Review

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Hypothalamic clocks and rhythms in feeding behaviour

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Daily rhythms are evident across our physiology, ranging from overt behavioural patterns like sleep to intricate molecular rhythms in epigenetic coding. Driving these rhythms at an anatomical and cellular level are circadian clock networks comprising core clock genes and an ever-expanding list of clock-controlled genes. Research over the past decade has revealed an intimate relationship between the clockwork and metabolic processes. In line with this, feeding behaviour in many species exhibits a strong circadian rhythm and, when restricted, food becomes the most potent entraining stimulus for clocks of the body. Critically, there are several indications that disturbance of our daily rhythms contributes to the development of obesity and diabetes. Given our 24-h society, it is important that we understand how the circadian clock influences what and when we eat.

Introduction

The regular 24-hourly rotation of the earth has led to the evolution of circadian oscillators in virtually all life forms, from prokaryotes to eukaryotes. Synchronised circadian rhythms provide an organism with a predictive mechanism to tune its internal physiology to the external world and numerous studies have shown that a robust internal clock offers a significant competitive advantage [1,2]. In higher organisms such as mammals, predictable environmental cycles such as daily and seasonal changes in food availability, likelihood of predation, and thermoregulatory constraints all provide a powerful evolutionary drive. Despite widely divergent origins, a common design principle applies to the molecular clockwork of many different types of organisms, in which timekeeping is hardwired into a rhythmic transcriptional–translational feedback oscillator. Coupling of this 'core' molecular oscillator to biochemical outputs provides a mechanism to drive temporally regulated rhythms in many physiological processes. In mammals, the clockwork centres on the reciprocal regulator feedback between the transcriptional activators CLOCK and BMAL and the repressors PERIOD and CRYPTOCHROME (Box 1). Remarkably, rather few genetic elements of the clockwork appear to be conserved, with different molecular components driving plant, fungal, and animal circadian rhythms. Recent studies indicate that cycles in cellular redox may represent the common ancestral origin of all biological circadian timing systems 2.5 billion years ago [3]. Combined with what we now know about the close interconnection between the molecular clockwork and cellular energy status, we may soon accept that, at its core, the circadian clock functions principally as a metabolic oscillator that anticipates, partitions, and responds to rhythmic metabolic flux [4].

The importance of circadian timing in maintaining normal physiology has become clear in recent years due to the association of numerous pathological states with disturbances in circadian rhythms driven by clock-gene mutations or disruptive lifestyles [5,6]. This association is especially strong with respect to cancer and metabolic disease. Clinical studies demonstrate that sleep restriction, chronic shift work, and night-eating conditions all carry an increased risk of metabolic disease, including obesity, diabetes, and cardiovascular disease [7–12]. Furthermore, metabolic disturbance appears rapidly in response to circadian alteration. Even one or two nights of sleep disruption can reduce glucose tolerance [13], increase appetite, and lead to a bias towards the intake of high-calorie food, in association with reduced anorexigenic (i.e., leptin) and elevated orexigenic (i.e., ghrelin) hormone levels in the circulation [14]. Short-term (10-day) desynchronisation studies in healthy human subjects cause similar suppression of circulating leptin, elevation of blood glucose, and early indications of hypertension [15]. Thus, both sleep disruption and circadian misalignment can trigger a state of perceived energy deficit and instigate an obesogenic program.

It has been clear for some time that the circadian clock plays an important role in determining patterns of food intake. In most mammals, feeding behaviour exhibits a pronounced circadian rhythmicity and disruption of the master clock located within the suprachiasmatic nucleus (SCN) of the hypothalamus disrupts rhythmic behaviours, including feeding [16]. Several genetic knockout models also show that modulation of the molecular clock and/or SCN function alters diurnal rhythms of food intake [17] (Table 1). For example, whole-body disruption of CLOCK [18] or PER2 [19] in mice results in abnormal circadian rhythms of food intake, with significantly increased food intake during the day, and increased susceptibility to diet-induced obesity. Of course, feeding behaviour (i.e., what, when, and how much we eat) is a complex process incorporating instinctual and homeostatic drives (which ensure adequate energy supply) and hedonistic and reward

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Box 1. The circadian clock machinery

The molecular machinery that provides circadian timekeeping comprises a complex circuitry of transcriptional, translational, and post-translational regulatory feedback loops. In mammals, these loops are centred on the reciprocal interaction of the transcriptional activators CLOCK (or homolog NPAS2) and BMAL1 and the repressors PERIOD (PER1, PER2, and PER3) and CRYPTOCHROME (CRY1 and CRY2) [113]. This feedback cycle provides close to 24-h timing and drives the rhythmic expression of several clock-controlled and clock-modulated genes, which in turn mediate circadian rhythms in behaviour and physiology. Acting on the primary feedback loop are auxiliary loops, which increase the stability and robustness of the oscillations. The most notable interlocking loop is that involving REV-ERB and ROR [114]. Clock proteins are also subject to extensive post-translational modulation that serves to reinforce and fine-tune its 24-h cycle length. For example, phosphorylation of PER proteins by CK1ε and δ isoforms has a significant influence over the duration of the circadian cycle duration (period) [111,115]. In addition to Rev-erb and ROR, the components of the circadian clock interact closely with numerous nuclear hormone receptors (NRs), such as PPAR and glucocorticoid receptors, and it is now clear that these interactions are central to the translation of circadian timing into physiological output pathways [102,116,117]. NR regulation of clock genes also renders the clock responsive to numerous circulating hormones (e.g., cortisol, oestrogen), nutrient signals (e.g., derivatives of fatty acids and retinoids), and cellular redox status (NADH/NAD^+ ratio). Importantly, clock components (e.g., Rev-erb, CK1, Cry1) have been shown to be amenable to pharmacological manipulation [118–120] and may offer a tangible route for improving disorders where circadian disruption is implicated, such as metabolic syndrome.

pathways (which reinforce pleasurable aspects of food intake), as well as higher cognitive mechanisms (which provide contextual and learned information). Many of these aspects are discussed in detail elsewhere within this issue, and here we focus on how the circadian clockwork may act on and within neural centres controlling feeding behaviour to sculpt daily patterns of food intake.

Circadian clock networks

In mammals, the SCN is the master of a circadian network controlling daily rhythms in behaviour and physiology. Its neurons exhibit 24-hourly rhythms in electrical activity [20] that continue in the absence of external timing cues and even when SCN tissue is isolated and maintained in culture [21]. *In vivo*, the SCN remains responsive to the environment through light information received from the retina directly via the retinohypothalamic tract and indirectly via the intergeniculate leaflet [22] (Figure 1). The dominance of the SCN in setting circadian rhythms is exemplified by the fact that destruction of the nucleus renders laboratory animals behaviourally arrhythmic [23,24]. However, identification of the core clock genes over the past two decades and the development of tools to study circadian function (such as the mPER2::Luciferase reporter mouse [25]) has demonstrated that the molecular clockwork is not limited to the SCN. Circadian clocks run in most cells and tissues of the body [26,27]. This includes numerous brain sites outside the SCN [22,28,29], many of which have established roles in feeding behaviour (Figure 2 and discussed below).

Under normal circumstances, extra-SCN brain oscillators and peripheral clocks are synchronised by the SCN through direct or polysynaptic neuronal connections, release of neuroactive peptides, and SCN-driven rhythmic hormone release (reviewed in [22]). Importantly, most evidence suggests that both central and local tissue clocks are required for proper tissue function. For example, within the liver, rhythmic expression of metabolic genes involved in gluconeogenesis, lipid metabolism, and oxidative phosphorylation are dependent on the local hepatic clockwork [30–32]. Selective genetic lesioning of this clock profoundly disrupts glucose homeostasis in otherwise normal mice, because the liver is no longer able to cope with rhythmic feeding patterns [31]. However, rhythmic autonomic outputs driven by the SCN [via pre-autonomic neurons of the paraventricular nucleus (PVN)] are also required for maintenance of circadian rhythms in hepatic glucose production [33]. Thus, optimal glucose control requires both SCN input and local clockwork. Similar multilevel circadian controls are likely to operate throughout the body (e.g., insulin secretion from the pancreas, lipid metabolism in adipose tissue [34–37]). This multilayered structure of the circadian clock network has numerous advantages. Firstly, subtle differences in how peripheral clocks are phased by the SCN allow different organ systems and functions to be optimally aligned. Secondly, embedding the molecular clockwork in each cell/tissue provides orchestrated rhythms in gene transcription that are highly tissue specific (despite 5–20% of all transcribed genes exhibiting circadian rhythmicity in any given tissue, little overlap in the identity of rhythmic genes is observed across different tissues [30,38–41]). Finally, differential sensitivity of clocks across the brain and body to external and internal entraining signals (such as food intake) allow dynamic shifts in some rhythmic processes, whereas others (such as the SCN) remain tied to the prevailing light cycle [42]. This process has been demonstrated in numerous animal studies showing that clock rhythms in peripheral tissues and extra-SCN brain regions will entrain to scheduled feeding even when it occurs outside the animal's normal active phase and in opposition to the SCN [6,42] (Box 2). This is not surprising, because components of the molecular clockwork are responsive to circulating nutrients [43,44], feeding related hormones (such as insulin and leptin) [45–48], and cellular redox and energy status [4,49]. The molecular basis for metabolic integration of the clock was nicely detailed in a recent review [4].

Neural clocks and food intake

SCN wiring to classic feeding centres

In its simplest form, homeostatic regulation of feeding is dictated by the relative activity of orexigenic and anorexigenic neurons within the hypothalamus. These cells respond to fluctuations in circulating nutrient (e.g., glucose, fatty acids, amino acids) and hormone (e.g., leptin, ghrelin, insulin) levels that reflect nutritional status and energy stores [50]. Obviously, indicators of peripheral energy status will rise and fall across the day, because food intake is generally partitioned to the active phase of the cycle. However, circadian patterns in feeding are not simply a passive secondary consequence of other rhythmic behaviours (i.e., sleep/wake). Neural tracing studies demonstrate that many hypothalamic structures receive projections from the SCN, thereby providing a direct route for clock gating of feeding responses

Table 1. Impact of global clock-gene disruption on feeding behaviour

Gene target	Metabolic/feeding phenotype	Food-anticipatory activity	Refs
BMAL1	Loss of feeding rhythm (arrhythmic)	Maintained	[121]
CK1	Altered activity, feeding, and metabolic rhythms in $CK1^{tau}$	Maintained	[111]
$CLOCK^{\Delta 19}$	Hyperphagic, altered feeding rhythm, obese	Maintained	[18,122]
CRY1/CRY2	Loss of feeding rhythm (arrhythmic), hyperglycaemic	Maintained	[32,123]
Per1	–	Maintained	[124]
Per2	Altered feeding rhythms, lean, altered lipid metabolism	Attenuated in $Per2^{brdm}$	[19,124]
Per1/2	–	Maintained in $Per1^{ldc}Per2^{ldc}$ Attenuated in $Per1^{-/-}$ $Per2^{brdm}$	[114,125]
Per3	Exacerbation of DIO	–	[126]
Reverbα	Obese, exacerbation of DIO, altered lipid metabolism	–	[127]
Reverbα/β	Arrhythmic, altered lipid metabolism	–	[114]
RORα	Hyperphagic, lean, resistant to DIO	–	[128]

Abbreviation: DIO, diet-induced obesity.

[51,52]. SCN efferent projection targets include the subparaventricular zone (SPZ), the preoptic area (POA), the bed nucleus of the stria terminalis (BNST), and the retrochiasmatic area and capsule of the ventromedial nucleus [53] (Figure 1). Moreover, sites receiving SCN input directly or via polysynaptic relays (principally via the SPZ) include neuroendocrine and pre-autonomic neurons in the PVN [54], arousal-promoting orexin neurons in the lateral hypothalamus (LH) [55], sleep-promoting neurons of the ventrolateral preoptic nucleus [56], energy-sensing neurons of the arcuate nucleus (ARC) [57], and neurons of the DMH, a key site for integration of circadian timing into numerous physiological processes (discussed below) [57]. Efferent projections of the SCN are principally GABAergic and serve to repress neuronal activity outside the SCN [58]. The SCN also modulates the activity of target neurons through rhythmic release of peptide signals, most notably vasoactive intestinal polypeptide and arginine-vasopressin, which signal heavily to the SPZ and DMH [59]. Other SCN-derived peptide signals include transforming growth factor alpha, prokineticin 2, cardiotrophin-like cytokine, and neuromedin S, most of which contribute to suppression of locomotor activity and feeding behaviours [60–63].

Importantly, the influence of the SCN over other neural sites is adaptive. Temporal patterns of SCN activity are similar in diurnal and nocturnal animals, with increased neuronal activity during the light period [64]. Some SCN-driven outputs reflect this, such as melatonin secretion, which peaks at night regardless of whether animals are active in the day or night. By contrast, other outputs, such as rhythms in corticosterone production, are inverted between nocturnal and diurnal species [33]. Plasticity in the polysynaptic relays that receive SCN inputs provides a mechanism for such phase reversal of behavioural responses relative to SCN activity (e.g., SCN-based GABAergic inhibition of excitatory versus inhibitory interneurons of the SPZ) [65]. Multistage integration of circadian timing allows animals to modulate the phasing of physiological and behavioural cycles to best adapt to (and anticipate) changes in environment fluctuation. Indeed, many species can switch between diurnal and nocturnal patterns of behaviour [66].

Hypothalamic clocks outside the SCN

In addition to receiving SCN projections, many extra-SCN sites in the hypothalamus (including the ARC and DMH) house autonomous circadian oscillators [28]. This can be clearly demonstrated in brain slice cultures taken from PER2::Luciferase reporter mice or by long-term electrophysiological recordings [29] (Figure 2). The importance of the ARC and DMH to energy balance and feeding behaviour are well established [50]. Both sites are also critical in sculpting circadian rhythms in feeding. Diurnal rhythms exist in the expression of major ARC neuropeptides [i.e., neuropeptide Y (NPY), agouti-related peptide, pro-opiomelanocortin (POMC), and cocaine and amphetamine regulated transcript (CART)] [67–69]. Targeted destruction of either leptin-responsive or NPY-responsive neurons in the ARC (but not in the VMH) using intraneural injection of saporin-conjugated ligand resulted in profound disruption of feeding rhythms in rats [70,71]. Furthermore, deletion of NPY receptors Y1 or Y5 in mice altered daily patterns of activity and feeding [72]. By contrast, neuron-selective deletion of POMC did not alter circadian rhythms in activity or feeding in mice [73], despite an apparent role for melanocortin signalling in dictating feeding patterns and food entrainment. Specifically, deletion of the melanocortin receptor 3 (MC3) gene in mice disrupted cortical expression of clock genes such as *Bmal1*, *Npas2*, and *Per2* and attenuated food-anticipatory activity during restricted feeding [74]. Moreover, obesity and altered rhythms in feeding observed in Per2 knockout mice have been linked to a disrupted diurnal rhythm of the POMC cleavage product αMSH (a major effector of appetite control) [19].

The DMH is often cited as essential for the integration of circadian rhythms into numerous behaviours due to its afferent and efferent connection to sites involved in regulating neuroendocrine output (PVN), thermoregulation (medial preoptic area, dorsal raphe), feeding behaviour (ARC), and sleep and arousal [LH, ventrolateral preoptic nucleus (VPO)] [75,76]. For example, DMH neurons innervating the VPO are predominantly GABAergic, whereas those innervating the LH are primarily glutamatergic, consistent with the DMH having a role in shaping circadian rhythms in wakefulness and arousal [76]. Lesions of the DMH can cause profound disruptions in the circadian rhythms of sleep/wake, feeding, locomotor activity, and corticosteroid secretion [77]. Numerous reports have also implicated the DMH as the principle site of a food-entrainable oscillator, although this remains controversial due to that fact that, in some studies, robust food entrainment is

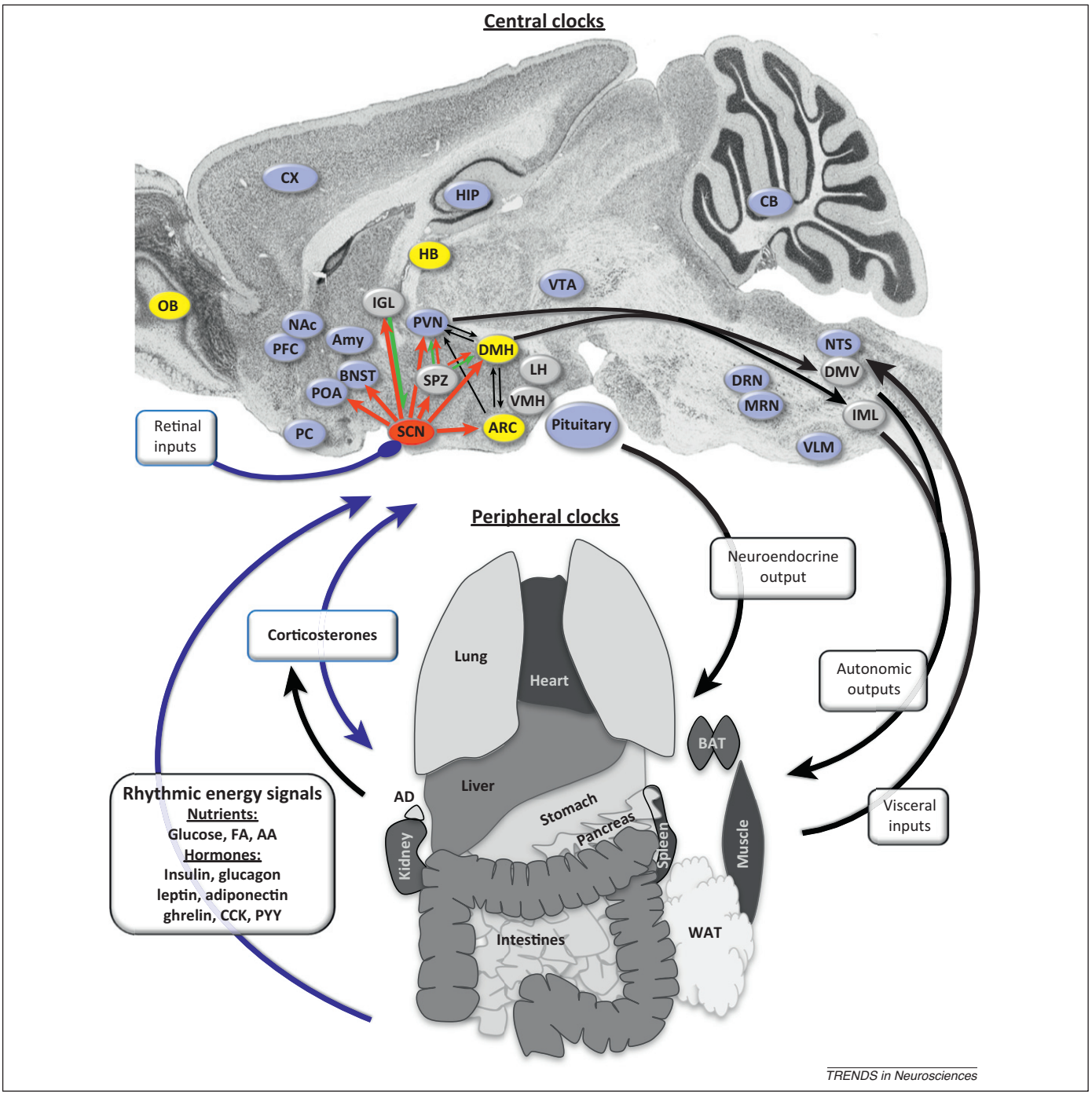

Figure 1. Architecture of the circadian system and its relationship to feeing control. Many neural feeding centres in the brain receive temporal information from suprachiasmatic nucleus (SCN) inputs (red), but also exhibit local capacity for clock function (robust semiautonomous circadian oscillators are shown in yellow, weak oscillators in purple). This neural clock network sculpts major output systems from the brain, including autonomic projections and neuroendocrine-driven hormone release, to drive rhythms in feeding. It also synchronises peripheral clocks across the body to feeding and modulates the sensitivity of organs to nutrient or hormonal signals. Neuronal and hormonal messages from the peripheral organ systems feed back to the brain and can act as entraining cues for neural clocks. Corticosterone is a major entraining signal for both central and peripheral clocks. Abbreviations: AA, amino acids; AD, adrenal gland; AMY, amygdala; ARC, arcuate nucleus; BAT, brown adipose tissue; BNST, bed nucleus of the stria terminalis; CB, cerebellum; CX, cortex; DMH, dorsomedial hypothalamus; DMV, dorsal motor nucleus of the vagus; DRN, dorsal raphe nucleus; FA, fatty acids; HB, habenula; IGL, intergeniculate leaflet; HIP, hippocampus; IGL, intergeniculate leaflet; IML, intermediolateral columns; LH, lateral hypothalamus; MRN, median raphe nucleus; NAc, nucleus accumbens; NTS, nucleus of the solitary tract; OB, olfactory bulb; PC, piriform cortex; POA, preoptic area; PVN, paraventricular nucleus of the hypothalamus; SPZ, subparaventricular zone; VLM, ventrolateral medulla; VMH, ventromedial hypothalamus; VTA, ventral tegmental area; WAT, white adipose tissue. Adapted from [22].

observed in DMH lesioned animals [78]. Recent work has highlighted the importance of reciprocal feedback between the SCN and DMH in shaping circadian behavioural rhythms, including food entrainment [79]. Specifically, increased activity in DMH neurons before meal times (during a restricted feeding paradigm) was demonstrated to suppress SCN neuronal activity, thereby allowing increased locomotor activity during the light period [79]. A role for the DMH in integrating energy status with circadian timekeeping is supported by the fact that the SPZ and DMH receive visceral afferent information from the parabrachial nucleus and that DMN neurons respond directly

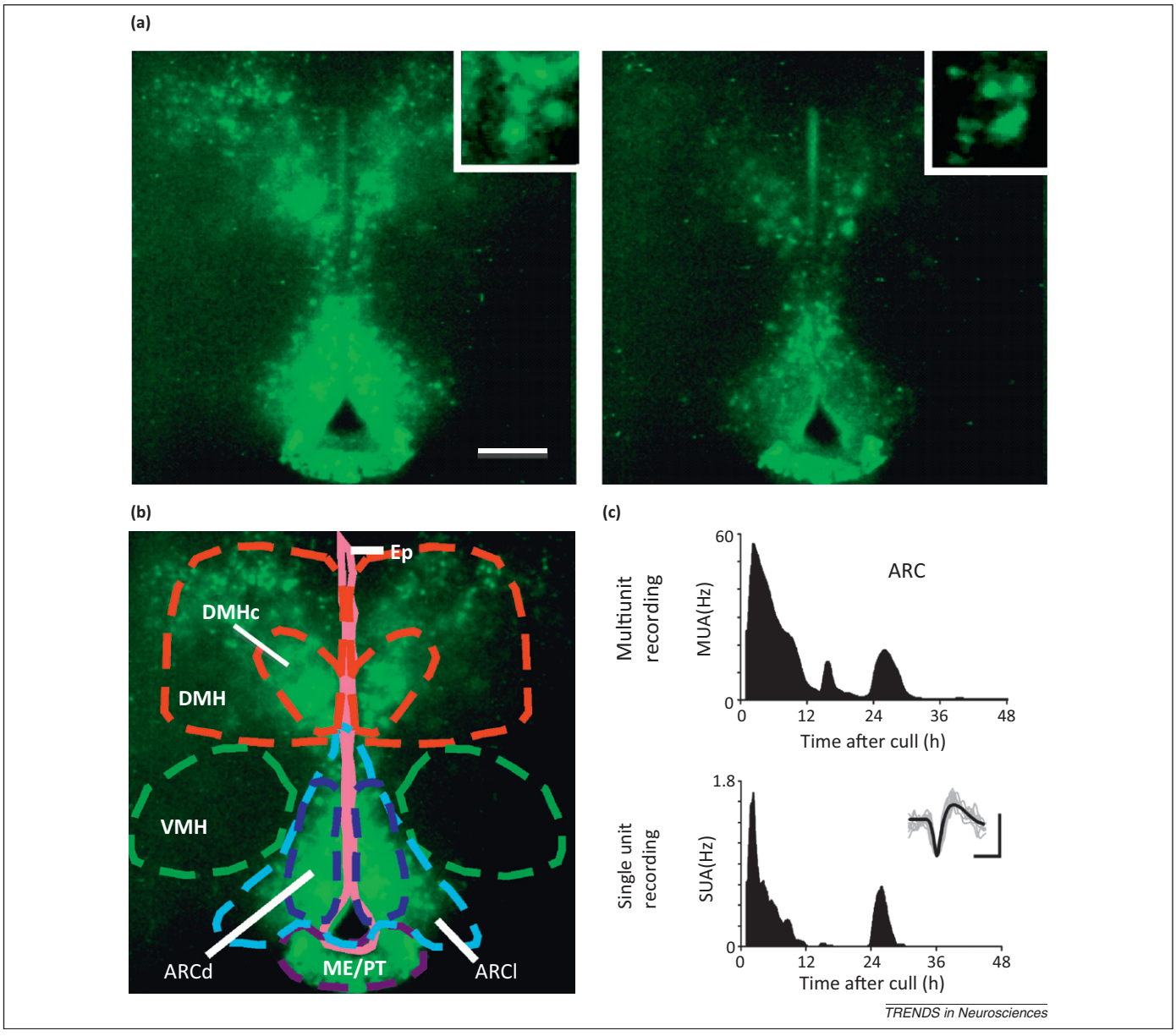

Figure 2. Autonomous clocks in the mediobasal hypothalamus. The existence of neural circadian clock centres outside the suprachiasmatic nucleus (SCN) has been clearly demonstrated, as depicted here using PER2-driven luciferase imaging and electrophysiological recording of brain-slice cultures. (**a**) Images illustrating PER2::LUC bioluminescence in mediobasal hypothalamic brain-slice cultures at peak (circadian time 12 [CT12]; left panel) and trough (CT24; right panel) expression. The insets depict individual bioluminescent neurons. Scale bar, 250 μm. (**b**) Delineation of nuclei of interest, illustrating the presence of PER2 oscillations in the dorsomedial hypothalamus (DMH), particularly in the pars compacta region (DMHc), in the lateral and dorsal arcuate (ARCL and ARCD), the median eminence/pars tuberalis (ME/PT), and the ependymal cell layer of the third ventricle (Ep), but not in the ventromedial hypothalamus (VMH). (**c**) The functional relevance of local hypothalamic clocks is evident from the temporal profiles observed during electrophysiological recordings of electrical activity. For example, recordings of the ARC exhibited robust multiunit and single-unit activity rhythms. Inset shows example profile of SUR action potential. Adapted from [29].

to feeding-related peripheral hormones (including leptin, cholecystokinin, and ghrelin) [75].

Other sites implicated as nodes for sculpting feeding drives across the day include the VMH and LH. The VMH does not contain an autonomous clock [29]. Nonetheless, lesioning of the VMH can alter the circadian rhythmicity of food intake and weaken entrainment to rhythmic feeding schedules [78], suggesting a role for this nucleus in setting feeding rhythms. However, it is unclear how directly VMH neurons contribute to feeding rhythms, because the pronounced hyperphagia and weight gain in VMH-lesioned animals [78] makes it difficult to judge purely circadian effects. Orexinergic neurons of the LH play a central role in wakefulness and will therefore affect feeding at least indirectly by modulating arousal levels. Central administration of orexin can induce feeding [80]. Moreover, under food restriction, the activity of orexinergic neurons increases in anticipation of food [81], and food-anticipatory activity is reduced in orexinergic neuron-ablated mice [82]. However, it is likely that the contribution of the LH to shaping circadian rhythms in feeding is secondary to its effects on wakefulness and arousal.

Central histamine signalling also shows a clear circadian rhythm, with high levels during the active period and low levels during sleep. It is also important in sustaining heightened arousal states during motivated behaviour [83]. Histaminergic activity also modulates energy balance by decreasing food intake and increasing energy

Box 2. Food entrainment and food anticipatory activity

Light-driven diurnal behaviour can be easily overcome by alterations in energy supply, such as during RFSs [129]. During RFS, food is available to the animals only during set periods that typically occur outside their normal feeding period (such as during the day for nocturnal rodents). Under RFSs, numerous physiological and metabolic functions become entrained to the availability of food (e.g., locomotor activity, body temperature, insulin, and corticosterone release). Food-anticipatory rhythms of activity (FAAs) and other physiological variables are still evident in SCN-ablated animals [130]. This implies the existence of other food-entrainable oscillators (FEOs), located outside the SCN, capable of coordinating behaviour and physiology with daily feeding schedules [129]. Once established by a RFS, the FEO appear to be robust, because anticipatory activity can continue for several cycles after the RFS is stopped and the animals are subsequently fasted or returned to *ad libitum* feeding. The location and mechanisms of the FEO have been the subject of much debate and controversy [78]. Unfortunately, extensive lesioning studies in the brain targeting all major feeding and timing centres fail to clearly disrupt the FEO [78]. Despite rapid entrainment of peripheral clocks to meal times [42,131], most evidence does not support the view that the FEO is of peripheral origin [52,132]. This suggests that the FEO is a network of neural sites that interact to provide timing and behavioural entrainment to feeding.

expenditure. Histamine neurons are localised exclusively in the tuberomammillary nucleus (TMN) in the posterior hypothalamus and project throughout the central nervous system (CNS) to regulate the release of neurotransmitters such as dopamine, acetylcholine, and serotonin [83]. Histamine neurons are activated during food anticipatory activity when animals are maintained on a restricted feeding schedule (RFS) [84] and disruption of histaminergic signalling in the histamine receptor 1 (H1) knockout mouse leads to obesity [85]. Interestingly, disruption of diurnal feeding patterns in these mice precedes the development of obesity [85]. Histamine may also feed back onto the clockwork, because mice lacking histidine decarboxylase exhibit disrupted clock gene rhythms in brain clocks outside the SCN [86]. Taken together, these studies suggest that histaminergic pathways contribute to patterns in feeding behaviour most likely as a consequence of enhanced wakefulness and arousal driven through SCN input to the TMN.

Clocks above and clocks below

In addition to the rhythmicity generated by central clocks, peripherally derived energy signals to which the brain responds (e.g., leptin, insulin, CCK, ghrelin, corticosterone, glucose, fatty acids) are produced or released in a highly rhythmic fashion. Furthermore, the circadian rhythms in most of these signals are not simply a passive response to rhythmic food intake, but are generated by circadian clocks in the peripheral tissues [31,35,37,87]. Receptors for leptin and ghrelin are present on SCN cells [88,89] and exogenous administration of ghrelin to cultured SCN slices has been shown to shift clock-gene rhythms [90]. Therefore, even within the light-driven SCN, the clockwork is responsive to major energy signals. In line with this, SCN rhythms can be phase shifted under highly restricted food-entrainment paradigms [91].

In addition to acting on (or within) homeostatic feeding centres, the circadian system has an established influence on learning and memory [92], reward and addiction [93,94], stress, and emotion [95], all of which can shape eating habits.

Coupling local clocks to food intake

Coupling of the molecular clockwork to metabolic pathways in peripheral tissues (such as the liver and adipose tissue) is an area of intense study. By contrast, our understanding of how clocks impact on functional processes within oscillating neurons remains relatively unclear (at least outside the SCN). Many parallels are likely to exist between peripheral and central cellular oscillators.

For example, studies have revealed that hypothalamic energy sensing [96,97] and activity of ARC neurons is closely tied to cellular reactive oxygen species (ROS) production [98–100]. Specifically, the magnitude of response observed in NPY/AGRP and POMC neurons to feeding-related cues (such as ghrelin administration or fasting), as well as during genetic or diet-induced obesity, has been demonstrated to be dependent on levels of ROS production [98–100]. Elevation of ROS levels increases activity in POMC neurons, while decreasing activity in NPY/AGRP neurons. These studies also implicate several of the regulatory components involved in modulation of ROS production: relative mitochondrial and peroxisome content, and the expression and activity of uncoupling protein 2 (UCP2), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor gamma (PPARγ) [98–100]. It is well established that the circadian clock is responsive (and contributes) to fluctuations in cellular redox (NAD^+/NADH ratio, closely tied to mitochondrial activity) [4]. CLOCK, NPAS2, BMAL1, and PER2 all contain a Per-Arnt-Sim (PAS) domain that is responsive to redox state [101]. Further, SIRT1 is an NAD^+-dependent protein deacetylase known to associate with CLOCK/BMAL1 in a circadian manner to drive rhythms in histone and non-histone protein acetylation [4]. Finally, both PPARγ and PPARγ coactivator 1 (PGC-1) are tightly linked to the circadian clock [102,103]. PGC-1α is a key regulator of mitochondrial biogenesis [104] and stimulates expression of the clock genes *Bmal1* and *Rev-erb*α through coactivation of the retinoid-related orphan receptor (ROR) family of orphan nuclear receptors [103]. Mice lacking PGC-1α exhibit disrupted activity rhythms, body temperature cycles, and metabolic rate [103]. Thus, within neurons of the ARC (and perhaps other neural sites), local clockwork control of mitochondrial activity and ROS production may serve as a route for temporally gating neural responses across the day.

AMP-dependent kinase (AMPK) signaling is also a likely route through which circadian and feeding related signals are integrated. AMPK activity is a powerful regulator of energy balance within the hypothalamus [105,106]. It is also integrated into the clock mechanism by directly phosphorylating two clock proteins, casein kinase 1 (CK1) and cryptochrome 1 (CRY1) [49,107]. AMPK phosphorylation leads to enhanced degradation of PER2 (via CK1) or CRY1, thereby tying the phase (and potentially period) on the clock to energy status.

Concluding remarks and future perspectives

Many of us experience persistent daily jetlag because our internal clockwork does not exactly match the social clock

by which we work, sleep, and eat. Unfortunately, this 'social jetlag' has recently been shown to be associated with increased body mass index and obesity [108]. Genetic disruption studies have now been undertaken targeting all of the mammalian core clock genes and many output genes, and reports indicate numerous effects on metabolism [17]. It is therefore clear that circadian timing mechanisms regulating food intake are critical to the body's ability to maintain normal energy homeostasis [109,110]. Recent reports in mice indicate that many of the metabolic defects associated with clock gene disruption or diet-induced obesity are alleviated if food intake is restricted to the appropriate (i.e., nocturnal) phase [110]. This indicates that misalignment between food intake and circadian-driven processes greatly undermines the ability of our bodies to maintain energy homeostasis and partition fuels sufficiently. It seems imperative that we now identify circadian pathways critically affected by such misalignment.

A question that remains unanswered in mammalian circadian biology is whether circadian rhythmicity *per se* is required for normal health. The detrimental effects of clock-gene knockouts are clear; however, a technical difficulty presented by such studies is that they do not address whether disrupted circadian clock function is the direct cause of the pathology or whether the effects are attributable to the impact of genetic disruption of non-circadian components also regulated by the clock gene (i.e., pleiotropic effects). One way of approaching this question is based on theories of circadian resonance. Genetic models now exist in mammals to allow the use of resonance approaches to test the hypothesis that metabolic homeostasis depends on a correctly timed circadian system. Two examples in which genetic mutations alter the speed of the clockwork, but in which normal circadian structure is retained, are the *tau* mutation, where a gain-of-function mutation in CK1ε leads to an accelerated 20-h clock, and the *afterhours* F-Box mutation, which leads to a decelerated 28-h cycle [111,112]. Using tissue-specific floxed techniques, it is now technically possible selectively to alter the pace of local oscillators in key metabolic tissues of the body and thereby achieve discordant circadian pacemakers within one organism, without overall loss of genetic function. Such studies will therefore provide a powerful test of the hypothesis that circadian clocks are critical for normal metabolic homeostasis.

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