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The circadian regulation of food intake

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Abstract | Feeding, which is essential for all animals, is regulated by homeostatic mechanisms. In addition, food consumption is temporally coordinated by the brain over the circadian (~24 h) cycle. A network of circadian clocks set daily windows during which food consumption can occur. These daily windows mostly overlap with the active phase. Brain clocks that ensure the circadian control of food intake include a master light-entrainable clock in the suprachiasmatic nuclei of the hypothalamus and secondary clocks in hypothalamic and brainstem regions. Metabolic hormones, circulating nutrients and visceral neural inputs transmit rhythmic cues that permit (via close and reciprocal molecular interactions that link metabolic processes and circadian clockwork) brain and peripheral organs to be synchronized to feeding time. As a consequence of these complex interactions, growing evidence shows that chronodisruption and mistimed eating have deleterious effects on metabolic health. Conversely, eating, even eating an unbalanced diet, during the normal active phase reduces metabolic disturbances. Therefore, in addition to energy intake and dietary composition, appropriately timed meal patterns are critical to prevent circadian desynchronization and limit metabolic risks. This Review provides insight into the dual modulation of food intake by homeostatic and circadian processes, describes the mechanisms regulating feeding time and highlights the beneficial effects of correctly timed eating, as opposed to the negative metabolic consequences of mistimed eating.

[H1] Introduction

Most aspects of physiology, metabolism and behaviour display circadian rhythms (that is, endogenous rhythms close to a 24 h cycle), which reflects the widespread effect of circadian rhythms on biological functions. Circadian rhythmicity is generated by endogenous clocks that are highly conserved internal timing mechanisms enabling cells, organs and animals to anticipate and thereby adapt to the daily changes in their environment. More precisely, circadian clocks are intracellular mechanisms that generate self-sustained oscillations of ~24 h by a set of specific proteins, called clock proteins, that work via autoregulatory feedback loops¹. The circadian clocks produce an internal timing by the rhythmic synthesis of clock-controlled proteins delivering intracellular and eventually extracellular temporal signals.

The endocrine glands are a remarkable example of a regulatory system whose activity is highly rhythmic on a 24 h cycle. In the absence of external stimulation, the daily timing of synthesis and release of hormones is highly predictable from one day to another owing to the strong influence of circadian clocks². In addition to hormone synthesis and release, energy intake is predictable throughout the circadian cycle. For example, food intake is temporally organized into distinct meals that are restricted to the active phase, which is a daily period when energy stores are replenished, while the sleep phase corresponds to a daily period of fasting and mobilization of energy stores. These daily variations of energy metabolism and feeding behaviour are also coordinated by circadian clocks³.

In mammals, circadian clocks are organized in a multi-oscillatory network comprising a master clock in the suprachiasmatic nuclei (SCN) of the hypothalamus and many **secondary clocks** in the brain and peripheral organs, including endocrine glands, which are phase-controlled by the SCN main clock⁴. Circadian rhythmicity of the SCN is generated by both neurons and astrocytes⁵⁻⁷.

The different circadian clocks in the body are synchronized (or reset) by cyclic environmental cues. The master clock in the SCN is mainly synchronized by ambient light detected by the retina⁸. A separate timing system, which in this Review is referred to as the food clock, is reset by food intake. The food clock participates in the feeding–fasting cycle and helps animals to be aroused and forage at the expected time of food availability⁹. A mistimed feeding time (that is, when feeding occurs during the usual resting period) can reset many circadian clocks in peripheral organs and the brain, albeit not in the SCN¹⁰⁻¹². In addition, a mistimed feeding can have deleterious effects on metabolic health^{13,14}. Therefore, studying the circadian regulation of food intake is important for understanding not only the basic mechanisms of energy homeostasis but also the aetiology of metabolic disorders.

This Review discusses the involvement of homeostatic and circadian processes in the daily regulation of feeding behaviour. The negative effect of mistimed eating on metabolism, which can be prevented or counteracted by timed meals during the usual active phase, is also discussed.

[H1] Temporal organization of food intake

The regulation of food intake and energy metabolism used to be mostly attributed to homeostatic feedback signals, as illustrated by the pioneering glucostatic and lipostatic theories^{15,16}. In the past two decades, however, growing evidence shows that circadian signals have an important role in energy homeostasis³. The benefits conferred by circadian clocks are twofold. First, they provide a temporal organization from the cellular level to the organism level. Therefore, circadian clocks facilitate the temporal occurrence of related functions, such as food intake and glycogenesis, and separate conflicting functions and behaviours, such as eating and sleep. Second, circadian clocks allow organisms and organs to anticipate or be in phase with foreseeable events from one day to another, such as sunrise and sunset or food availability.

In a more simple view, the homeostatic processes that regulate food intake rely on a balance between orexigenic and anorexic factors. Orexinergic pathways gradually increase the homeostatic drive for feeding and arousal over the fasting (sleep) phase and are predominantly activated at the onset of activity¹⁷. In response to meals, anorexigenic pathways increase satiety over the active phase, which decreases the homeostatic drive for feeding to a minimum at sleep onset. In animals, evidence for circadian control in food intake is highlighted by transient hyperphagia after food deprivation. The amount of food ingested during unexpected meals markedly depends on the daily timing of food reinstatement, not only for a 24 h fast, but also in response to increasing duration of fasting (up to 66 h). In both conditions, refed rats eat more late at night (which is at the end of their active phase) and less late in the day (which is at the end of their sleep phase)¹⁸.

Under laboratory conditions with food and water ad libitum, rodents eat their diets in discrete feeding bouts (meals), mostly during their active phase at night. It has long been known that increased meal frequency of rats over the nocturnal phase results from a reduced postprandial satiety¹⁹. The nocturnal pattern of eating in rodents is typically bimodal, with respective peaks at dawn and dusk. Dusk meals calm hunger and facilitate replenishing of energy stores depleted in the course of sleep¹⁷. During the phase of activity onset, rats express a clear preference for carbohydrates, a selective choice of nutrients that involves the release of glucocorticoids and noradrenaline in the paraventricular nuclei (PVN) of the hypothalamus. In sharp contrast, dawn meals are aimed at providing energy during the forthcoming sleep–fasting phase. At dawn, protein and fat are preferred as macronutrients at the expense of carbohydrates²⁰.

The eating pattern of humans is circadian in nature (meaning that it is endogenously rhythmic). The rhythmicity of human feeding was observed in a study of singly housed participants who had no external time cues (so-called **free-running conditions**). In these conditions, humans spontaneously have 2–3 meals during their active phase, independently of massive inter-individual variations in circadian period and duration of wakefulness²¹. Compared with nocturnal rodents, an oppositely phased circadian rhythm in hunger and appetite has been demonstrated in humans, with an evening peak thought to promote large meals before sleep-induced overnight fast^{22,23}. In turn, the satiating value of ingested nutrients decreases over the waking phase²³. Reminiscent of the two-process model for sleep, which states that sleep is regulated by two separate biological mechanisms²⁴, food intake is thus regulated by both homeostatic and circadian mechanisms, which interact continuously with each other throughout the 24 h cycle (FIG. 1).

[H1] Homeostatic control of food consumption

Energy balance is a remarkable example of long-term homeostasis. A tight equilibrium between energy intake and expenditure and resulting body mass is kept fairly stable over time. During the fasted state, ghrelin is released from gastric cells and enters the plasma, where it transmits the major hormonal orexinergic signal to energy-sensing arcuate nuclei (ARC) of the hypothalamus, in which ghrelin stimulates release of neuropeptide Y (NPY) and Agouti-related peptide (AgRP)²⁵. In turn, NPY–AgRP-expressing neurons activate second-order neurons in the lateral and perifornical hypothalamic areas, which contain orexins (hypocretins) and melanin-concentrating hormone (MCH)^{26,27}. In addition, when activated, NPY–AgRP-expressing neurons inhibit oxytocin-expressing PVN neurons to evoke acute feeding²⁸.

The firing of orexin neurons has been directly linked to feeding behaviour²⁹ and to energy expenditure through modulation of physical activity and the autonomic nervous system³⁰. Excitatory inputs from the PVN, in particular, from neurons synthesizing thyrotropin-releasing hormone (TRH), feed back to AgRP neurons³¹. Ghrelin also provides orexinergic signals to the brainstem via the area postrema³². These coordinated effects contribute to stimulating foraging and food intake and decrease energy expenditure in rodents^{29–32}.

After eating, the postprandial phase is marked by a number of hormonal changes that all favour satiety. Anorexigenic humoral signals are conveyed by pancreatic insulin, adipocyte-derived leptin and intestinal gluco-incretins (including glucagon-like peptide 1 (GLP1) and oxyntomodulin) to the ARC, where they converge to activate pro-opiomelanocortin (POMC) neurons^{33–35}. α -Melanocyte stimulating hormone (α -MSH) released from ARC projections binds to melanocortin 3 and 4 receptors in other hypothalamic regions, such as PVN and dorsomedial and ventromedial nuclei to mediate long-term hypophagic effects and lead to increased energy expenditure^{36,37}.

Mice lacking *Pomc* expression in hypothalamic neurons are hyperphagic owing to increased meal size and duration, without modifications of meal number or daily distribution³⁸. Histaminergic neurons of the hypothalamic tuberomammillary nuclei participate in the satiating effects of food intake, in part via the ventromedial nuclei³⁹. Prandial hormonal cues (such as leptin, GLP1 and cholecystokinin (CCK)) also act through the area postrema on the nuclei of the solitary tract (NTS), where they activate a number of neurons, including POMC neurons, to signal acute satiety^{37,40}. Aside from hormonal cues, visceral inputs that inform the brain of gastric distension reach the NTS via CCK-activated vagal afferents⁴¹.

The homeostatic regulation of food intake involves additional neurochemical systems, such as the endocannabinoids, that exert a widespread influence on feeding and energy metabolism. For instance, depending on the energy status — either fasted or high-fat fed — and the nature of the stimulated neurons — glutamatergic or GABAergic — activation of endocannabinoid pathways might have hyperphagic or hypophagic effects⁴². Their modulatory effects also vary according to the hedonic value of food, which is an important aspect of feeding that will not be covered in this Review.

In summary, the homeostatic control of hunger-linked food intake, nutrient availability and feeding cues and satiety is integrated within the brain by an intermingled network of hypothalamic and brainstem structures (FIG. 1).

[H1] Circadian control of feeding

As mentioned earlier in the Review, food intake is temporally structured across the ~24 h circadian cycle and is strongly influenced by circadian clocks³. In general, the daily feeding–fasting cycle is altered in mice with impaired clock machinery. For instance, mice with a global deletion of **clock genes**, including *Per1* and/or *Per2*, *Cry1* and/or *Cry2* or *Rev-erba* (also known as *Nr1d1*), display dampened day–night variations of food intake^{43–46}. Such a behavioural defect is not always detectable under a light–dark cycle because light during daytime can inhibit food consumption in nocturnal mice, which indirectly triggers day–night (non-circadian) differences. Mice with brain-specific deletion of *Rev-erba* lose their circadian feeding–fasting cycle, which highlights the involvement of cerebral clocks in the rhythmic behaviour of feeding⁴³.

Variations in the concentration of MCH in the cerebrospinal fluid have been implicated in the control of feeding behaviour⁴⁷. This newly identified regulation of daily behaviours might be strongly influenced by daily variations in the production rate of cerebrospinal fluid⁴⁸. In humans, rates of cerebrospinal fluid production are lowest in the late afternoon and highest in late night⁴⁹. Of note, the main source of cerebrospinal fluid is the choroid plexus, which houses a robust circadian clock⁵⁰.

[H2] Master light-entrainable clock. It used to be a challenge to determine which brain clock, or clocks, controls the circadian rhythm of feeding. We now know that the master clock in the SCN tightly controls the sleep–wake cycle and hormonal rhythms, such as those for the release of glucocorticoids and melatonin, and participates in the **daily rhythm** of feeding (FIG. 2). Notably, SCN lesions lead to behavioural arrhythmicity and the loss of the feeding–fasting cycle without a change in food intake or the number of meals over a 24 h cycle. These data suggest that the SCN clock has a major role in the daily timing of food intake^{51,52}. As erratic waking states might result in an abnormal feeding pattern, it is possible that an endogenous feeding–fasting cycle is actually masked by behavioural arrhythmicity in animals with SCN lesions, which is the case for several peripheral rhythms⁵³.

Ambient light perceived by the retina, which itself contains a circadian clock⁵⁴, activates melanopsin-containing ganglion cells and provides photic cues that reset the SCN clock to the external light–dark cycle⁵⁵. In contrast to secondary clocks, the master clock is somewhat impervious to the synchronizing effects of meal time, especially when animals are exposed to a light–dark cycle. Therefore, the master clock remains mostly entrained by light^{56,57}. Nevertheless, the dawn peak of the bimodal pattern of nocturnal food intake in rodents could be modulated by the light-entrainable SCN clock¹⁷. In the rodent brain, the SCN projects directly into many of the hypothalamic structures that regulate food intake, and these projections probably modulate circadian control in the feeding responses^{4,58}.

[H2] The food clock — a breakfast timing system. A specific timing system, known as a food clock, tracks predictable changes in food availability and drives a rhythmic behaviour in anticipation of food availability. In animals, when access to food is limited to the resting phase, the food clock drives changes in behavioural rhythms⁹. In addition, some diurnal components, such as anticipatory rises in body temperature and plasma glucocorticoids, become uncoupled from the normal murine nocturnal pattern⁵⁹.

An animal's response to restricted food access is best illustrated by an anticipatory bout of activity, termed food-anticipatory activity, which animals express before the expected phase of food availability⁹ (FIG. 2). This anticipatory bout of activity corresponds to a strong homeostatic drive for feeding. Food-anticipatory activity is mainly controlled by the food clock, which is located outside the master clock in the SCN^{9,60}. When food is available ad libitum, the food clock, which in this state is coupled to the master clock, might de facto control the dusk peak of meals following the resting phase (in mice, this is etymologically speaking 'break-fast').

The molecular mechanisms underlying food anticipation in mammals remain controversial. The circadian properties of food-anticipatory activity have suggested that core clock genes would participate in its clock machinery (FIG. 2). Accordingly, food-anticipatory activity in mice with genetically defective clocks is markedly reduced in several studies^{61–64}. Other researchers, however, find normal, if not increased, behavioural anticipation in the same or other strains of clock mutant mice^{65–67}. In the latter studies, the apparent food-anticipatory activity might actually correspond to the locomotor output of a defective SCN clock that would then become sensitive to meal time. This synchronization process sometimes occurs in wild-type mice that are challenged with restricted feeding in constant darkness. In this scenario, the nocturnal pattern of activity controlled by the SCN clock becomes synchronized in anticipation to food access^{56,57}. Further investigations in clock mutant mice with targeted SCN lesions will be needed to solve this issue. Nevertheless, altered behavioural responses in food-restricted mice with brain-specific deletion of clock genes support the notion that food-anticipatory activity is a clock-controlled rhythmic behaviour^{68,69}. It should be noted, however, that in addition to their circadian roles, clock proteins might also have non-circadian functions that could interfere with circadian outputs, such as the feeding–fasting cycle or food-anticipatory activity. For instance, both period 2 (PER2) and REV-ERBa interact with nuclear receptors involved in numerous cellular and physiological mechanisms^{70,71}.

A number of circadian clocks in the brain that are reset by peripheral metabolic signals might contribute to food-anticipatory rhythms controlled by the food clock. In rodents fed ad libitum with a chow diet, a daily palatable food reward can sometimes, but not always, trigger an anticipatory bout of locomotor activity and arousal^{72,73}, suggesting that, in addition to metabolic cues, the dopaminergic reward pathways play a modulatory role in food anticipation⁷⁴. As defined in this Review, food-entrainable clocks that do not drive behavioural anticipation are not considered as part of the food clock. For instance, the olfactory bulb contains a circadian clock that is reset by timed feeding, indicating that it is food-entrainable⁷⁵, but its impairment by bulbectomy or olfactory deafferentation does not prevent food-anticipatory activity in rats^{76,77}. Despite intensive investigation, the brain location of the food clock is still elusive. The likely structures underlying the food clock might be located not only in the metabolic hypothalamus, including the ARC and lateral hypothalamus^{78–80}, and the hindbrain (that is, the parabrachial nuclei)^{78,81} but also in the dorsal striatum⁸² and the cerebellum⁸³ (FIG. 1).

[H2] Secondary food-entrainable clocks in the brain. Outside the master clock in the SCN, most brain regions and peripheral organs harbour secondary clocks^{84,85}. Imposed restricted feeding in rodents has been instrumental to demonstrate that timed food intake uncouples most secondary clocks from the master clock^{10,11}. This property was initially illustrated for circadian oscillations in peripheral tissues, such as liver, heart and lung^{10,11}. When food access is limited to the resting phase, these clocks become entrained to meal time, while the SCN clock remains phase-locked to the light–dark cycle. Thus, in contrast to peripheral clocks, the master clock in the SCN of the hypothalamus is not shifted by timed feeding when feeding schedules are in competition with light–dark cycles^{10,11}. In humans too, timed meals can phase-shift peripheral rhythms without affecting phase markers in the SCN^{86,87}.

Many, but not all, cerebral clocks outside the master clock can be phase-adjusted by feeding time. This does not mean, however, that all brain food-entrainable clocks belong to the food clock and participate in the anticipation of food availability and/or feeding rhythm. Among food-entrainable clocks in the brain, the ARC contains a circadian clock that is phase-shifted by restricted feeding but remains unaltered by high-fat feeding^{12,88,89}. In mice and rats, levels of *Npy* RNA in the ARC typically increase only at night^{43,90}, while plasma concentrations of NPY are generally increased in the daytime, with peaks at dawn and dusk⁹¹. Daytime-restricted feeding leads to dampened daily expression of *Npy*⁹⁰. RNA levels of *Agrp* in mice display clear daily variations with a peak in early active phase^{92,93}. The rhythmic transcription of *Agrp* is probably regulated by the ARC clock, although it is noteworthy that it is also partly controlled by circulating glucocorticoids via binding of glucocorticoid response elements in the *Agrp* promoter^{92,93}. While *Pomc* RNA levels in the ARC are consistent throughout the daily cycle, neuronal activity of α -MSH neurons is highest in late active phase, and hypothalamic content of α -MSH peaks at dawn^{43,44,58,93}. The α -MSH rhythm gets flattened with daytime-restricted feeding⁹⁴. Hyperphagia that results from lesions to NPY receptor-expressing neurons in the ARC is associated with a loss of feeding rhythm, which highlights the importance of the ARC clock in the regulation of the daily pattern of food intake⁹⁵. Furthermore, damage to AgRP and/or NPY neurons or genetic ablation of melanocortin 3 receptors reduces expression of food-anticipatory activity^{96,97}.

Expression of *Hcrt* (which encodes orexin) and *Pmch* (which encodes MCH), which are clock-controlled genes, displays daily variations in the lateral hypothalamus and perifornical area, with higher values at night than in the day^{43,89,90,98–100}, while extracellular levels of orexin A peak at dawn¹⁰¹. Furthermore, there are daily changes to the synaptic rearrangement of excitatory and inhibitory inputs to orexin neurons¹⁰². Oscillatory processes in the lateral hypothalamus can be phase-shifted or flattened by daytime-restricted feeding^{79,90,94,103}, while ablation of orexin-containing neurons severely blunts anticipation of food availability^{79,90,94,103}.

The PVN are a hypothalamic hub that control neuroendocrine pathways and sympathetic outputs under circadian supervision from the SCN¹⁰⁴.

The PVN also harbour a weak intrinsic clock that can be phase-adjusted by meal time^{12,89}. Neurons of the PVN that express corticotropin-releasing hormone (CRH) might participate in the circadian control of feeding because in mice impaired CRH signalling specifically increases food consumption during the resting phase, an effect that is counteracted by exogenous glucocorticoid treatment¹⁰⁵. During a restricted feeding schedule, release of NPY in the vicinity of PVN arises from ARC, dorsomedial hypothalamic nuclei and/or NTS just before food access, concomitant with behavioural anticipation. Such a peak of NPY is thought to be controlled by the food clock because it persists during subsequent meal omission¹⁰⁶.

The dorsomedial nuclei, which contain NPY-expressing and RFamide-related peptide 3-expressing neurons, have been involved in the control of energy balance and meal patterning at night¹⁰⁷. In rodents, clock proteins are rhythmically expressed in the dorsomedial nuclei, but depending on the schedules of restricted feeding, these daily oscillations are more or less phase-shifted by timed feeding^{12,108}. Regarding the role of the dorsomedial nuclei clock, it is noteworthy that dorsomedial nuclei lesions reduce the circadian amplitude of feeding rhythm and other behaviours¹⁰⁹. Neuronal activity in the dorsomedial nuclei is slightly or strongly increased right before and during timed food access, respectively^{110,111}. Aside from the role of the dorsomedial nuclei clock in feeding rhythm, the possible implication of the dorsomedial nuclei in behavioural anticipation of food availability has been a subject of intensive debate^{9,81}.

In hypothalamic tuberomammillary nuclei, expression of the rate-limiting enzyme of histamine biosynthesis (histidine decarboxylase) shows daily oscillations with peak at dusk, with these oscillations being controlled by the hypothalamic tuberomammillary nuclei circadian clock¹¹². Moreover, in rats, neuronal activity in the hypothalamic tuberomammillary nuclei is increased during the active phase under ad libitum food conditions. Although this rhythm is not phase-shifted by daytime-restricted feeding⁹⁴, hypothalamic tuberomammillary nuclei neurons are selectively activated during food anticipation¹¹³. In mice that lack the histamine H1 receptor, the daily amount of food intake is only marginally enhanced, whereas daily feeding rhythm is blunted owing to daytime hyperphagia¹¹⁴. Together, these findings indicate that the neurochemical pathways of the mediobasal hypothalamus involved in the motivation to feed participate in daily feeding rhythm and the food clock.

The ventromedial nuclei display daily oscillations that are phase-shifted by daytime-restricted feeding and disrupted by genetic ablation of the clock gene *Bmal1* (also known as *Arntl*)^{12,115}. The ventromedial nuclei participate in increased arousal associated with food anticipation¹¹⁶, albeit ventromedial nuclei lesions do not markedly impair food-anticipatory activity¹¹⁷. Of note, without altering energy intake or its daily distribution, genetic impairment of the ventromedial nuclei clock leads to increased energy expenditure and thermogenic capacity, especially during the usual active phase¹¹⁵. These data, and other findings¹¹⁵, demonstrate that the ventromedial nuclei have a critical role in the daily control of energy expenditure via cyclic activation of brown adipose tissue thermogenic activity by the sympathetic nervous fibres¹¹⁵.

Circadian aspects of brainstem structures involved in food intake have been studied much less thoroughly. Daily variations in clock genes have been reported in both the NTS and parabrachial nuclei^{118,119}. In the NTS, timing of clock gene expression is dampened in mouse models of diet-induced and genetic obesity¹¹⁸. However, the functional importance of these putative circadian clocks remains elusive. Rat studies have shown that in response to a timed meal, several hindbrain structures, including NTS and parabrachial nuclei, display increased neuronal activity during food access and following meals but not in anticipation¹²⁰. Nevertheless, rhythmic expression of clock proteins in the parabrachial nuclei is phase-shifted by meal time, and NTS lesions impair food anticipation, indicating that this hindbrain structure could be a network link of the food clock^{81,119}.

To sum up, the daily control of the feeding–fasting cycle relies on interactions between the master clock in the SCN, which is predominantly reset by ambient light, and secondary food-entrainable clocks, which are phase-controlled by the SCN and shifted by meal time. Several food-entrainable clocks in the brain define a food clock, that is, a clock mechanism driving rhythmic behaviours that anticipate the expected time of food availability.

[H1] Keeping feeding on time

[H2] Metabolic hormones. Various metabolic endocrine signals target not only neurons in the ARC and NTS but also brain astrocytes^{121,122}. Among feeding-related hormones, glucocorticoids, ghrelin and glucagon secreted before meal time are recognized as pre-feeding timers. On the other hand, hormonal cues induced by meal intake or glucose production following a meal, such as insulin and leptin, can be called post-feeding timers¹²³.

Glucocorticoids, such as cortisol and corticosterone, are synthesized in the adrenal glands and released in a pulsatile manner. In the absence of stress, glucocorticoid release, which occurs in a circadian manner, is characterized by a daily increase in anticipation of the active phase¹²⁴. The robust rhythmicity of glucocorticoid release is closely controlled by the SCN and acts as an internal time-giver that distributes SCN-derived circadian signals to peripheral tissues that express glucocorticoid receptors, thereby synchronizing their circadian clocks¹²⁴. These secondary clocks in peripheral tissues are reset by glucocorticoids through the transcriptional modulation of clock genes, including the transient upregulation of *Per1* and *Per2* and downregulation of *Rev-erba* expression¹²⁴ (FIG. 3).

When humans are fed three carbohydrate-rich meals during daytime, each meal induces an acute increase in plasma levels of cortisol that is superimposed onto the overall daily rhythm controlled by the SCN clock¹²⁵. In nocturnal rats, imposed feeding during the resting phase (that is, daytime) markedly alters the temporal organization of the hypothalamo–pituitary–adrenal axis. In addition to the major rise of corticosterone at dusk, which is phased by the master clock in the SCN, a pre-prandial peak of corticosterone that occurs before food access positively modulates food-anticipatory activity¹¹¹. Of note, this anticipatory peak of corticosterone is not induced by increased release of ACTH, indicating that restricted feeding cannot be considered as a classic stress¹²⁶. In humans that limit their calorie intake to night-time (for example, during Ramadan), a comparable pre-prandial increase in plasma levels of cortisol is observed at dusk before the expected time for eating, while the major peak of cortisol release — known to be controlled by the SCN — is still expressed at dawn¹²⁷. The anticipatory rise in glucocorticoids could have a role not only in favouring glucose supply during phases of increased energy demand but also as a time-giver to synchronize behavioural and physiological functions to coming food intake.

The pre-feeding peak of glucocorticoids might be triggered by the release of noradrenaline within the PVN¹²⁸, thus suggesting that the locus coeruleus participates in the mechanisms underlying the food clock. This hypothesis is also supported by a study that shows an impaired anticipation of food availability in *Ear2*-deficient mice. In these mice, the locus coeruleus, a structure critical for daily arousal, is severely impaired¹²⁹. When plenty of food is available, the pre-prandial release of noradrenaline would then be phased to the onset of the active period, where it regulates carbohydrate preference, as mentioned previously¹³⁰. Similarly, the pre-prandial release of corticosterone would be merged into the SCN-controlled circadian rhythm and phased to concur to anticipation of activity onset.

In humans, plasma levels of ghrelin rise before and fall after each daytime meal and progressively increase during the overnight fast phase, leading to the concept that ghrelin secretion triggers meal initiation¹³¹. In rodents, when food is provided ad libitum, plasma concentrations of ghrelin display

a robust rhythm, which is characterized by increased levels during the resting phase. Timed food access leads to phase shifts of the circadian clock located in the stomach oxyntic cells that synthesize ghrelin and to a phase-shifted rhythm of plasma levels of ghrelin that then peaks in anticipation of food availability^{132,133}. The relative contribution of ghrelin signalling in meal anticipation is still a subject of debate¹³⁴, although impaired ghrelin receptors (including growth hormone secretagogue receptors) in both the dorsomedial nuclei and ventromedial nuclei lead to reduced behavioural anticipation to food access¹³⁵.

In mice, plasma levels of glucagon, which is released by pancreatic α -cells, rise progressively over short-term food deprivation and the daily period of fasting during timed restricted feeding¹³⁶. Increased levels of glucagon lead to the activation of hepatic gluconeogenesis and differential transcription of the clock genes *Per1*, *Per2* and *Bmal1* via combined effects mediated by cAMP-response element-binding protein (CREB) and its co-activator CREB-regulated transcription co-activator 2 (CRTC2)^{136,137} (FIG. 3). The timing role of glucagon in feeding synchronization of peripheral clocks is confirmed using restricted access to diets whose ingestion does not induce insulin secretion (that is, protein-only or specific amino acids)¹³⁸.

Meal-induced secretion of insulin from pancreatic β -cells, however, also has a key role as a post-feeding timer¹³⁹. Activation of insulin signalling pathways can reset the peripheral clocks by acting at transcriptional and post-transcriptional levels. More precisely, insulin triggers hepatic transcription of *Per1* and *Per2*, represses *Rev-erba* expression and stimulates AKT-mediated phosphorylation of brain and muscle ARNT-like 1 (BMAL1), which in turn suppresses its transcriptional activity^{139–141} (FIG. 3). Neither glucagon nor insulin signalling influences the generation of behavioural anticipation to food from one day to another¹³⁴.

With respect to leptin, there is no clear evidence that its meal-induced secretion contributes to feeding synchronization, even if leptin modulates the daily rhythm of plasma levels of glucose^{123,142}. The inhibitory role of leptin on food-anticipatory activity has been inferred from its potentiation in food-restricted rodents with impaired leptin signalling¹³⁴.

Melatonin is a hormone secreted from the pineal gland only at night¹²³. The selective nocturnal secretion delivers internal timing cues to circadian clocks¹²³. Although not strictly speaking a metabolic hormone, melatonin can influence glucose homeostasis. Notably, human variants in the melatonin receptor MT2 are associated with an increased risk of type 2 diabetes mellitus¹⁴³. Even if melatonin does affect food intake, it may indirectly modulate the regulation of feeding via its effects on circadian clocks.

Glucocorticoids, such as GLP1 and oxyntomodulin, secreted during the postprandial phase can phase-shift secondary clocks in peripheral organs^{144,145}. The possible role of incretins as post-feeding timers for food-entrainable clocks in the brain warrants further investigation.

Collectively, these results indicate that, among endocrine signals, glucocorticoids and pancreatic hormones are important time-givers related to food intake. Recent investigations, however, indicate that many other metabolic hormones, including adipokines and incretins, also play some role in feeding synchronization of circadian clocks. Further work is needed to unravel the proper effect of each hormone and to determine whether pre-feeding and post-feeding synchronizing cues act independently from each other and whether they interact synergistically or antagonistically.

[H2] Nutrients. In addition to hormonal feeding-related cues, circulating nutrients including glucose, non-esterified fatty acids and ketone bodies probably signal to the brain to regulate the timing of cues related to peripheral energy status. Glucose supply is essential to sustain neuronal activity. However, plasma levels of glucose display daily variations that are phase-shifted by restricted feeding^{136,142}. Changes in brain glucose availability are predominantly detected by glucose-sensing neurons located in the mediobasal hypothalamus, which includes the ARC, dorsomedial nuclei, lateral hypothalamus and ventromedial nuclei, and the NTS^{146,147}. Aside from neurons, tanycytes, which are glucosensing glial cells of the third ventricle that contact the cerebrospinal fluid, send processes to ARC and ventromedial nuclei neighbouring regions¹⁴⁸. In hypothalamic neurons, large changes in glucose concentration (such as from 0.5 nM to 5.5 nM) affect the clock machinery by shortening the circadian period and phase-delaying *Per2* expression¹⁴⁹.

Plasma concentrations of non-esterified fatty acids increase during daily sleep and during the feeding phase in mice with a high-fat diet^{142,150}. Lipid-sensing neurons whose firing rate is activated or inhibited by fatty acids are found in the ARC and ventromedial nuclei¹⁵¹. Palmitate applied on cultured mouse hypothalamic neurons affects their clock machinery by dampening expression of *Per2* and *Rev-erba* and enhancing *Clock* RNA levels. Furthermore, palmitate treatment upregulates, and possibly phase-shifts, the daily expression of *Npy* without affecting *Agrp* RNA¹⁵². By contrast, high-fat feeding promotes the downregulation and flattened expression of both *Npy* and *Agrp* in the hypothalamus, while *Pomc* RNA levels are increased over the daily cycle compared with those during the day phase of mice on a normal diet¹⁵⁰. Independently of diet-induced obesity, free access to a high-fat diet produces widespread changes in peripheral clocks owing to impaired CLOCK and/or BMAL1 chromatin recruitment and cyclic activation of peroxisome proliferator-activated receptor- γ (PPAR γ) downstream targets¹⁵³. A high-fat diet available ad libitum also disrupts feeding rhythm owing to a rapid increase in daytime food consumption^{150,154}. The underlying brain mechanisms for the high-fat diet-associated changes in feeding rhythm are not fully understood, but connexins (which are gap junction proteins) could be involved¹⁵⁵. Of note, however, mistimed feeding is observed only in male mice and ovariectomized female mice, which indicates that ovarian hormones have a protective effect on this temporal disturbance¹⁵⁶.

Ketone bodies, such as β -hydroxybutyrate, are released by the liver and provide an alternative energetic substrate to neurons during periods of food shortage, an effect that is counteracted by glucose supply^{136,157}. Under high-fat feeding, hypothalamic astrocytes also convert fatty acids to ketone bodies, which might be exported to neurons to produce ATP¹⁵⁸. Furthermore, it is meaningful that the anticipatory rise of plasma β -hydroxybutyrate before timed food access participates in the mechanisms that control food anticipation¹⁵⁷.

[H2] Intracellular metabolic interactions. Research performed over the past 10 years has revealed functional and redundant interplays that link oscillations in the expression of clock genes and intracellular metabolism¹⁵⁹. These data offer multiple intermingled possibilities by which feeding cues can affect the secondary circadian clocks. Transcriptional interactions are mediated by PPARs, which are transcription factors activated when bound with fatty acids that are released during either fasting or high-fat feeding. PPAR α , which controls many target genes involved in lipid metabolism and energy homeostasis, modulates the transcription of *Bmal1* (REF. 160) and is a key transducer of the synchronizing effects of meal time on peripheral clocks¹³⁶. PPAR γ was mentioned earlier in the Review as a mediator of the molecular changes that occur in the circadian clock during high-fat feeding¹⁵³ (FIG. 2).

The NAD⁺-dependent deacetylase sirtuin 1 (SIRT1) is a key intracellular metabolic sensor that directly interacts with clock proteins, CLOCK and PER2, and therefore modulates clock machinery in the SCN and peripheral clocks^{161–163}. Poly(ADP-ribose) polymerase 1 (PARP1) is activated by

feeding and directly fine-tunes the clock machinery by reducing the DNA-binding activity of CLOCK and/or BMAL1 (REF.¹⁶⁴). In addition, AMP-activated protein kinase (AMPK) is a fuel sensor, whose activity increases in response to a reduction in the concentration of ATP within cells, which destabilizes the clock proteins cryptochrome 1 (CRY1) and PER2 (REF.¹⁶⁵). The molecular clock machinery also responds to mechanistic target of rapamycin (mTOR), a crucial metabolic sensor, and therefore provides another direct metabolic modulation of the cellular clocks¹⁶⁶ (FIG. 2).

Many clock proteins are regulated by intracellular redox status. Moreover, circadian changes in redox pathways involve daily oxidation of peroxiredoxins¹⁶⁷. Remarkably, these oxidation rhythms result not only from interactions with the classic molecular clock machinery but also from metabolic oscillations, independent of any transcriptional mechanism, and are thought to be phylogenetically ancient clocks¹⁶⁷ (FIG. 2).

[H2] Responsiveness of the suprachiasmatic nuclei clock to metabolic cues. Provided that a light–dark cycle is present, the SCN clock is resistant to food synchronization. Compared with secondary clocks, this difference could be because putative transducers including glucocorticoid receptor, glucagon receptors and PPAR α are not expressed in the adult SCN^{124,168}. Such resistance to food synchronization does not mean, however, that the SCN does not receive any information regarding peripheral energy status. Indeed, independently of meal timing, metabolic cues associated with calorie restriction or a high-fat diet can interfere with SCN function, whereby they alter its intrinsic period and synchronization to light^{169,170}. Notably, SCN neurons contain glucose sensors using ATP-sensitive K⁺ channels¹⁷¹. Contrary to PPAR α , PPAR β/δ is expressed in SCN cells, and its activation by fatty acids can alter SCN activity¹⁷². Cues released during fasting could be conveyed to the master clock by circulating FGF21 through β -Klotho expressed in SCN cells¹⁷³. With respect to hormonal cues, modulatory effects of ghrelin and leptin on SCN responses are probably mediated via the mediobasal hypothalamus^{123,174}, while insulin might directly inhibit the firing of SCN neurons¹²³. Therefore, even if the master clock is not reset by meal timing under light–dark conditions, the tight crosstalk between circadian oscillations and metabolic pathways occurs in various organs, including the brain and the master clock itself.

[H2] Microbiota. Mounting evidence suggests that, depending on feeding state and diet composition, the gut microbiota influences the control of a host's energy homeostasis and modulates the development of obesity and type 2 diabetes mellitus. Microbial products, such as short-chain fatty acids and succinate, change intestinal gluconeogenesis^{175,176}. In addition, the microbiota affects circulating signals, enteric neurons and vagal afferents that convey hunger and satiety cues to the brain¹⁷⁷. The gut microbiota also contributes to the rhythmic interactions between gut and brain, thus participating in the circadian regulation of food intake. In particular, the gut microbiota modulates various host clocks, such as those in the colon, gut and liver, and sex-specific daily rhythms^{178–180}. In turn, the host circadian clocks, feeding schedules and diet composition have a major effect on daily functions and oscillations of the microbiota in mice, as well as humans^{181–183}.

In summary, the nature of the local and systemic signals that allow the synchronization of food-entrainable clocks to bouts of feeding is complex because of the multilayer implication of a wide variety of regulatory factors, from whole-organism (hormones) to intracellular pathways (enzymes and redox state) in peripheral and cerebral structures. In addition, newly identified interactions that link the gut microbiota, circadian clocks and meal time are being investigated in more detail.

[H1] Negative effects of mistimed eating

[H2] Chronodisruption. Circadian disruption and metabolic disturbances are reciprocally linked. On the one hand, the cardio-metabolic syndrome is frequently associated with alterations in the sleep–wake cycle and the circadian rhythmicity of metabolic parameters¹⁸⁴. On the other hand, **syn-chronizing factors** that are able to reset circadian clocks, such as light, hormones and feeding time, become desynchronizers when they are perceived or provided at the wrong time of the daily cycle (for example, light at night and food intake during the usual resting phase). The miss-timing of synchronizing factors leads to circadian disturbances that, in turn, will trigger or favour adverse effects on metabolic health.

In animals, chronodisruption caused by either genetic deletion of clock genes, light at night or chronic jet-lag alters metabolic health by increasing body mass, triggering inflammation and metabolic defects and accelerating cellular ageing^{45,46,184–189}.

In humans, epidemiological investigations highlight that circadian disruption induced by long-term shift-work is correlated with an increased risk of developing obesity and type 2 diabetes mellitus^{190,191}. Furthermore, short-term circadian misalignment induced by forced desynchrony or acute shift in the light–dark cycle impairs glucose tolerance and reduces insulin sensitivity^{192,193}. Importantly, the increase in diabetes mellitus risk after acute chronodisruption is distinct from the metabolic effects of sleep loss that also promote insulin resistance¹⁹⁴.

[H2] Mistimed eating. As mentioned earlier in the Review, an imposed feeding schedule restricted to the rest phase has potent synchronizing effects on secondary clocks. In addition, mistimed eating has numerous metabolic consequences, varying according to the feeding schedule and the species. Light-fed mice with a chow diet ingest more calories and gain more body mass than night-fed controls¹⁴. Imposed fasting on mice in early night, equivalent to breakfast skipping, favours body mass gain and de novo lipid synthesis¹⁹⁵. Light-fed rats eat less but can still gain more body mass than night-fed or ad libitum-fed animals, thus indicating increased feeding efficiency⁹⁴. Moreover, spontaneous overfeeding during the rest phase is observed in chow-fed genetically obese Zucker (*fa/fa*) rats, as is it in wild-type mice fed only with a high-fat diet^{150,196}. During high-fat feeding ad libitum, mistimed eating takes place from the first days of fat availability, that is, before the onset of diet-induced obesity¹⁵⁰. If food consists of only high fat limited to the resting phase (daytime), mice gain more body mass than those fed with a high-fat diet only at night¹⁹⁷. The metabolic consequences of mistimed high-fat feeding, however, are mitigated by regular food intake during the active phase¹⁹⁸.

In humans, skipping breakfast is associated with an increase in metabolic risk factors, including obesity and weak glycaemic control^{199,200}. In addition, repeated late dinner in the evening or at night is significantly correlated with increased adiposity and elevated BMI¹³. Another study did not confirm these findings in either healthy males or females²⁰¹. In addition, circadian misalignment under controlled laboratory conditions reduces insulin sensitivity^{194,202}.

Altogether, these studies indicate that daily timing of food intake is crucial for energy balance in the short term and long term. Furthermore, both chronodisruption and mistimed eating favour increases in metabolic risks factors.

[H1] Benefits of correctly timed eating

Accordingly, avoiding excessive energy intake during the rest phase has healthy consequences on metabolism. Compared with Zucker rats that have

ad libitum access to a balanced chow diet, animals fed only at night with the same diet display reduced body mass gain¹⁹⁶. Limiting food access to the normal waking phase also improves robustness of daily oscillations at molecular (clock and metabolic genes) and physiological (respiratory exchange ratio) levels¹⁴. In mice with whole-body or liver-specific deletion of clock genes, restricting access to a chow diet prevents excessive gain in body mass and metabolic disturbances²⁰³. In humans, an increased energy intake for lunch is associated with a reduced risk of body mass gain²⁰⁴.

Remarkably, limiting access to an unbalanced (that is, high-fat) diet reduces diet-induced obesity and fat accumulation in the liver of mice²⁰⁵. In the same line, blocking spontaneous daytime overfeeding with therapeutics also prevents diet-induced obesity in mice, which further demonstrates the importance of timing food intake for energy balance¹⁵⁵. Finally, it is noteworthy that meal timing restricted to the regular active phase prevents metabolic disturbances in animal models of shift-work¹⁸⁹.

In short, limiting the timing of food intake — even if the ingested diet is unbalanced — to the normal active phase (that is, during the right phase) reduces metabolic disturbances.

[H1] Conclusions

The feeding–fasting cycle is controlled by a multi-oscillatory network that involves peripheral and brain clocks, including a master clock in the SCN and secondary clocks elsewhere in the body. The next challenge for researchers in the circadian field will be to determine the exact role extra-SCN brain structures within the hypothalamus and brainstem have in the regulation of the daily rhythm of feeding. Advances in circadian nutrition reveal that, aside from what and how much to eat, when to eat is also critical for energy balance. As a rule, eating during the usual active phase and combining a large breakfast and lunch with a small dinner are beneficial for metabolic health. Taking into account the timing of food intake can also be useful for improving weight loss strategies. For instance, the effectiveness of weight loss during dieting is improved in people who have their lunch around midday compared with those who eat their lunch later in the afternoon²⁰⁶. Similarly, weight loss in patients with severe obesity who underwent bariatric surgery is more efficient in those who have an early lunch²⁰⁷. On the basis of daily distribution of energy consumed, macronutrients and meal frequency, future investigations are needed to determine appropriately timed dietary patterns to prevent circadian desynchronization and limit metabolic disturbances.

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Competing interests

The author declares no competing interests.

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Key points

- Short-term food consumption is regulated by a balance between orexigenic and anorexigenic factors.
- Daily pattern of eating is controlled by circadian clocks, including the master clock in the suprachiasmatic nuclei reset by ambient light and other brain clocks reset by feeding time, via hormonal, nutrient and visceral cues.
- Circadian desynchronization — owing to mistimed eating or chronodisruption — has deleterious consequences on metabolic health.
- Timed dietary patterns may help to prevent circadian desynchronization and reduce metabolic disorders.

Fig. 1 | Circadian control of the daily feeding–fasting cycle by brain clocks. a | The daily feeding–fasting cycle is controlled by a multi-oscillatory system linking the light-entrainable master clock in the suprachiasmatic nuclei (SCN) of the hypothalamus with food-entrainable clocks in the metabolic hypothalamus and brainstem. In addition, animals can predict time of food availability, leading to anticipatory changes in behaviour and physiology. Such food-anticipatory changes rely on a food clock comprising food-entrainable clocks in the metabolic hypothalamus, the dorsal striatum, the cerebellum and the parabrachial nuclei (PB). Feeding and fasting cues generated by peripheral organs provide information on energy status and meal time to the brain via circulating nutrients and hormonal inputs as well as visceral neural inputs. **b** | Food intake is regulated on a daily basis by homeostatic drive (dashed grey line) and circadian gating (dotted blue line). The feeding phase at night in nocturnal rodents corresponds to a period when energy reserves are replenished, while their sleep–fasting phase during daytime is a period of depletion of energy stores. ARC, arcuate nuclei; DMH, dorsomedial hypothalamic nuclei; GLP1, glucagon-like peptide 1; LH, hypothalamic lateral areas; NTS, nuclei of the solitary tract; PVN, paraventricular nuclei; TMN, tuberomammillary nuclei; VMH, ventromedial hypothalamic nuclei.

Fig. 2 | Reciprocal interactions between the circadian clocks and metabolism at cellular and systemic levels. Circadian clocks are intracellular mechanisms that generate self-sustained oscillations close to 24 h. The molecular clock involves intermingled feedback loops of clock proteins, including CLOCK and brain and muscle ARNT-like 1 (BMAL1), that activate the transcription of many clock genes and rhythmic expression of target genes, called clock-controlled genes. In turn, PER1 and PER2, and cryptochrome 1 (CRY1) and CRY2 repress the transcriptional activity mediated by CLOCK and/or BMAL1, while REV-ERB α , REV-ERB β and retinoic acid receptor-related orphan receptor- α (ROR α), ROR β and/or ROR γ regulate the transcription of *Clock* and *Bmal1*. Clock-controlled proteins provide intracellular and extracellular rhythmic signals. Multiple functional interplays link the molecular clockwork with intracellular metabolism via changes in redox state, sirtuin 1 (SIRT1), AMP-activated protein kinase (AMPK) and other metabolic sensors and with the metabolic transcription factors called peroxisome proliferator-activated receptors (PPARs). The master clock in the suprachiasmatic nuclei (SCN), mainly reset by ambient light, adjusts the phase of secondary clocks in the brain and peripheral organs, controls the sleep–wake cycle and hormonal rhythms and participates in

the feeding–fasting cycle. Many secondary brain clocks reset by feeding time also participate in the feeding–fasting cycle and control food-anticipatory processes. Peripheral organs, whose circadian clocks are reset by food-related signals, control the rhythmicity of glucose and lipid metabolism and generate feeding cues conveyed to the secondary clocks in the brain. Albeit not reset by timed feeding when restricted feeding schedules are in competition with light–dark cycles, the master clock in the SCN can be affected by metabolic cues associated with unbalanced diets, such as a high-fat diet or calorie restriction. mTOR, mechanistic target of rapamycin; PARP1, poly(ADP-ribose) polymerase 1. Adapted with permission from REF.²⁰⁸, Elsevier.

Fig. 3 | Synchronization of food-entrainable clocks by metabolic hormones. Synchronization to meal time of secondary clocks is partly mediated by pancreatic hormones and glucocorticoids. Glucagon (yellow) and glucocorticoids (blue) are pre-feeding timers because they are predominantly secreted before meal time during restricted feeding. By contrast, insulin (red) secreted in response to food intake is a post-feeding timer. It is noteworthy that both glucocorticoids and insulin signalling target the same clock genes. AKT, protein kinase B; BMAL1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; CREB, cAMP-response element-binding protein; CRTC2, CREB-regulated transcriptional co-activator 2; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase.

Glossary

Secondary clocks

Circadian clocks found in brain structures outside of the suprachiasmatic nuclei and in peripheral organs. Self-sustained rhythmicity of extra-suprachiasmatic clocks and their cellular coupling are less robust, which might confer more flexibility to resetting cues, than the more rigid, master suprachiasmatic clock. The majority of the secondary clocks can be shifted by timed feeding (see the glossary entry for 'Food-entrainable clocks').

Free-running conditions

Housing conditions without external time cues, such as constant light or dark or constant temperature, that allow for the detection of the endogenous nature of circadian rhythms.

Clock genes

Specific genes involved in the molecular clock machinery.

Daily rhythm

A 24 h rhythm expressed under a light–dark cycle that is not necessarily endogenous.

Phase-shift

Change in phase of a circadian clock (or its readout, a circadian rhythm)

Food-entrainable clocks

Secondary clocks in the brain and peripheral tissues that can be phase-shifted by timed feeding.

Synchronizing factors

Sometimes called zeitgebers or time-givers; temporal signals, such as light or feeding time, that are able to reset circadian clocks, that is, to adjust their phase.

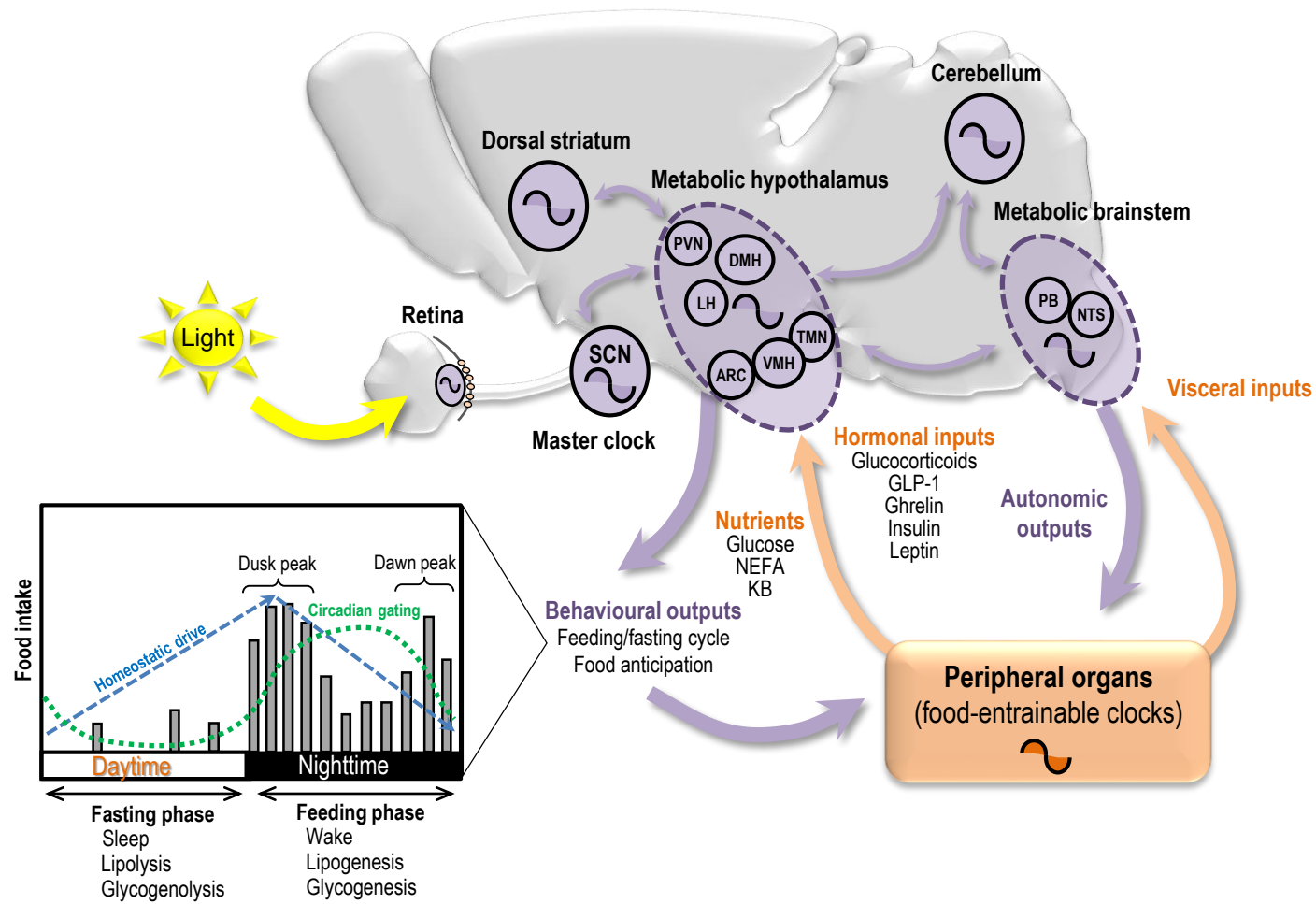


Fig. 1 revised - Challet

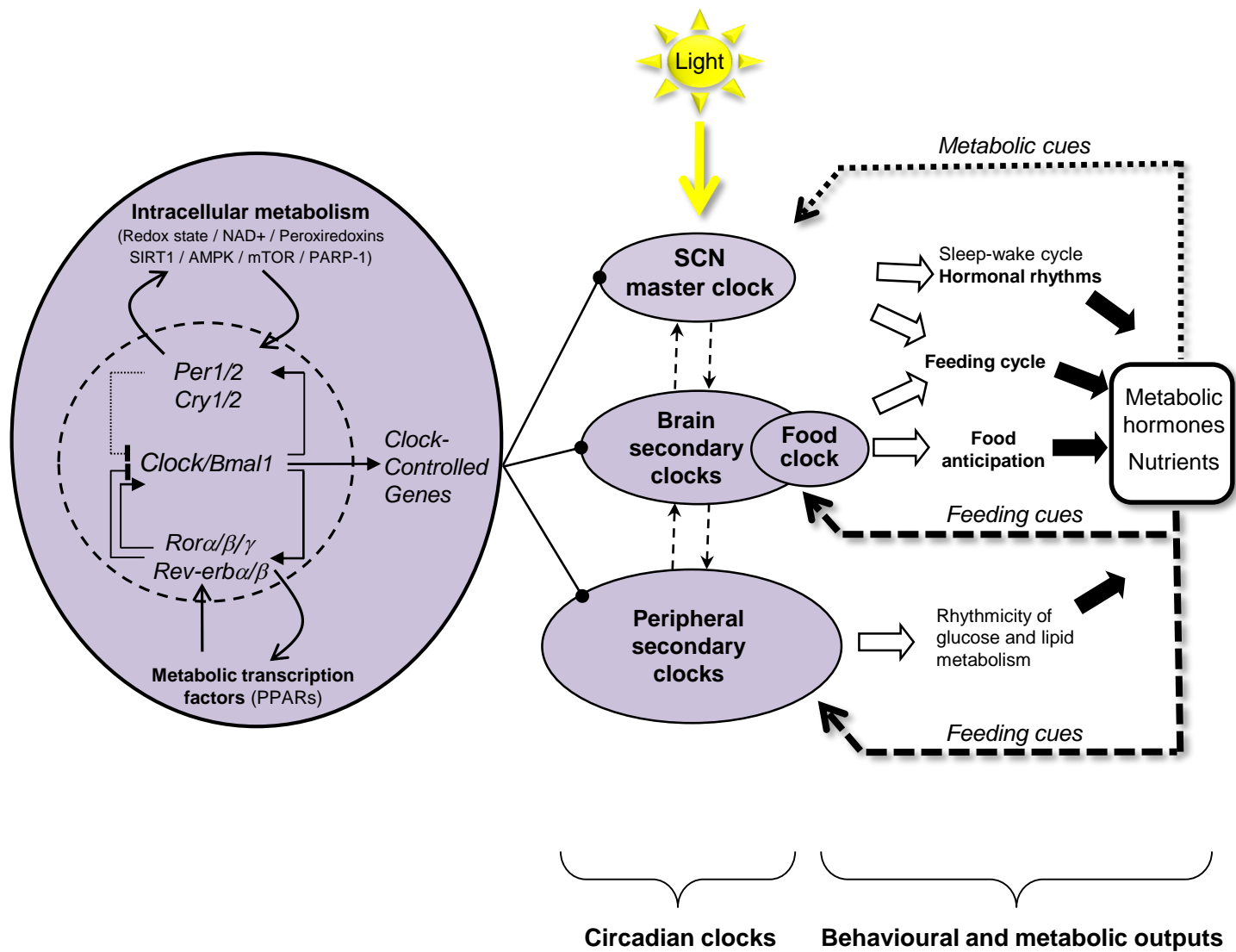


Fig. 2 revised - Challet

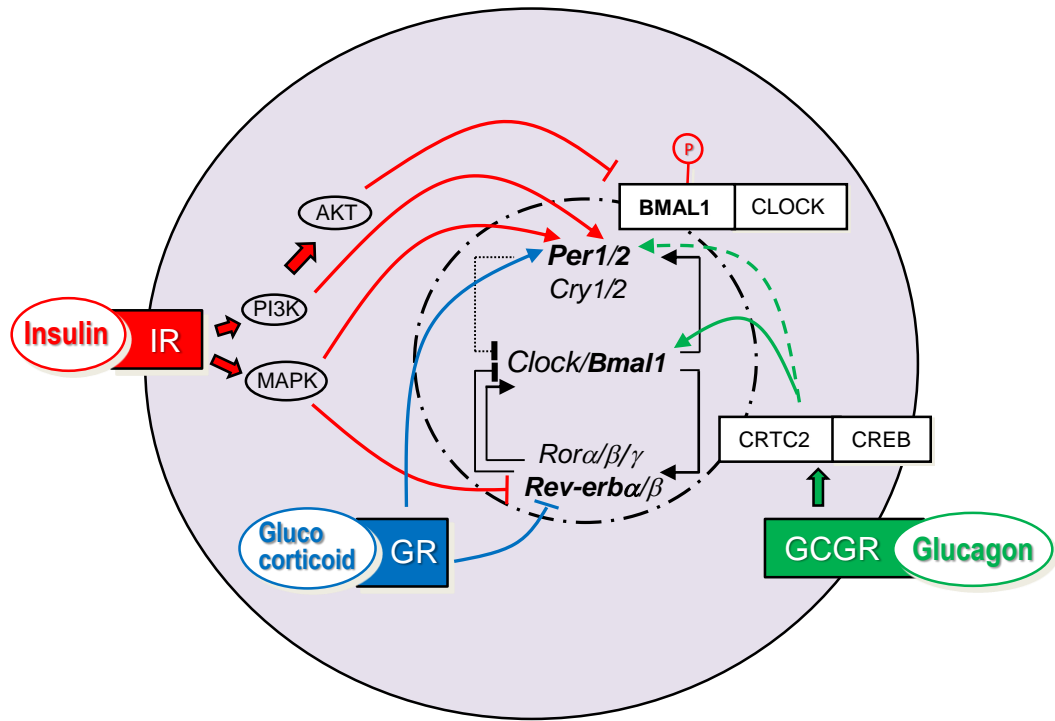


Fig. 3 revised - Challet