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REVIEW

Interactions between light, mealtime and calorie restriction to control daily timing in mammals

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Abstract Daily variations in behaviour and physiology are controlled by a circadian timing system consisting of a network of oscillatory structures. In mammals, a master clock, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, adjusts timing of other self-sustained oscillators in the brain and peripheral organs. Synchronisation to external cues is mainly achieved by ambient light, which resets the SCN clock. Other environmental factors, in particular food availability and time of feeding, also influence internal timing. Timed feeding can reset the phase of the peripheral oscillators whilst having almost no effect in shifting the phase of the SCN clockwork when animals are exposed (synchronised) to a light–dark cycle. Food deprivation and calorie restriction lead not only to loss of body mass (>15%) and increased motor activity, but also affect the timing of daily activity, nocturnal animals becoming partially diurnal (i.e. they are active during their usual sleep period). This change in behavioural timing is due in part to the fact that metabolic cues associated with calorie restriction affect the SCN clock and its synchronisation to light.

Keywords Circadian rhythm · Suprachiasmatic nucleus · Mealtime · Restricted feeding · Hypocaloric diet

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Introduction

Mammals usually maintain a high metabolic rate, albeit they do not feed continuously. Rather, they ingest energy substrates periodically via food sampling from their environment. On a daily basis, the timing of feeding does not occur randomly across a 24-h period, but follows instead predictable patterns of daily rhythmicity for a given species, in close relation with the sleep–wake cycle (Armstrong 1980). To keep narrow the margin of variation in the availability of glucose to cells, energy substrates have to be stored in anticipation to cover basal energy expenditure during the ongoing period of sleep. On a longer scale (days or weeks), energy stores are needed to cope with recurrent periods of food shortage or even fasting. Energy may be stored in two main forms including, on the one hand, glycogen (i.e. carbohydrate stores) that is easily usable for short-term needs (exercise, overnight fast) and, on the other hand, triacylglycerides (i.e. lipid stores) with high energy content and useful for withstanding prolonged food deprivation.

When challenged with food shortage, animals without extensive energy stores or individuals with depleted reserves have to either spare energy loss, for instance by inactivity or deep torpor (Cherel et al. 1995; Giroud et al. 2008; Lovegrove et al. 2001), or optimise food foraging (Lynn et al. 2003; Robin et al. 1998). Some species such as the golden spiny mouse, *Acomys russatus*, use both strategies (Gutman et al. 2007). However, most rodents, when food restricted or fasted under laboratory-controlled conditions, increase their wheel-running activity (Cornish and Mrosovsky 1965), a behavioural change likely triggered by hunger and sometimes interpreted as a forage-like activity, though several hibernators do not increase running activity when food is lacking (Cornish and Mrosovsky 1965).

The impact of nutritional deficits in wild animals depends on many parameters, including amongst others body size, body reserves, diet, intra- and interspecific competition, digestive capacity and duration of fasting (for a review, see Barboza and Hume 2006). Another physiological constraint is daily rhythmicity. In addition to the need for maintaining energy homeostasis, not only feeding but also sleep are under strong circadian influence (i.e. they do not occur randomly at any time of the day). Irrespective of the temporal niche of wakefulness, daytime and nighttime for diurnal and nocturnal species, respectively, behavioural and physiological rhythmicity is controlled by a circadian timing system. During periods of food scarcity in the field or in laboratory conditions, whilst some species maintain their normal pattern of activity (e.g. deer mice, *Peromyscus maniculatus*, Blank and Desjardins 1985), a number of nocturnal rodents shift their activity pattern to the light period (i.e. they become partially diurnal), e.g. Siberian hamsters, *Phodopus sungorus* (Challet et al. 2000a; Masuda and Oishi 1995), house mice, *Mus musculus* (Blank and Desjardins 1985) or cotton rats, *Sigmodon hispidus* (Kilduff and Dube 1979). This apparent switch in behavioural timing may be of adaptive significance as it may increase the opportunity to find food in an unusual temporal niche. The purpose of this review is to show that this behavioural switch is in part mediated by metabolic cues affecting the circadian system.

The circadian system: a network of oscillating structures

The circadian system comprises a network of endogenous circadian clocks that generate, via their outputs, an internal cyclic timing. At the top of the circadian system is a master clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus (Fig. 1). Many circadian rhythms in behaviour (e.g. the sleep–wake cycle) and physiology (e.g. hormonal secretion like pineal melatonin or adrenal glucocorticoids) are controlled by this structure (Ralph

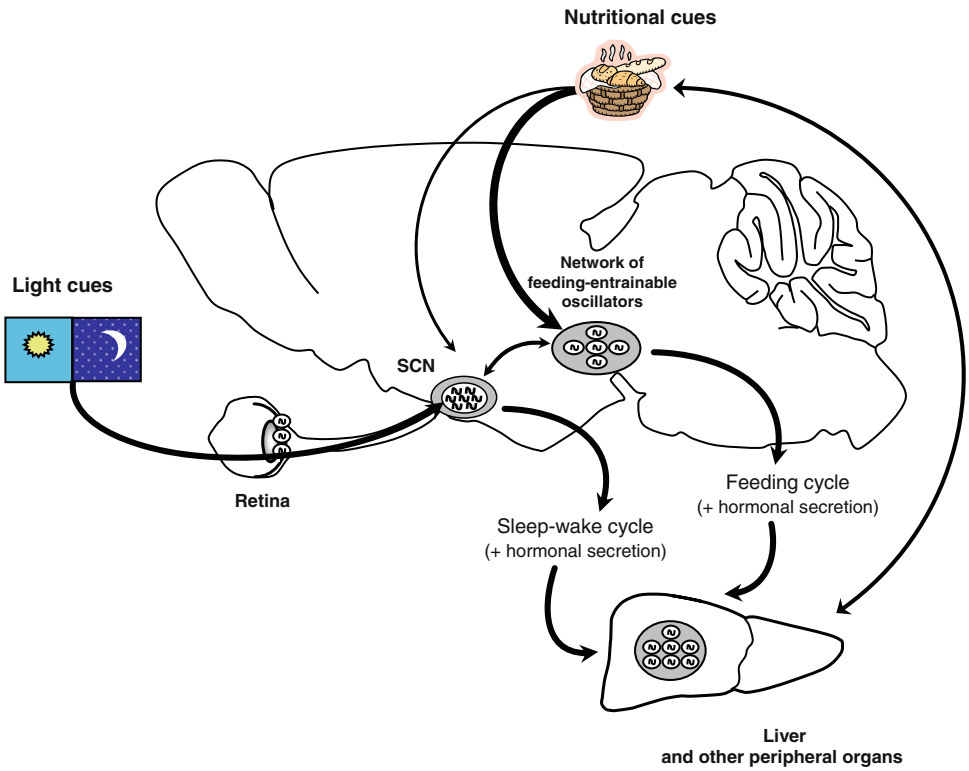

Fig. 1 Functional pathways between cerebral and peripheral components of the circadian timing system. The master circadian clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The SCN clock controls the sleep–wake cycle and several hormonal rhythms (e.g. melatonin and glucocorticoids). Light cues are mainly conveyed to the SCN clock by direct projections from retinal ganglion cells. Circadian oscillations in peripheral tissues, such as the liver, are normally synchronised by circadian outputs from the SCN. When the mealtime is shifted (using temporal restricted feeding), feeding cues are potent synchronisers for peripheral organs, but not for the SCN clock, which remains synchronised to the light–dark cycle. In the brain, a network of feeding-entrainable oscillators is thought to control food anticipation and possibly feeding cycle. Timing of feeding-entrainable oscillators is phase adjusted by mealtime. Under certain circumstances (e.g. when the diet is hypo- or hyper-caloric), some yet unknown metabolic cues affect the function of the SCN clock and its light resetting. SCN, suprachiasmatic nuclei

et al. 1990; Takahashi et al. 2001). The identification of clock genes (that is, molecular actors of the clockwork) started in the late 1990s in mammals. Since then, almost all organs including liver or skin have been shown to express circadian oscillations of clock genes (Dardente and Cermakian 2007). The internal temporal coordination is now viewed as a multi-step control, with the SCN acting as a conductor, which provides timing signals to many secondary clocks and oscillators in the brain and the periphery (Cuninkova and Brown 2008; Guilding and Piggins 2007; Mendoza and Challet 2009).

A daily timed meal triggers the expression of several rhythms anticipating the time of food access in many mammalian species (Mistlberger 1994; Stephan 2001). For example, rabbit pups are fed once per day by lactating dam and express increased locomotor activity before mealtime (Caba and González-Mariscal 2009). Food-anticipatory activity is the most studied behaviour associated with daily timing of food availability in food-restricted rodents. Because it exhibits circadian properties, even in SCN-lesioned animals, the food-anticipatory activity is thus considered to be driven by a food-entrainable clock. Besides the SCN clock that controls the sleep–wake cycle, the supposed food-entrainable clock is the only oscillatory structure having a behavioural circadian output. Detailed reviews on the food-entrainable system and its coupling with the light-entrainable SCN can be found elsewhere (Mistlberger 1994, 2009; Stephan 2001). The molecular mechanisms driving the food-entrainable clock are not yet fully identified, although the food-entrainable clockwork controlling food-anticipatory activity may use some of the known clock genes (Challet et al. 2009).

Even though its location is not yet clearly determined, the food-entrainable clock likely resides in the brain, possibly as a network coupling several cerebral oscillators (Davidson 2009). Under conditions of food available ad libitum and light–dark cycle, the daily pattern of feeding could be controlled by the food-entrainable neural system (Fig. 1).

Photic cues as synchroniser

The major environmental synchroniser (Zeitgeber = time giver) of the SCN clock is ambient light (Fig. 1). Since the retina is the only photosensitive organ in mammals, detection of the amount of ambient light, also called irradiance, is mainly achieved by a specific photopigment, melanopsin, expressed in a small subset of ganglion cells (Hankins et al. 2008), and also by classical photoreceptors (i.e. rods and cones; Boudard et al. 2009; Dkhissi-Benyahya et al. 2007). In the framework of the multi-oscillator circadian system, it should be mentioned that the retina as a whole has been identified as a light-entrainable circadian clock (Tosini and Fukuhara 2002). In fact, the retinal clock may gate the photic cues before these reach the SCN clock. Photosensitive ganglion cells project into the SCN either directly via the retinohypothalamic tract or indirectly via the intergeniculate leaflet of the thalamus (IGL; Hannibal and Fahrenkrug 2004; Harrington 1997).

The process of synchronisation (entrainment) of the SCN clock to light is characterised by a photosensitive temporal zone (i.e. nighttime) during which light exposure can shift the clock, as opposed to a dead temporal zone around midday, during which light has no phase-resetting effect (Daan and Pittendrigh 1976). Under regular conditions of light–dark cycle, light has only indirect effects on peripheral organs via photic signals coming from the SCN. Daily rhythmicity, however, can also be modulated by direct, clock-independent responses to light. For instance, exposure of nocturnal rodents to bright light at night (an unexpected stimulus under natural conditions) has an immediate inhibitory effect on locomotor activity and melatonin secretion (Redlin 2001). Other examples of masking responses in nocturnal animals exposed to light at night include increased plasma glucose (Challet et al. 1999, 2004) and corticosterone levels (Ishida et al. 2005) and reduction of heart rate (Scheer et al. 2001). These masking effects of light are thought to be conveyed successively via the SCN clock, the (sub)paraventricular hypothalamic region and the autonomous nervous system (Ishida et al. 2005; Scheer et al. 2001). Because retinal ganglion cells project directly into several targets beyond the SCN, including the subparaventricular hypothalamic zone (Hannibal and Fahrenkrug 2004), this extra-SCN region could also mediate masking cues via sympathetic fibres, thus bypassing the SCN clock.

Feeding cues (mealtime) as synchroniser

Providing food access for a daily limited time (so-called restricted feeding schedules) is a common experimental protocol to force the animals to eat at unusual times of their daily life cycle (i.e. most often during the sleeping period, like the light phase in nocturnal animals). As mentioned earlier, daily restricted feeding triggers the expression of food-anticipatory behaviour. In those protocols of restricted feeding, which are used to test the effects of mealtime, animals are not supposed to mobilise their energy stores and lose body mass (i.e. body mass should be stable compared to values before restricted feeding or increase over the course of the experiment). Otherwise, for example, if the duration of daily access to food is too short to maintain a steady or positive energy balance, then

nutritional conditions change to hypocaloric conditions associated with 15–20% body mass loss, which induce different metabolic, behavioural and circadian changes (see below).

In rodents challenged with temporal restricted feeding, a transient loss in body mass may occur in the first few days of restricted feeding, but loss of body mass is usually negligible or absent after several weeks of treatment. In laboratory rats (*Rattus norvegicus*) fed daily with 2-h food access, a gain in body mass can even be detected (+13%) as compared to baseline values (Martínez-Merlos et al. 2004). Mice fed 6 h/day for weeks do not differ in body mass compared with animals fed ad libitum (Castillo et al. 2004). In our hands, wild-type mice having an 8-h food access/day show similar body mass after 3 weeks of restricted feeding compared to baseline values (Feillet et al. 2006). Mice with only 4-h food access/day during 12 consecutive days lose around 10% of body mass compared to pre-restricted feeding mass (Sutton et al. 2008). The daily duration of food access per se is not sufficient to predict the ongoing changes. Amongst many other parameters, physiology and behaviour of the species studied (see above for the differences between rats and mice), initial body mass, initial body reserves, age, composition of food, access to a wheel and room temperature should also be taken into account.

Effects of mealtime on extra-SCN oscillators

Daytime feeding in nocturnal rodents shifts circadian oscillations in the liver (Fig. 1), indicating the sensitivity of this peripheral tissue to timing cues associated with feeding (Damiola et al. 2000; Hara et al. 2001; Stokkan et al. 2001; Wakamatsu et al. 2001). Daily oscillations of clock gene expression in many peripheral organs other than the liver (e.g. heart, lung, kidney, white adipose tissue, gastrointestinal tract) are phase reset by mealtime (Damiola et al. 2000; Hoogerwerf et al. 2007; Zvonic et al. 2006).

In the retina, complex consequences of restricted feeding on daily rhythmicity have been described (Oishi et al. 2003). Within the brain, circadian oscillations out of the SCN are affected by restricted feeding in many, but not all, cerebral regions. For example, daytime feeding markedly affects daily timing in the central amygdala (Waddington Lamont et al. 2007). Conversely, the basolateral amygdala and hippocampus are less sensitive to synchronising effects of mealtime (Waddington Lamont et al. 2007). The findings also depend on the clock genes/proteins used as phase markers of circadian oscillations (Feillet et al. 2008b; Verwey and Amir 2009). Together, the brain oscillators that are sensitive to mealtime may define a feeding-entrainable network (Fig. 1).

Effects of mealtime on the SCN clock

In sharp contrast with peripheral organs, daily timing in the SCN is rather impervious to mealtime. It has been shown for a long time that the rhythm of neuronal firing in the SCN is unchanged by daytime restricted feeding schedules (Inouye 1982a). More recent findings have confirmed that the SCN clockwork in animals exposed to LD is relatively insensitive to the resetting effects of mealtime (Damiola et al. 2000; Hara et al. 2001; Stokkan et al. 2001). Furthermore, in rodents housed in constant darkness, restricted feeding schedules generally do not have major synchronising effects in most strains of laboratory rats and mice (Abe et al. 1989; Caldelas et al. 2005; Honma et al. 1983; Mistlberger 1994; Stephan 2001), although cases of entrainment to mealtime have been reported (Abe et al. 1989; Caldelas et al. 2005; Cambras et al. 1993; Castillo et al. 2004; Holmes and Mistlberger 2000). Moreover, a daily opportunity to eat a palatable pellet in rats fed ad libitum with regular food can also entrain circadian rhythms (Mendoza et al. 2005a). Under a light–dark cycle, temporal restricted feeding can lead to a short behavioural phase advance in mice (Holmes and Mistlberger 2000) and a slower re-entrainment after an advance of the light–dark cycle in rats (Kalsbeek et al. 2000).

Metabolic cues

A prolonged fasting for several days in constant light or darkness has already been shown to produce phase shifts in the laboratory rat (Challet et al. 1997a; Coleman and Francis 1991) and a marsupial, *Sminthopsis macroura* (Coleman et al. 1989). In addition, phase delays are found during refeeding, independent of the circadian time of the first meal (Challet et al. 1997a). In the golden (or Syrian) hamster, *Mesocricetus auratus*, 1-day food deprivation under constant dim light induces large phase shifts with increased running during (subjective) daytime (Mistlberger et al. 2006). Moreover, refeeding after food deprivation has minimal effects on circadian phase of the hamsters, unless the animals are hyperactive (Mistlberger et al. 1997), suggesting that in that species, the resetting effects of fasting/refeeding are mediated mostly by behavioural inputs. Under a light–dark cycle, prolonged food deprivation in nocturnal rats also triggers an increase in diurnal activity, associated with reduced nocturnal activity, especially in late night (Challet et al. 1996c; Koubi et al. 1991). These data, therefore, suggest that the daily temporal organisation in mammals (golden hamsters excepted, see below for other peculiarities in that species) could be modulated by the metabolic status.

Effects of chronic calorie restriction on life span

In contrast to malnutrition (i.e. low intake of diets unbalanced in essential nutrients), chronic calorie restriction (i.e. moderate reduction in calorie intake combined with adequate nutrient supply) extends life span by delaying age-associated physiologic changes and pathologies in many animal species, including mammals (Masoro 2005). The reduced energy intake or rather its metabolic consequences are considered to be crucial for the anti-ageing action of calorie restriction (Duffy et al. 1990; Masoro 2005). Reduction of free radical production, enhanced DNA repair and lower carcinogen activation are amongst important changes observed in calorie-restricted rodents (Gredilla and Barja 2005; Weindruch 1992). The intracellular signalling pathways mediating the anti-ageing action are not yet fully identified. Recent evidence, however, has linked NAD^+-dependent histone deacetylases called sirtuins (SIRT) with extension of life span induced by calorie restriction (Canto and Auwerx 2009; Wolf 2006).

Of note, the anti-ageing action of long-term calorie restriction does not rely on the temporal pattern of food intake (Masoro et al. 1995; Nelson 1988). Calorie restriction can be achieved either by providing a daily hypocaloric diet or by shortening the duration of daily access to food. In both cases, the most salient effect is an initial loss of body mass (10–20% of the body mass) followed by a phase of stabilised low body mass (Challet et al. 1998b; Mendoza et al. 2005b). As soon as food is provided ad libitum, animals regain body mass by replenishing energy stores (Mendoza et al. 2005b; Fig. 2). As a control procedure of hypocaloric feeding, we used normocaloric feeding, that is, a full diet given every day at the same time. The temporal pattern of food intake in mice given a daytime normocaloric feeding corresponds roughly to a 12-h temporal restricted feeding, with food being eaten from midday to midnight. In contrast, in a hypocaloric feeding protocol, food is eaten in a short time, that is, less than 3 h (Mendoza et al. 2005b).

Effects of hypocaloric feeding on extra-SCN oscillators

Synchronisation of the liver clockwork by daytime hypocaloric feeding (Feillet et al. 2006; Froy et al. 2008) is comparable to that produced by restricted feeding schedules (Damiola et al. 2000; Hara et al. 2001; Stokkan et al. 2001). Moreover, in the brain outside the SCN, circadian oscillations of clock proteins in several brain regions, such as in the paraventricular nuclei of the hypothalamus, are phase advanced by hypocaloric feeding. Clock protein oscillations in other cerebral structures, such as the hippocampus, remain relatively unchanged in spite of the hypometabolic state (Feillet et al. 2008b).

Effects of hypocaloric feeding on daily pattern of locomotor activity

In constant darkness, daily hypocaloric feeding entrains behavioural and physiological rhythms in rats (Challet et al. 1996a). Timed hypocaloric feeding also synchronises the SCN clockwork and intriguingly induces a diurnal-like activity phase in reference to clock gene oscillations in the SCN (Caldelas et al. 2005).

When exposed to light–dark cycles, rats, mice and Siberian hamsters challenged with timed calorie restriction become partially diurnal as their "nocturnal" pattern of activity starts in the late afternoon, in addition to the bout of activity expressed prior to the time of food access (Fig. 3). Furthermore, a phase advance is detectable by measuring the initial phase of the nocturnal pattern in these rodents transferred to constant darkness and subsequently fed ad libitum. This large phase-shifting effect can be attributed to caloric restriction per se (i.e. to its behavioural, metabolic, and/or hormonal correlates) because it is not observed in animals fed with a timed normocaloric diet (Challet et al. 1997d, 1998b, 2000a; Mendoza et al. 2005b). The partial switch in behavioural timing of nocturnal species during calorie restriction may be of adaptive significance as it may ultimately increase the opportunity to find food in an unusual temporal niche (i.e. daytime in nocturnal species). According to this hypothesis, it is interesting to note that a diurnal rodent species, the Sudanian grass rat, *Arvicanthis ansorgei*, subjected to a timed calorie restriction becomes partially nocturnal (Mendoza and Challet, unpublished data).

At least one rodent species does not display any behavioural phase advance during chronic calorie restriction: the golden hamster, a photoperiodic rodent that exhibits increased adiposity under winter-like short photoperiods (Bartness and Wade 1984). Compared to another photoperiodic species, the Siberian (or Djungarian) hamster, *Phodopus djungorus*, which decreases body mass during short photoperiods (Steinlechner et al. 1983), and most other rodents, the golden hamster is also known not to express reactive changes in food intake during energy challenges. In particular, these hamsters do not show the typical transient hyperphagia after food deprivation (Rowland 1982; Silverman and Zucker 1976) or calorie restriction (Challet et al. 2000a). They also fail to increase the rate of food intake during schedules of restricted feeding (Rowland 1982). Golden hamsters, however, cannot be considered as behaviourally insensitive to metabolic challenges because they increase their daily activity during food deprivation (Mistlberger et al. 1997, 2006) and calorie restriction, as do Siberian hamsters (Challet et al. 2000a) or rats (Challet et al. 1997d). Furthermore, golden hamsters, in which both food and water availability is restricted to the middle of the light phase, lose around 18% of their baseline

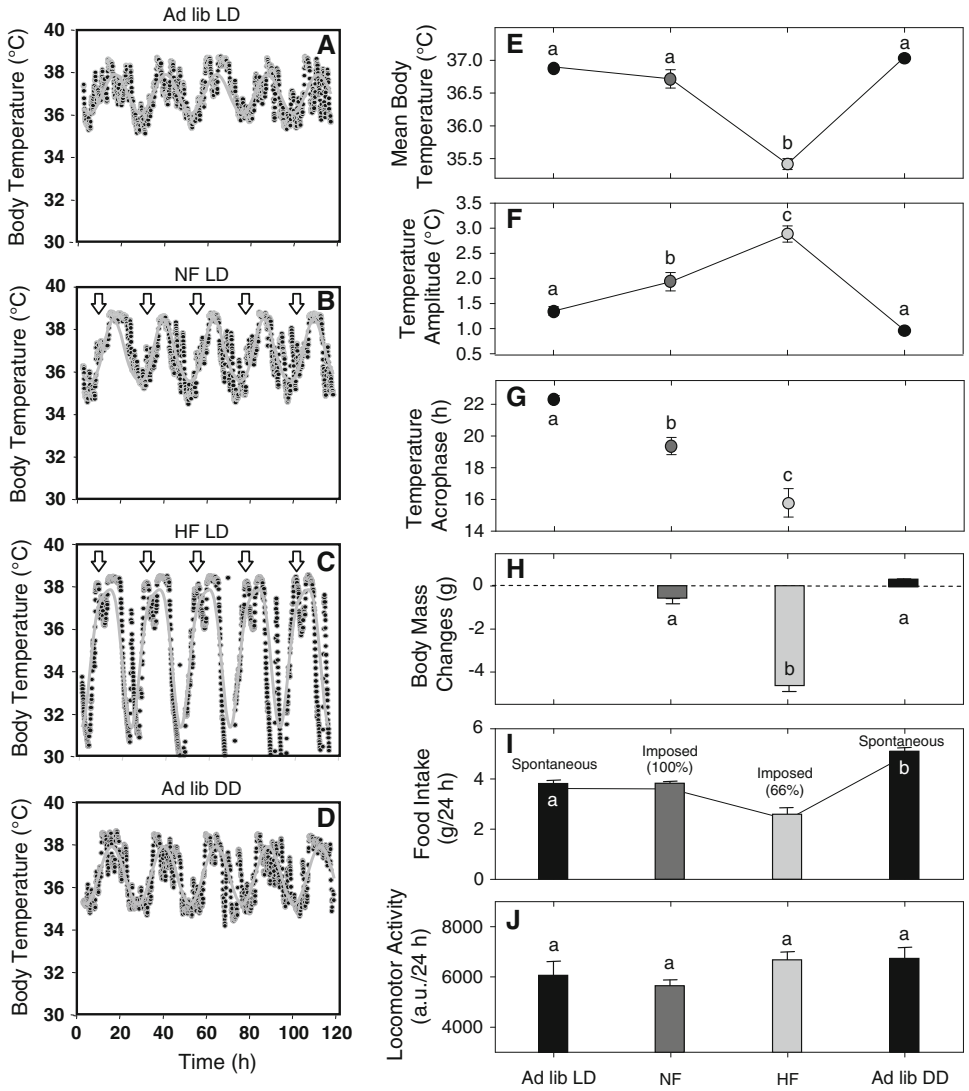

Fig. 2 Effects of daytime normocaloric and hypocaloric feeding on body temperature rhythm, body mass, food intake and locomotor activity in C57 mice ($n = 6$). **a–d** Body temperature rhythm in mice successively fed ad libitum (ad lib) under a light–dark cycle (LD; **a**), in LD with a full diet at midday (normocaloric feeding = 100% of baseline diet, NF; **b**), in LD with a hypocaloric diet at midday (hypocaloric feeding = 66% of baseline diet, HF; **c**), and finally fed ad libitum after transfer to constant darkness (ad lib DD; **d**). *Arrows* indicate the time of feeding. Sinusoidal grey lines are curves fitted to the raw data using a cosinor analysis. **e–g** Comparison of body temperature parameters after cosinor analysis to assess the mean levels (**e**), the daily amplitude (**f**) and the acrophase (daily peak; not determined in constant darkness; **g**) of body temperature rhythm. Means without common letters are significantly different ($P < 0.05$). Note the increased amplitude and the phase-advanced acrophase during normocaloric feeding. Note also the lower body temperature, the largest amplitude and the most phase-advanced acrophase during hypocaloric feeding. **h** Relative changes in body mass during normocaloric feeding, hypocaloric feeding and food ad libitum in constant darkness, as compared to baseline conditions. Only hypocaloric conditions are associated with body mass loss, which is reversed during ad libitum refeeding. **i** Spontaneous food intake during ad libitum refeeding in constant darkness is larger than that during baseline under a light–dark cycle. Imposed diets (i.e. (normocaloric and hypocaloric feeding = 100 and 66% of baseline diet, respectively) are shown for visual comparison. **j** Daily locomotor activity is not changed according to the feeding conditions. E. Challet, unpublished data

body mass by the third week of restriction (i.e. they are in a hypocaloric state) and show a small, but consistent, advanced phase of nocturnal onset of activity (Mistlberger 1993). Studying the species-specific difference in golden hamsters with regard to metabolic modulation of circadian rhythmicity may be useful to understand the mechanisms underlying the synchronising effects of calorie restriction.

Interestingly, whatever the time of day at which limited food is given (i.e. early or late daytime, early or late nighttime) and thus independently of when no food is available, timed calorie restriction in mice leads always to a phase advance of the SCN clock (Challet et al. 1998b). The phase-shifting effects of timed calorie restriction are different from the classical families of phase–response

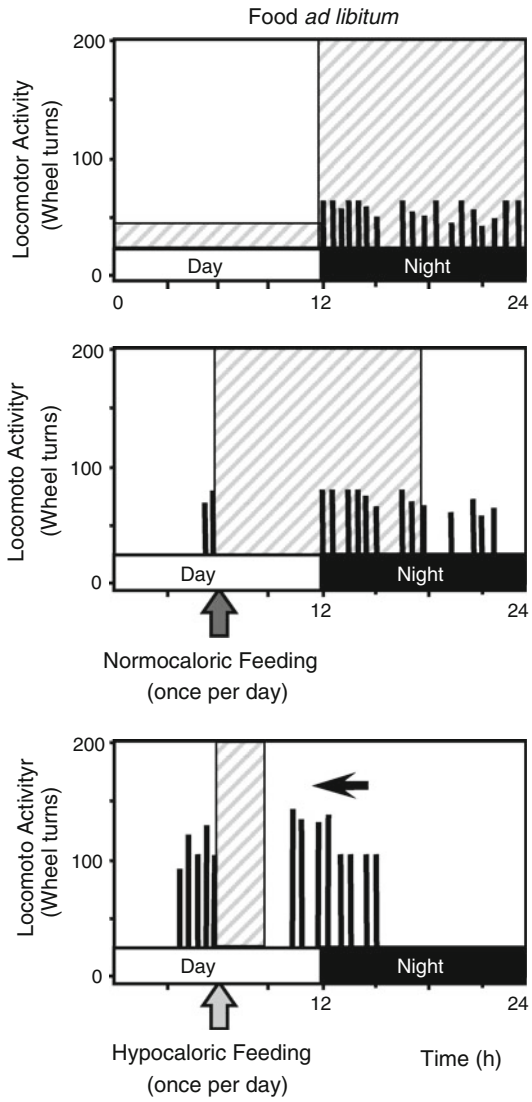

Fig. 3 Effects of daytime normocaloric and hypocaloric feeding on daily timing of locomotor activity in nocturnal rodents. Note the occurrence of a bout of activity prior to the time of feeding for both normocaloric and hypocaloric feeding. Only hypocaloric conditions are associated with advanced nocturnal activity. Hatched areas indicate the duration of food intake (redrawn from Challet et al. 1997d; Mendoza et al. 2005b)

curves using single phase-shifting "pulses" in constant dark conditions such as circadian responses to light pulses and to behavioural factors (for review, see Challet 2007; Challet and Pévet 2003; Smith et al. 1992).

Rather than synchronising the effects due to a single timed meal per day, calorie restriction actually may have tonic effects of the SCN function that would lead to phase-advanced clockwork. This hypothesis would explain why timed calorie restriction leads to phase advances independent of the timing of single daily meals.

Another strong argument supporting this assumption is the fact that behavioural phase shifts occur in response to hypocaloric feeding without daily synchronisation to a single meal. To demonstrate this, we used six-meal schedules daily according to the protocol developed by Kalsbeek and Strubbe (1998). The length of each of the six food accesses per day was adjusted to maintain either normocaloric or hypocaloric conditions. Rats fed with sufficiently long six-meal schedules expressed a regular nocturnal pattern of activity, in spite of the fact that they ate half of their daily food intake during daytime. In contrast, rats that were exposed to daily schedules of six short meals, and had lost body mass (−17%), displayed behavioural phase shifts in their daily timing of locomotor activity (Mendoza et al. 2008b).

Effects of hypocaloric feeding on body temperature rhythm

In rats, the nocturnal rise in body temperature controlled by the SCN is phase advanced by hypocaloric and normocaloric feedings, with more pronounced effects with calorie restriction (Challet et al. 1997b, d). In addition, timed calorie restriction leads to the expression of food-anticipatory increase in thermogenesis (Challet et al. 1997d; Duffy et al. 1990). In a longitudinal study, mice were successively challenged with daytime normocaloric feeding, followed by daytime hypocaloric feeding before being transferred to constant darkness with food provided ad libitum (Fig. 2). In agreement with previous data in rats (Challet et al. 1997d), a daytime normocaloric feeding in mice modifies several characteristics of body temperature rhythm: amplitude is increased and acrophase is phase advanced by 3 h. These changes are accentuated when feeding becomes hypocaloric, with the temperature amplitude being further increased and the acrophase being further phase advanced (6 h compared to baseline conditions), in accordance with findings in rats (Challet et al. 1997b, d). There is also hypothermia during late night. During the 1st week of refeeding, all the changes are reversed because they go back to the baseline values, except for food intake, which is larger than that during baseline ad libitum conditions (Fig. 2).

Effects of hypocaloric feeding on the SCN and its synchronisation to light

Considering that timed calorie restriction affects the SCN, it may change the free-running period and/or the circadian responses to light. In support to the tonic effects of nutritional cues on the period of the SCN clock, the endogenous period (tau) is shortened after long-term restricted feeding (Cambras et al. 1993). However, no significant differences in tau were found between previously normocalorie- and hypocalorie-fed mice after transfer to constant darkness

with food ad libitum (Challet et al. 1998b) or in the same mice before and after 3 weeks of calorie restriction (Mendoza et al. 2005b). Oscillatory expression of clock genes and neuropeptides in the mouse SCN are altered by hypocaloric feeding (Andrade et al. 2004; Mendoza et al. 2005b, 2007), supporting the hypothesis that calorie restriction has effects within the SCN clock.

Another, not mutually exclusive explanation for the advanced nocturnal activity period under a light–dark cycle is that timed calorie restriction alters the phase–response curve to light. With Jorge Mendoza and Caroline Graff, when we compared the circadian responses to light in mice previously fed with a hypocaloric diet to those in control mice fed ad libitum, we did not get a shift in the phase–response curve to light, but found a shape distortion characterised by an extended phase-advance region of the photic phase–response curve in calorie-restricted mice. More precisely, whilst the light-induced delays produced in early night were more or less normal, if not reduced, the light-induced phase advances produced in the late night were markedly increased. Furthermore, significant phase advances were found during the usual dead zone of the phase–response curve to light (i.e. during daytime, when light usually has no shifting effect; Mendoza et al. 2005b). Interestingly, chronic calorie restriction in mice produces a more rapid re-entrainment after a shift of the light–dark cycle (Resuehr and Olcese 2005). Moreover, light-induced expression of clock and clock-controlled proteins in the SCN is delayed and further increased in mice previously fed with a hypocaloric diet (Mendoza et al. 2007).

At the opposite scale of the negative energy balance associated with fasting or calorie restriction is high-fat feeding. It is worth noting that chronic high-fat feeding induces changes in daily rhythmicity of behaviour and physiology (Kohsaka et al. 2007; Mendoza et al. 2008a). Of interest, high-fat feeding alters synchronisation by light in an opposite way compared to hypocaloric feeding: light-induced phase advances are reduced and re-entrainment after a shift of the light–dark cycle is slower (Mendoza et al. 2008a).

Causes of the behavioural phase advance during calorie restriction

Acute or repeated stimuli triggering transient hyperactivity and/or behavioural activation during subjective daytime are capable of phase shifting the circadian rhythm of activity in hamsters (Mistlberger 1991; Mistlberger et al. 2003; Mrosovsky 1996) and mice (Challet et al. 2000b; Marchant and Mistlberger 1996). It is thus possible that a strong expression of food-anticipatory activity during calorie restriction participates in the phase advance of the SCN clock through locomotor activity feedback. However, daily immobilisation of the calorie-restricted mice before the expected food access (i.e. during the period in which they would have normally expressed food-anticipatory activity) does not eliminate or modify the behavioural phase advance (Challet et al. 1998b). This finding rules out the possibility that activity feedback to the SCN through increased daytime activity plays a crucial role for the phase-shifting effect of timed calorie restriction.

Afferent pathways to SCN

Behavioural and other non-photic cues have shown to be conveyed to the SCN clock via afferent pathways including serotonergic projections from the raphe nuclei and projections from the intergeniculate leaflets (IGL) that release neuropeptide Y in the SCN (review in Challet and Pévet 2003; Harrington 1997; Morin and Allen 2006). It is thus possible that metabolic cues associated with calorie restriction are also transmitted via the same neuronal pathways (Fig. 4). To test a serotonergic involvement, a neurotoxin damaging selectively serotonergic terminals in the SCN (i.e. 5,7-DHT) was microinjected in rats that were thereafter challenged with timed calorie restriction. A significant reduction was found in the phase advance of body temperature and locomotor activity rhythms (Challet et al. 1997b). To investigate a putative participation of the afferents releasing neuropeptide Y to the SCN, bilateral electrolytic lesions were performed in the IGL region of rats that were subsequently fed with a daily hypocaloric diet. Behavioural phase advance induced by calorie restriction was almost undetectable in rats bearing complete intergeniculate lesions (Challet et al. 1996b). Moreover, c-FOS expression in the IGL is specifically increased before feeding time in calorie-restricted rats (Challet et al. 1997e). Together, these findings strongly suggest that the IGL can receive metabolic cues associated with calorie restriction and convey them to the SCN.

How can nutritional cues reach the IGL? Reduced plasma glucose, as occurs during calorie restriction (Mendoza et al. 2005b), activates cerebral sensors of glucopenia, mainly located in the ventromedial hypothalamus (Oomura 1983; Yang et al. 1999). Metabolic cues (e.g. circulating glucose) may activate the ventromedial nuclei of the hypothalamus (VMH) directly or indirectly via arcuate POMC projections into the VMH (King 2006; Fig. 4). In turn, the VMH project into the IGL (Vrang et al. 2003; Fig. 4). Of note, the VMH also send direct, glutamatergic projections into the SCN (Moga and Moore 1996; Fig. 4). Not only ibotenic lesions of the ventromedial hypothalamus, but also destruction of the glucose-response neurons in the ventromedial hypothalamus (i.e. VMH and arcuate nuclei) prevent the behavioural phase advances in

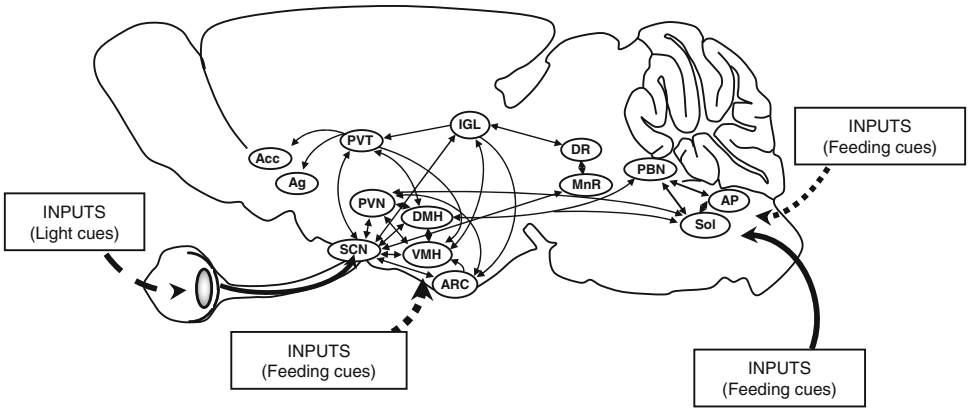

Fig. 4 The suprachiasmatic nuclei and several neuronal pathways (*thin arrows*) connecting the 'metabolic' brainstem (*AP*, *PBN*, *Sol*), the 'metabolic' (*ARC*, *DMH*, *PVN*, *VMH*) and circadian hypothalamus (*SCN*), two thalamic structures (*IGL* and *PVT*) and two forebrain structures (*Acc* and *Ag*). Afferent pathways (neuronal: *thick*, *solid arrows*; humoral: *thick*, *dotted arrows*) conveying light cues from the retina and feeding cues from peripheral organs to the brain. *Acc* accumbens nuclei, *Ag* amygdala, *AP* area postrema, *ARC* arcuate nuclei, *DMH* dorsomedial hypothalamic nuclei, *DR* dorsal raphe nucleus, *IGL* intergeniculate leaflets of the thalamus, *PBN* parabrachial nucleus, *MnR* median raphe nucleus, *PVN* paraventricular nuclei of the hypothalamus, *PVT* paraventricular nuclei of the thalamus, *SCN* suprachiasmatic nuclei, *Sol* nucleus of the solitary tract, VMH ventromedial hypothalamic nuclei (adapted from Davidson 2009; Horvath 1998; King 2006; Moga and Moore 1996; Moga et al. 1995; Morin and Allen 2006; Thompson and Swanson 1998; Vrang et al. 2003; Yi et al. 2006)

calorie-restricted rodents (Challet et al. 1997c, 1998a). Interestingly, c-FOS expression in the VMH appears to be selectively increased before feeding time in food-restricted mice (Ribeiro et al. 2007). In another study, a 50% increase of c-FOS expression in the VMH of food-restricted rats 1 h prior to food access is found to be nonsignificant (Angeles-Castellanos et al. 2004). A rhythm of multiple unit activity in the VMH of food-restricted rats has been described with a peak of activity immediately after and a trough right before the feeding (Inouye 1983). In addition, ventromedial hypothalamic lesions in rats impair food-anticipatory behaviour, at least during the first few weeks of restricted feeding (Inouye 1982b; Mistlberger and Rechtschaffen 1984). Most of these data thus support the hypothesis of integration in the ventromedial hypothalamus of nutritional signals that would in turn modulate the SCN function through direct projections or indirectly via activation of the IGL.

Direct effects on the SCN

It cannot be fully excluded yet that metabolic consequences of timed calorie restriction are capable of interacting directly with the SCN clockwork. Amongst these could be changes in hormones or plasma metabolites.

The phase of the firing rate peak in an SCN slice preparation can be modified temporarily by changing the bathing concentration of glucose, although without permanent resetting of the clock (Hall et al. 1997). However, this kind of signal repeated every day in vivo may well produce a diurnal rhythmicity or an apparent phase shift.

During chronic calorie restriction, hypoglycaemia is associated with lipid mobilisation, leading to an increase in plasma free fatty acids and ketone bodies (Mahoney et al. 2006). Free fatty acids or ketone bodies may affect the firing rate of hypothalamic neurons (Oomura 1983). During the daily period of fasting, therefore, the metabolic modulation of photic phase shifting may be mediated, in part, by these fuels derived from lipid stores. It is worth mentioning here that mice fed a ketogenic diet not only display an expected loss of body mass and lipid mobilisation, but also show a phase-advanced rhythm of locomotor activity (Oishi et al. 2009).

Food restriction induces a daily peak of plasma corticosterone before feeding, even in SCN-lesioned animals (Challet et al. 1997d; Feillet et al. 2008a; Honma et al. 1984). This daily increase in circulating corticosterone may have participated in the behavioural phase advance during calorie restriction. Stress-induced immobilisation also induce an increase in plasma corticosterone (Bradbury et al. 1991). The association of timed immobilisation and calorie restriction does not potentiate the phase advance induced by timed calorie restriction alone. Furthermore, timed immobilisation in mice fed ad libitum does not induce any phase shift of circadian activity rhythm (Challet et al. 1998b). It is therefore unlikely that the daily peak of plasma corticosterone before feeding plays a major role in the behavioural phase advance during calorie restriction.

Receptors both to insulin and leptin are present in the SCN (Hakansson et al. 1998; Unger et al. 1989). Insulin applied during the subjective day inhibits the firing rate of SCN cells in vitro (Shibata et al. 1986). Moreover, insulin

injected into the SCN in vivo modifies the sympathetic firing rate (Sakaguchi et al. 1988). These findings raise the possibility of a direct action of insulin on the SCN cells. However, the calorie restriction-induced decrease in insulin (Masoro 2005) suggests that insulin may not play a necessary role in the behavioural phase advance. For leptin, it has been shown that it can shift slices of SCN maintained in vitro (Prosser and Bergeron 2003). Leptin injected into the rat brain in vivo does not produce salient shifts of circadian rhythms (Martínez-Merlos et al. 2004). Furthermore, calorie restriction reduces the amplitude of daily variations in plasma leptin (Chacón et al. 2005), making unlikely that this hormone plays a crucial role in the behavioural phase advances during calorie restriction.

Ghrelin is an orexigenic peptide, principally secreted in the stomach and acts on hypothalamic targets, such as the ventromedial hypothalamic or arcuate nuclei, to trigger food intake (Zigman et al. 2006). Receptors to leptin are expressed in the SCN region in both rats and mice (Zigman et al. 2006). Plasma ghrelin is increased in calorie-restricted laboratory rats (Johansson et al. 2008) and grey mouse lemurs, *Microcebus murinus* (Giroud et al. 2009). Stimulation of the ghrelinergic system can affect SCN activity in rodents (Yannielli et al. 2007). Most interestingly, studies in mice with targeted mutation of the ghrelin receptor gene have observed altered pattern of food-anticipatory activity (Blum et al. 2009; Le Sauter et al. 2009), although other studies rule out a causal role of ghrelin in food anticipation (Morgado et al. 2008; Szentirmai et al. 2010). Furthermore, ghrelin has phase-advancing effects only in fasted mice, but not in fed individuals (Yannielli et al. 2007). Ghrelin is thus a chronomodulating hormone, possibly involved in the changes of activity timing during calorie restriction.

Circadian oscillations of clock genes in vitro can be modulated by the cellular redox state (Rutter et al. 2001). Actually, the functional connections between cellular metabolism and the circadian clockwork involve the redox-sensing histone deacetylase SIRT1 (Asher et al. 2008; Nakahata et al. 2009; Ramsey et al. 2009). *Sirt1* mRNA is expressed in the suprachiasmatic nuclei, and SIRT1 protein levels are increased in the hypothalamus of fasted mice (Ramadori et al. 2008). Unexpectedly, no modulating effect of redox state has been detected in an SCN cell line (Wise and Shear 2004). However, considering that calorie restriction increases the redox system in brain cells (Hyun et al. 2006), it is conceivable that chronic hypocaloric feeding modifies the SCN clockwork by adjusting the cellular redox state.

This review has summarised evidence demonstrating that both timed restricted feeding and calorie restriction adjust the phase of oscillators in peripheral tissues and several extra-SCN regions. Both conditions of food shortage trigger food-anticipatory behaviour. In rodents exposed to a light–dark cycle, only calorie restriction markedly affects the SCN clock and changes the daily timing of activity. These data suggest that reduced food availability in the field can affect the behavioural timing and/or photic synchronisation in mammals. This may partly account for the changes in the daily timing of activity in rodents during periods of food shortage.

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References

Abe H, Kida M, Tsuji K, Mano T (1989) Feeding cycles entrain circadian rhythms of locomotor activity in CS mice but not in C57BL/6J mice. Physiol Behav 45:397–401

Andrade JP, Pereira PA, Silva SM, Sá SI, Lukoyanov NV (2004) Timed hypocaloric food restriction alters the synthesis and expression of vasopressin and vasoactive intestinal peptide in the suprachiasmatic nucleus. Brain Res 1022:226–233

Angeles-Castellanos M, Aguilar-Roblero R, Escobar C (2004) c-Fos expression in hypothalamic nuclei of food-entrained rats. Am J Physiol Regul Integr Comp Physiol 286:R158–R165

Armstrong S (1980) A chronometric approach to the study of feeding behavior. Neurosci Biobehav Rev 4:27–53

Asher G, Gatfield D, Stratmann M, Reinke H, Dibner C, Kreppel F, Mostoslavsky R, Alt FW, Schibler U (2008) SIRT1 regulates circadian clock gene expression through PER2 deacetylation. Cell 134:317–328

Barboza PS, Hume ID (2006) Physiology of intermittent feeding: integrating responses of vertebrates to nutritional deficit and excess. Physiol Biochem Zool 79:250–264

Bartness TJ, Wade GN (1984) Photoperiodic control of body weight and energy metabolism in Syrian hamsters (*Mesocricetus auratus*): role of pineal gland, melatonin, gonads, and diet. Endocrinology 114:492–498

Blank JL, Desjardins C (1985) Differential effects of food restriction on pituitary-testicular function in mice. Am J Physiol Regul Integr Comp Physiol 248:R181–R189

Blum ID, Patterson Z, Khazall R, Lamont EW, Sleeman MW, Horvath TL, Abizaid A (2009) Reduced anticipatory locomotor responses to scheduled meals in ghrelin receptor-deficient mice. Neuroscience 164:351–359

Boudard DL, Mendoza J, Hicks D (2009) Loss of photic entrainment at low illuminances in rats with acute photoreceptor degeneration. Eur J Neurosci 30:1527–1536

Bradbury MJ, Cascio CS, Scribner KA, Dallman MF (1991) Stress-induced adrenocorticotropin secretion: diurnal responses and decreases during stress in the evening are not dependent on corticosterone. Endocrinology 128:680–688

Caba M, González-Mariscal G (2009) The rabbit pup, a natural model of nursing anticipatory activity. Eur J Neurosci 30:1697–1706

Caldelas I, Feillet CA, Dardente H, Eclancher F, Malan A, Gourmelen S, Pévet P, Challet E (2005) Timed hypocaloric feeding and melatonin synchronize the suprachiasmatic clockwork in rats, but with opposite timing of behavioral output. Eur J Neurosci 22:921–929

Cambras T, Vilaplana J, Diez-Noguera A (1993) Effects of long-term restricted feeding on motor activity rhythm in the rat. Am J Physiol Regul Integr Comp Physiol 265:R467–R473

Canto C, Auwerx J (2009) Caloric restriction, SIRT1 and longevity. Trends Endocrinol Metab 20:325–331

Castillo MR, Hochstetler KJ, Travernier RJ, Greene DM, Bult-Ito A (2004) Entrainment of the master circadian clock by scheduled feeding. Am J Physiol Regul Integr Comp Physiol 287:R551–R555

Chacón F, Esquifino AI, Perello M, Cardinali DP, Spinedi E, Alvarez MP (2005) 24-Hour changes in ACTH, corticosterone, growth hormone, and leptin levels in young male rats subjected to calorie restriction. Chronobiol Int 22:253–265

Challet E (2007) Minireview: entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. Endocrinology 148:5648–5655

Challet E, Pévet P (2003) Interactions between photic and nonphotic stimuli to synchronize the master circadian clock in mammals. Front Biosci 8:S246–S257

Challet E, Malan A, Pévet P (1996a) Daily hypocaloric feeding entrains circadian rhythms of wheel-running and body temperature in rats kept in constant darkness. Neurosci Lett 211:1–4

Challet E, Pévet P, Malan A (1996b) Intergeniculate leaflet lesion and daily rhythms in food- restricted rats fed during daytime. Neurosci Lett 216:214–218

Challet E, Le Maho Y, Pévet P, Nobelis P, Malan A (1996c) Ventromedial hypothalamic lesions prevent the fasting-induced changes in day–night pattern of locomotor activity. Behav Brain Res 77:155–163

Challet E, Pévet P, Malan A (1997a) Effects of prolonged fasting and subsequent refeeding on free-running rhythms of temperature and locomotor activity in rats. Behav Brain Res 84:275–284

Challet E, Pévet P, Malan A (1997b) Lesion of the serotonergic terminals in the suprachiasmatic nuclei limits the phase advance of body temperature rhythm in food-restricted rats fed during daytime. J Biol Rhythms 12:235–244

Challet E, Pévet P, Lakhdar-Ghazal N, Malan A (1997c) Ventromedial nuclei of the hypothalamus are involved in the phase advance of temperature and activity rhythms in food-restricted rats fed during daytime. Brain Res Bull 43:209–218

Challet E, Pévet P, Vivien-Roels B, Malan A (1997d) Phase-advanced daily rhythms of melatonin, body temperature, locomotor activity in food-restricted rats fed during daytime. J Biol Rhythms 12:65–79

Challet E, Jacob N, Vuillez P, Pévet P, Malan A (1997e) Fos-like immunoreactivity in the circadian timing system of calorie-restricted rats fed at dawn: daily rhythms and light pulse-induced changes. Brain Res 770:228–236

Challet E, Bernard DJ, Turek FW (1998a) Lesions of glucose-responsive neurons impair synchronizing effects of calorie restriction in mice. Brain Res 801:244–250

Challet E, Solberg LC, Turek FW (1998b) Entrainment in calorie-restricted mice: conflicting zeitgebers and free-running conditions. Am J Physiol Regul Integr Comp Physiol 274:R1751–R1761

Challet E, Losee-Olson S, Turek FW (1999) Reduced glucose availability attenuates circadian responses to light in mice. Am J Physiol Regul Integr Comp Physiol 276:R1063–R1070

Challet E, Kolker DE, Turek FW (2000a) Metabolic influences on circadian rhythmicity in Siberian and Syrian hamsters exposed to long photoperiods. J Neuroendocrinol 12:69–78

Challet E, Takahashi JS, Turek FW (2000b) Nonphotic phase shifting in clock mutant mice. Brain Res 859:398–403

Challet E, Malan A, Turek FW, Van Reeth O (2004) Daily variations of blood glucose, acid–base state and PCO_2 in rats: effect of light exposure. Neurosci Lett 355:131–135

Challet E, Mendoza J, Dardente H, Pévet P (2009) Neurogenetics of food anticipation. Eur J Neurosci 30:1676–1687

Cherel Y, El Omari B, Le Maho Y, Saboureau M (1995) Protein utilization during fasting with shallow and deep torpor in the European hedgehog (*Erinaceus europaeus*). J Comp Physiol B 164:653–658

Coleman GJ, Francis AJ (1991) Food deprivation and reinstatement phase shifts rat activity rhythms in constant light but not constant dark. Physiol Behav 50:167–171

Coleman GJ, O'Reilly HM, Armstrong SM (1989) Food-deprivation-induced phase shifts in *Sminthopsis macroura froggatti*. J Biol Rhythms 4:49–60

Cornish ER, Mrosovsky N (1965) Activity during food deprivation and satiation of six species of rodent. Anim Behav 13:242–248

Cuninkova L, Brown SA (2008) Peripheral circadian oscillators: interesting mechanisms and powerful tools. Ann N Y Acad Sci 1129:358–370

Daan S, Pittendrigh CS (1976) A functional analysis of circadian pacemakers in nocturnal rodents. II. The variability of phase–response curves. J Comp Physiol 106:253–266

Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U (2000) Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. Genes Dev 14:2950–2961

Dardente H, Cermakian N (2007) Molecular circadian rhythms in central and peripheral clocks in mammals. Chronobiol Int 24:195–213

Davidson AJ (2009) Lesion studies targeting food-anticipatory activity. Eur J Neurosci 30:1658–1664

Dkhissi-Benyahya O, Gronfier C, De Vanssay W, Flamant F, Cooper HM (2007) Modeling the role of mid-wavelength cones in circadian responses to light. Neuron 53:677–687

Duffy PH, Feuers R, Nakamura KD, Leakey J, Hart RW (1990) Effect of chronic caloric restriction on the synchronization of various physiological measures in old female Fischer 344 rats. Chronobiol Int 7:113–124

Feillet CA, Ripperger JA, Magnone MC, Dulloo A, Albrecht U, Challet E (2006) Lack of food anticipation in Per2 mutant mice. Curr Biol 16:2016–2022

Feillet CA, Mendoza J, Pévet P, Challet E (2008a) Restricted feeding restores rhythmicity in the pineal gland of arrhythmic suprachiasmatic-lesioned rats. Eur J Neurosci 28:2451–2458

Feillet CA, Mendoza J, Albrecht U, Pévet P, Challet E (2008b) Forebrain oscillators ticking with different clock hands. Mol Cell Neurosci 37:209–221

Froy O, Chapnik N, Miskin R (2008) The suprachiasmatic nuclei are involved in determining circadian rhythms during restricted feeding. Neuroscience 155:1152–1159

Giroud S, Blanc S, Aujard F, Bertrand F, Gilbert C, Perret M (2008) Chronic food shortage and seasonal modulations of daily torpor and locomotor activity in the grey mouse lemur (*Microcebus murinus*). Am J Physiol Regul Integr Comp Physiol 294:R1958–R1967

Giroud S, Perret M, Le Maho Y, Momken I, Gilbert C, Blanc S (2009) Gut hormones in relation to body mass and torpor pattern changes during food restriction and re-feeding in the gray mouse lemur. J Comp Physiol B 179:99–111

Gredilla R, Barja G (2005) Minireview: the role of oxidative stress in relation to caloric restriction and longevity. Endocrinology 146:3713–3717

Guilding C, Piggins HD (2007) Challenging the omnipotence of the suprachiasmatic timekeeper: are circadian oscillators present throughout the mammalian brain? Eur J Neurosci 25:3195–3216

Gutman R, Yosha D, Choshniak I, Kronfeld-Schor N (2007) Two strategies for coping with food shortage in desert golden spiny mice. Physiol Behav 90:95–102

Hakansson ML, Brown H, Ghilardi N, Skoda RC, Meister B (1998) Leptin receptor immunoreactivity in chemically defined target neurons of the hypothalamus. J Neurosci 18:559–572

Hall AC, Hoffmaster RM, Stern EL, Harrington ME, Bickar D (1997) Suprachiasmatic nucleus neurons are glucose sensitive. J Biol Rhythms 12:388–400

Hankins MW, Peirson SN, Foster RG (2008) Melanopsin: an exciting photopigment. Trends Neurosci 31:27–36

Hannibal J, Fahrenkrug J (2004) Target areas innervated by PACAP-immunoreactive retinal ganglion cells. Cell Tissue Res 316:99–113

Hara R, Wan K, Wakamatsu H, Aida R, Moriya T, Akiyama M, Shibata S (2001) Restricted feeding entrains liver clock without participation of the suprachiasmatic nucleus. Genes Cells 6:269–278

Harrington ME (1997) The ventral lateral geniculate nucleus and the intergeniculate leaflet: interrelated structures in the visual and circadian systems. Neurosci Biobehav Rev 21:705–727

Holmes MM, Mistlberger RE (2000) Food anticipatory activity and photic entrainment in food-restricted BALB/c mice. Physiol Behav 68:655–666

Honma KI, Von Goetz C, Aschoff J (1983) Effects of restricted daily feeding on freerunning circadian rhythms in rats. Physiol Behav 30:905–913

Honma KI, Honma S, Hiroshige T (1984) Feeding-associated corticosterone peak in rats under various feeding cycles. Am J Physiol Regul Integr Comp Physiol 246:R721–R726

Hoogerwerf WA, Hellmich HL, Cornelissen G, Halberg F, Shahinian VB, Bostwick J, Savidge TC, Cassone VM (2007) Clock gene expression in the murine gastrointestinal tract: endogenous rhythmicity and effects of a feeding regimen. Gastroenterology 133:1250–1260

Horvath TL (1998) An alternate pathway for visual signal integration into the hypothalamo-pituitary axis: retinorecipient intergeniculate neurons project to various regions of the hypothalamus and innervate neuroendocrine cells including those producing dopamine. J Neurosci 18:1546–1558

Hyun DH, Emerson SS, Jo DG, Mattson MP, de Cabo R (2006) Calorie restriction up-regulates the plasma membrane redox system in brain cells and suppresses oxidative stress during aging. Proc Natl Acad Sci USA 103:19908–19912

Inouye ST (1982a) Restricted daily feeding does not entrain circadian rhythms of the suprachiasmatic nucleus in the rat. Brain Res 232:194–199

Inouye ST (1982b) Ventromedial hypothalamic lesions eliminate anticipatory activities of restricted daily feeding schedules in the rat. Brain Res 250:183–187

Inouye ST (1983) Does the ventromedial hypothalamic nucleus contain a self-sustained circadian oscillator associated with periodic feedings? Brain Res 279:53–63

Ishida A, Mutoh T, Ueyama T, Bando H, Masubuchi S, Nakahara D, Tsujimoto G, Okamura H (2005) Light activates the adrenal gland: timing of gene expression and glucocorticoid release. Cell Metab 2:297–307

Johansson A, Fredriksson R, Winnergren S, Hulting AL, Schioth HB, Lindblom J (2008) The relative impact of chronic food restriction and acute food deprivation on plasma hormone levels and hypothalamic neuropeptide expression. Peptides 29:1588–1595

Kalsbeek A, Strubbe JH (1998) Circadian control of insulin secretion is independent of the temporal distribution of feeding. Physiol Behav 63:553–558

Kalsbeek A, Barassin S, van Heerikhuize JJ, van der Vliet J, Buijs RM (2000) Restricted daytime feeding attenuates reentrainment of the circadian melatonin rhythm after an 8-h phase advance of the light–dark cycle. J Biol Rhythms 15:57–66

Kilduff TS, Dube MG (1979) The effects of seasonal photoperiods on the activity of cotton rats and rice rats. J Mammal 60:169–176

King BM (2006) The rise, fall, and resurrection of the ventromedial hypothalamus in the regulation of feeding behavior and body weight. Physiol Behav 87:221–244

Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW, Bass J (2007) High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metab 6:414–421

Koubi HE, Robin JP, Dewasmes G, Le Maho Y, Minaire Y (1991) Fasting-induced rise in locomotor activity in rats coincides with increased protein utilization. Physiol Behav 50:337–343

Le Sauter J, Hoque N, Weintraub M, Pfaff DW, Silver R (2009) Stomach ghrelin-secreting cells as food-entrainable circadian clocks. Proc Natl Acad Sci USA 106:13582–13587

Lovegrove BG, Raman J, Perrin MR (2001) Daily torpor in elephant shrews (Macroscelidea: *Elephantulus* spp.) in response to food deprivation. J Comp Physiol B 171:11–21

Lynn SE, Breuner CW, Wingfield JC (2003) Short-term fasting affects locomotor activity, corticosterone, and corticosterone-binding globulin in a migratory songbird. Horm Behav 43:150–157

Mahoney LB, Denny CA, Seyfried TN (2006) Caloric restriction in C57BL/6J mice mimics therapeutic fasting in humans. Lipids Health Dis 5:e13

Marchant EG, Mistlberger RE (1996) Entrainment and phase shifting of circadian rhythms in mice by forced treadmill running. Physiol Behav 60:657–663

Martínez-Merlos MT, Angeles-Castellanos M, Diaz-Munoz M, Aguilar-Roblero R, Mendoza J, Escobar C (2004) Dissociation between adipose tissue signals, behavior and the food-entrained oscillator. J Endocrinol 181:53–63

Masoro EJ (2005) Overview of caloric restriction and ageing. Mech Ageing Dev 126:913–922

Masoro EJ, Shimokawa I, Higami Y, McMahan CA, Yu BP (1995) Temporal pattern of food intake not a factor in the retardation of aging processes by dietary restriction. J Gerontol A Biol Sci Med Sci 50A:B48–B53

Masuda A, Oishi T (1995) Effects of restricted feeding on the light-induced body weight change and locomotor activity in the Djungarian hamster. Physiol Behav 58:153–159

Mendoza J, Challet E (2009) Brain clocks: from the suprachiasmatic nuclei to a cerebral network. Neuroscientist 15:477–488

Mendoza J, Angeles-Castellanos M, Escobar C (2005a) A daily palatable meal without food deprivation entrains the suprachiasmatic nucleus of rats. Eur J Neurosci 22:2855–2862

Mendoza J, Graff C, Dardente H, Pévet P, Challet E (2005b) Feeding cues alter clock gene oscillations and photic responses in the suprachiasmatic nuclei of mice exposed to a light–dark cycle. J Neurosci 25:1514–1522

Mendoza J, Pévet P, Challet E (2007) Circadian and photic regulation of clock and clock-controlled proteins in the suprachiasmatic nuclei of calorie-restricted mice. Eur J Neurosci 25:3691–3701

Mendoza J, Pévet P, Challet E (2008a) High-fat feeding alters the clock synchronization to light. J Physiol 586:5901–5910

Mendoza J, Drevet K, Pévet P, Challet E (2008b) Daily meal timing is not necessary for resetting the main circadian clock by calorie restriction. J Neuroendocrinol 20:251–260

Mistlberger RE (1991) Scheduled daily exercise or feeding alters the phase of photic entrainment in Syrian hamsters. Physiol Behav 50:1257–1260

Mistlberger RE (1993) Effects of scheduled food and water access on circadian rhythms of hamsters in constant light, dark, and light:dark. Physiol Behav 53:509–516

Mistlberger RE (1994) Circadian food-anticipatory activity: Formal models and physiological mechanisms. Neurosci Biobehav Rev 18:171–195

Mistlberger R (2009) Food-anticipatory circadian rhythms: concepts and methods. Eur J Neurosci 30:1718–1729

Mistlberger RE, Rechtschaffen A (1984) Recovery of anticipatory activity to restricted feeding in rats with ventromedial hypothalamic lesions. Physiol Behav 33:227–235

Mistlberger RE, Sinclair SV, Marchant EG, Neil L (1997) Phase shifts to refeeding in the Syrian hamster mediated by running activity. Physiol Behav 61:273–278

Mistlberger RE, Antle MC, Webb IC, Jones M, Weinberg J, Pollock MS (2003) Circadian clock resetting by arousal in Syrian hamsters: the role of stress and activity. Am J Physiol Regul Integr Comp Physiol 285:R917–R925

Mistlberger RE, Webb IC, Simon MM, Tse D, Su C (2006) Effects of food deprivation on locomotor activity, plasma glucose, and circadian clock resetting in Syrian hamsters. J Biol Rhythms 21:33–44

Moga MM, Moore RY (1996) Putative excitatory amino acid projections to the suprachiasmatic nucleus in the rat. Brain Res 743:171–177

Moga MM, Weis RP, Moore RY (1995) Efferent projections of the paraventricular thalamic nucleus in the rat. J Comp Neurol 359:221–238

Morgado E, Gordon MK, Miñana-Solis MC, Meza E, Levine S, Escobar C, Caba M (2008) Hormonal and metabolic rhythms associated with the daily scheduled nursing in rabbit pups. Am J Physiol Regul Integr Comp Physiol 295:R690–R695

Morin LP, Allen CN (2006) The circadian visual system, 2005. Brain Res Rev 51:1–60

Mrosovsky N (1996) Locomotor activity and non-photic influences on circadian clocks. Biol Rev 71:343–372

Nakahata Y, Sahar S, Astarita G, Kaluzova M, Sassone-Corsi P (2009) Circadian control of the NAD+ salvage pathway by CLOCK-SIRT1. Science 324:654–657

Nelson W (1988) Food restriction, circadian disorder and longevity of rats and mice. J Nutr 118:286–289

Oishi K, Sakamoto K, Ishida N (2003) Bimodal circadian expression of serotonin *N*-acetyltransferase mRNA in the retina of rats under restricted feeding. Neurosci Lett 351:21–24

Oishi K, Uchida D, Ohkura N, Doi R, Ishida N, Kadota K, Horie S (2009) Ketogenic diet disrupts the circadian clock and increases hypofibrinolytic risk by inducing expression of plasminogen activator inhibitor-1. Arterioscler Thromb Vasc Biol 29:1571–1577

Oomura Y (1983) Glucose as a regulator of neuronal activity. Adv Metab Disord 10:31–65

Prosser RA, Bergeron HE (2003) Leptin phase advances the rat suprachiasmatic circadian clock in vitro. Neurosci Lett 336:139–142

Ralph MR, Foster RG, Davis FC, Menaker M (1990) Transplanted suprachiasmatic nucleus determines circadian period. Science 247:975–978

Ramadori G, Lee CE, Bookout AL, Lee S, Williams KW, Anderson J, Elmquist JK, Coppari R (2008) Brain SIRT1: anatomical distribution and regulation by energy availability. J Neurosci 28:9989–9996

Ramsey KM, Yoshino J, Brace CS, Abrassart D, Kobayashi Y, Marcheva B, Hong HK, Chong JL, Buhr ED, Lee C, Takahashi JS, Imai S, Bass J (2009) Circadian clock feedback cycle through NAMPT-mediated NAD+ biosynthesis. Science 324:651–654

Redlin U (2001) Neural basis and biological function of masking by light in mammals: suppression of melatonin and locomotor activity. Chronobiol Int 18:737–758

Resuehr D, Olcese J (2005) Caloric restriction and melatonin substitution: effects on murine circadian parameters. Brain Res 1048:146–152

Ribeiro AC, Sawa E, Carren-Le Sauter I, Le Sauter J, Silver R, Pfaff DW (2007) Two forces for arousal: pitting hunger versus circadian influences and identifying neurons responsible for changes in behavioral arousal. Proc Natl Acad Sci USA 104:20078–20083

Robin JP, Boucontet L, Chillet P, Groscolas R (1998) Behavioral changes in fasting emperor penguins: evidence for a 'refeeding signal' linked to a metabolic shift. Am J Physiol Regul Integr Comp Physiol 274:R746–R753

Rowland N (1982) Failure by deprived hamsters to increase food intake: some behavioral and physiological determinants. J Comp Physiol Psychol 96:591–603

Rutter J, Reick M, Wu LC, McKnight SL (2001) Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. Science 293:510–514

Sakaguchi T, Takahashi M, Bray GA (1988) Diurnal changes in sympathetic activity: relation to food intake and to insulin injected into the ventromedial or suprachiasmatic nucleus. J Clin Invest 82:282–286

Scheer FA, Ter Horst GJ, van der Vliet J, Buijs RM (2001) Physiological and anatomic evidence for regulation of the heart by suprachiasmatic nucleus in rats. Am J Physiol Heart Circ Physiol 280:H1391–H1399

Shibata S, Liou SY, Ueki S, Oomura Y (1986) Inhibitory action of insulin on suprachiasmatic nucleus neurons in rat hypothalamic slice preparations. Physiol Behav 36:79–81

Silverman HJ, Zucker I (1976) Absence of post-fast food compensation in the golden hamster (*Mesocricetus auratus*). Physiol Behav 17:271–285

Smith RD, Turek FW, Takahashi JS (1992) Two families of phase–response curves characterize the resetting of the hamster circadian clock. Am J Physiol Regul Integr Comp Physiol 262:R1149–R1153

Steinlechner S, Heldmaier G, Becker H (1983) The seasonal cycle of body weight in the Djungarian hamster: photoperiodic control and the influence of starvation and melatonin. Oecologia (Berlin) 60:401–405

Stephan FK (2001) Food-entrainable oscillators in mammals. In: Takahashi JS, Turek FW, Moore RY (eds) Circadian clocks. Handbook of behavioral neurobiology, vol 12. Kluwer, New York, pp 223–246

Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M (2001) Entrainment of the circadian clock in the liver by feeding. Science 291:490–493

Sutton GM, Perez-Tilve D, Nogueiras R, Fang J, Kim JK, Cone RD, Gimble JM, Tschop MH, Butler AA (2008) The melanocortin-3 receptor is required for entrainment to meal intake. J Neurosci 28:12946–12955

Szentirmai E, Kapás L, Sun Y, Smith RG, Krueger JM (2010) Restricted feeding-induced sleep, activity and body temperature changes in normal and preproghrelin deficient mice. Am J Physiol Regul Integr Comp Physiol 298:R467–R477

Takahashi JS, Turek FW, Moore RY (2001) Circadian clocks. Handbook of behavioral neurobiology, vol 12. Kluwer, New York

Thompson RH, Swanson LW (1998) Organization of inputs to the dorsomedial nucleus of the hypothalamus: a reexamination with fluorogold and PHAL in the rat. Brain Res Rev 27:89–118

Tosini G, Fukuhara C (2002) The mammalian retina as a clock. Cell Tissue Res 309:119–126

Unger J, McNeill TH, Moxley RT, White M, Moss A, Livingston JN (1989) Distribution of insulin receptor-like immunoreactivity in the rat forebrain. Neuroscience 31:143–157

Verwey M, Amir S (2009) Food-entrainable circadian oscillators in the brain. Eur J Neurosci 30:1650–1657

Vrang N, Mrosovsky N, Mikkelsen JD (2003) Afferent projections to the hamster intergeniculate leaflet demonstrated by retrograde and anterograde tracing. Brain Res Bull 59:267–288

Waddington Lamont E, Harbour VL, Barry-Shaw J, Renteria Diaz L, Robinson B, Stewart J, Amir S (2007) Restricted access to food, but not sucrose, saccharine, or salt, synchronizes the expression of Period2 protein in the limbic forebrain. Neuroscience 144:402–411

Wakamatsu H, Yoshinobu Y, Aida R, Moriya T, Akiyama M, Shibata S (2001) Restricted-feeding-induced anticipatory activity rhythm is associated with a phase shift of the expression of mPer1 and mPer2 mRNA in the cerebral cortex and hippocampus but not in the suprachiasmatic nucleus of mice. Eur J Neurosci 13:1190–1196

Weindruch R (1992) Effect of caloric restriction on age-associated cancers. Exp Gerontol 27:575–581

Wise DD, Shear JB (2004) Circadian tracking of nicotinamide cofactor levels in an immortalized suprachiasmatic nucleus cell line. Neuroscience 128:263–268

Wolf G (2006) Calorie restriction increases life span: a molecular mechanism. Nutr Rev 64:89–92

Yang XJ, Kow LM, Funabashi T, Mobbs CV (1999) Hypothalamic glucose sensor: similarities to and differences from pancreatic beta-cell mechanisms. Diabetes 48:1763–1772

Yannielli PC, Molyneux PC, Harrington ME, Golombek DA (2007) Ghrelin effects on the circadian system of mice. J Neurosci 27:2890–2895

Yi CX, van der Vliet J, Dai J, Yin G, Ru L, Buijs RM (2006) Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. Endocrinology 147:283–294

Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK (2006) Expression of ghrelin receptor mRNA in the rat and the mouse brain. J Comp Neurol 494:528–548

Zvonic S, Ptitsyn AA, Conrad SA, Scott LK, Floyd ZE, Kilroy G, Wu X, Goh BC, Mynatt RL, Gimble JM (2006) Characterization of peripheral circadian clocks in adipose tissues. Diabetes 55:962–970