents. Further research is needed to see whether such compounds might be useful in humans, however; if they are, what are the best times to consume them to maximise their impact, and what are the dose–response and phase–response curves of these compounds?

Conclusions and directions for future research

Growing interest in nutrition and the circadian system has produced many insights into the reciprocal relationships between the two in recent years. Findings from these studies have many implications. When assessing nutritional status and the efficacy of nutritional interventions, for example, test timing is an important consideration. More specifically, physiological measures should be taken relative to internal time (DLMO, for example) where feasible. Related to this, chronotype classifies individuals into morning or evening types according to their preference for when to be active and when to sleep. Where laboratory measures of internal time are impractical, chronotype can be estimated by simple questionnaires such as the Morningness–Eveningness Questionnaire and the Munich Chronotype Questionnaire Test[115,116]. As chronotype influences the times at which various physiological processes are optimised, consideration of chronotype will be important for personalised nutrition recommendations. Recent studies have also begun exploring how clock gene SNP may influence responses to dietary interventions[117], and ultimately knowledge of circadian system gene variants may also help inform personalised nutrition.

Pressing questions remain unanswered, and there is a glaring need for human studies addressing these. Regarding eating patterns, whether TRF can accelerate entrainment in populations experiencing circadian disruption is a question of relevance to many. With respect to specific foods and supplements, are there dietary interventions with consistently beneficial effects on sleep? It is known that the composition of human breast milk varies daily[118], and perhaps infant formulae should reflect this.

Continuing collaboration between chronobiologists and nutritionists will further clarify interactions between nutrition and the circadian system, and ultimately has the potential to reduce the prevalence and burden of chronic diseases.

Acknowledgements

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