CIRCADIAN AND SEASONAL RHYTHMS

Photoperiodic programming of body weight through the neuroendocrine hypothalamus

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Abstract

The photoperiodic mammal undergoes quite remarkable changes in physiology as part of its natural adaptations to seasonal fluctuations in the environment. Changes in energy balance and body weight are among these adaptations. In some seasonal mammals, such as the Siberian hamster (*Phodopus sungorus*), these changes in body weight have been explored in detail, and there is evidence for tightly controlled systems of energy balance that are coordinated by photoperiod acting via the temporal pattern of melatonin secretion from the pineal gland. The pathways and systems involved appear to be quite distinct

from the hypothalamic pathways identified to regulate energy balance in studies of both mice and rats thus far. Instead it appears that in the Siberian hamster a tightly regulated system under the control of photoperiod is able to reset the tone of the systems involved in energy balance regulation. Understanding how photoperiod and melatonin act within the hypothalamus to regulate energy balance offers potentially fundamental and important new insights into the control of energy balance. This review describes the current state of our knowledge.

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Introduction

Over the past decade there have been some remarkable advances in our understanding of the hypothalamic mechanisms involved in the regulation of body weight. Prior to this our knowledge of the role of the hypothalamus in the regulation of energy balance had been derived from rather crude lesioning studies, which had led to the concept of a satiety centre in the lateral hypothalamic (LH) area, and a hunger centre in the ventromedial region of the hypothalamus (VMH) (Kalra *et al.* 1999). The discovery of the leptin gene through positional cloning from the *ob/ob* fat mutant mouse (Zhang *et al.* 1994) was a pioneering breakthrough that catalysed a revolution in our understanding of the hypothalamic neural networks involved in the regulation of energy balance. From this, the anatomical importance of the arcuate (ARC) and the paraventricular (PVN) hypothalamic nuclei to energy balance regulation was highlighted as well as the discovery of a number of new and important regulators such as those of the melanocortin system (Kalra *et al.* 1999).

In much the same way, over the past 5 years outstanding progress has transformed our understanding of the biological clock from black box phenomenology into a

molecular and mechanistic basis for the generation of self-sustaining biological rhythms (Reppert & Weaver 2001).

Superficially the fields of energy balance and biological rhythms would appear unconnected. Yet given how biological rhythms pervade almost every physiological process, including thermoregulation, food intake and activity–rest cycles, it is inevitable that there must be strong interconnections, which have yet to be explored. One of these is in seasonally breeding animals, where the regulation of body weight, as well as other aspects of physiology, is strongly controlled by the biological clock (Morgan & Mercer 2001). Understanding the mechanistic basis of this interaction potentially offers fundamental and novel insights into the neuroendocrine control of energy balance, with the benefit that they may provide the basis for the development of novel therapeutics.

The body weight model

Seasonality is a general term, usually used to describe the annual waxing and waning in reproductive activity displayed by many mammals that live at temperate latitudes.

Figure 1 (A) The change in body weight of male Siberian hamsters in response to short photoperiod. Hamsters held on long photoperiod (16 h light:8 h darkness) (●) exhibit a stable body weight over 18 weeks, whereas hamsters transferred into short photoperiod (8 h light:16 h darkness) at time 0 (▽) show a progressive loss of body weight over the same period. (B) The effect of superimposing a period of food restriction on body weights of male Siberian hamsters already losing body weight as a result of short photoperiod. All hamsters were transferred from a long photoperiod (16 h light:8 h darkness) onto a short photoperiod (8 h light:16 h darkness) at time 0. Hamsters given the period of food restriction superimposed on the photoperiodically driven weight cycle are shown by ▽, whereas control animals are shown by ●. Data are means $\pm$ S.E.M., $n=5-11$ per point.

However, the change in reproductive status is just one of a number of physiological changes that these animals display as a natural part of their annual cycle. These physiological adaptations include altered body weight and pelage condition, as well as a range of behaviours associated with reproduction (Hoffman 1973, Wade & Bartness 1984, Bartness *et al.* 2002). Most importantly, since these changes (e.g. body weight and testicular regression) are of large magnitude, the initiation of the process of change must be made well in advance (i.e. in anticipation) of need. As a consequence the animals use daylength or photoperiod as an environmental cue to track the time of year, since this parameter is unaffected by the vagaries of local climatic conditions and provides the temporal trigger to initiate the suite of physiological adaptations associated with seasonality.

While most animals that express a seasonal phenotype display a change in body weight as part of their repertoire of adaptive changes, the Siberian hamster (*Phodopus sungorus*) is one of the best studied and characterised (Figala *et al.* 1973, Hoffman 1973, Steinlechner *et al.* 1983, Heldmaier *et al.* 1981, Wade & Bartness 1984, Bartness *et al.* 2002). As shown in Fig. 1A the body weight of a non-juvenile male Siberian hamster remains relatively constant when maintained on a long photoperiodic schedule of 16 h light:8 h darkness. Yet a simple and abrupt change in photoperiod to a short photoperiod schedule of

8 h light:16 h darkness induces a robust and progressive loss in body weight. While some of this weight loss will be due to loss of testicular mass, the majority of the weight loss is due to a reduction in adipose tissue (Mercer *et al.* 2001). It is important to note that the weight loss reaches a maximum of about 30–40% of the initial body weight after 12–18 weeks. Eventually the animals become refractory to the short photoperiod signal, and spontaneously regain body weight, reaching the body weight previously attained under long photoperiod.

The most remarkable feature of the Siberian hamster was revealed in a classic experiment reported by Steinlechner *et al.* (1983), in which the phenomenon of so-called 'sliding set-point' regulation of body weight was reported, where the hamsters progressively adjust the body weight they defend to a new lower level relative to the time they have experienced under short photoperiod. In this study Siberian hamsters were maintained under ambient photoperiodic conditions (Steinlechner *et al.* 1983). Since then we have confirmed these results using male Siberian hamsters held under constant laboratory conditions, and artificial photoperiod schedules as described above (Mercer *et al.* 2001). As can be seen in Fig. 2, hamsters transferred from long to short photoperiod progressively lose body weight as described in Fig. 1B. When a period of food restriction is superimposed on the body weight loss induced under short days, a more

Figure 2 (A) Changes in body weight of male Siberian hamsters in response to short photoperiod, and as a result of food restriction to mimic changes under short photoperiod. LP and SP represent hamsters held on photoperiods of 16 h light:8 h darkness and 8 h light:16 h darkness respectively (see Fig. 1A). LP-R shows a third group of hamsters, which were held on long photoperiod (16 h light:8 h darkness), but which were food-restricted so that body weight loss mimicked that achieved under short photoperiod. (B) The changes in gene expression in the ARC, of two orexigenic and two anorexigenic genes are shown. The changes are expressed relative to the expression of these genes in hamsters held in LP. Also shown are the changes in gene expression seen in animals held under SP, as well as the predicted changes in gene expression of these genes if they were involved in driving the body weight loss under SP (SP predicted). (Adapted from Mercer *et al.* 2001.) Data are means $\pm$ S.E.M., $n=9-10$ per point.

dramatic loss in body weight occurs. Remarkably when the hamsters are subsequently allowed to re-feed freely following the short period of food restriction, a period of hyperphagia occurs enabling them to regain body weight (Mercer *et al.* 2001). However, the animals regain body weight only to a level appropriate for the temporal position within the short-day-induced body weight cycle.

These experiments strongly support the concept that Siberian hamsters constantly re-adjust their energy balance following transition from long to short photoperiod. In some experiments it has been reported that the reduction in body weight of Siberian hamsters occurs as a result of reduced food intake, followed by a decrease in energy expenditure (Knopper & Boily 2000). However, others have reported that an increase in energy expenditure temporally precedes the decline in food intake, and therefore the decline in food intake is secondary to the change in energy expenditure (Wade & Bartness 1984). At present it is difficult to discriminate the temporal order of such events with any certainty, and this issue remains to be resolved.

The progressive re-adjustment of defended body weight by Siberian hamsters under short photoperiod implies that the animals must have a 'tracking system' that defines the tone of the energy balance systems operating within the brain and hypothalamus. At present how such a system might operate is completely unknown, but the rewards for understanding its mechanism could be substantial if elements of the system are present in non-seasonal mammals such as humans.

The role of candidate hypothalamic regulators of energy balance

The first question to address is the role of the known regulators of energy balance within the hypothalamus in seasonal body weight regulation of the Siberian hamster. As in other rodent species, the orexigenic peptide, neuropeptide Y (NPY), potently stimulates food intake (Boss-Williams & Bartness 1996), while the anorexigenic peptide, α -melanocyte-stimulating hormone (α -MSH), inhibits food intake when administered i.c.v. into Siberian hamsters (Schuhler *et al.* 2002), consistent with their role in the regulation of energy balance in this species. The role and function of hypothalamic peptides and genes in the regulation of energy balance have also been investigated by imposing energy deficits through short-term food restriction and by altering leptin status (Morgan & Mercer 2001), and these studies have further emphasised the similarities in regulation to other rodent models. The hypothalamic nuclei involved in the regulation of energy balance include the ARC, PVN, dorsomedial (DMN), VMH and LH nuclei. In general food restriction and low levels of leptin induce increased hypothalamic expression of a range of genes known to be orexigenic in the ARC, such as NPY and Agouti-related peptide (AgRP), whereas the expression of anorexigenic genes in the ARC, such as pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) are suppressed (for references, see Kalra *et al.* 1999, Morgan & Mercer 2001). However, while the expression of these genes

change concordantly in Siberian hamsters in response to energy deficit, the changes in expression of these genes in hamsters under short photoperiod do not reflect an animal in energy deficit (Reddy *et al.* 1999, Mercer *et al.* 2000, 2001, Robson *et al.* 2002, Rousseau *et al.* 2002). This was shown by comparing hypothalamic gene expression of short-photoperiod animals with long-day animals that were food-restricted to simulate the body weight loss observed in short-day animals (Mercer *et al.* 2001). Relative to the long-day control animals the short-day hamsters and the food-restricted long-day hamsters had distinct gene expression profiles (Fig. 2), and therefore animals in short days do not reflect hamsters that are food-restricted (Mercer *et al.* 2001). Conversely, the body weight loss under short days could be induced by increased activity of the anorexigenic and decreased activity of the orexigenic regulators in the hypothalamus. Using gene expression as a proxy for this activity, only CART expression in the ARC increased in accord with this prediction. Other genes such as POMC and AgRP changed in a direction opposite to that predicted, whereas NPY showed no change in expression. With the exception of CART, the gene expression changes observed are largely consistent with those observed by other groups in similar experiments (Reddy *et al.* 1999, Mercer *et al.* 2000, 2001, Robson *et al.* 2002, Rousseau *et al.* 2002). CART is an interesting peptide, since in other studies we have observed that it is the only peptide to show altered gene expression prior to a change in body weight after only 2 weeks in short photoperiod (Adam *et al.* 2000). However, it is important to note that other groups have failed to observe this change in CART gene expression in either male or female Siberian hamsters held on short photoperiod for 8 weeks (Robson *et al.* 2002, Rousseau *et al.* 2002). Even if CART gene expression and peptide activity were to increase to contribute to the anorexic tone in short-day Siberian hamsters, set against a decrease in anorexigenic tone that would result from reduced expression of POMC and increased expression of AgRP, it is difficult to predict the net effects of such changes on the orexigenic/anorexigenic drive. Thus at present the potential role of CART in the photoperiodic responses of Siberian hamsters is unclear.

Changes in gene expression in other hypothalamic nuclei in response to energy deficits and manipulation of leptin levels have been reported for mice and rats (see Kalra *et al.* 1999). For example food deprivation caused a decrease in melanin-concentrating hormone (MCH) expression in the LH of mice (Qu *et al.* 1996) and increased expression of orexin in the LH of rats (De Lecca *et al.* 1998). Few studies have examined the role of the LH, DMN and VMH in relation to energy balance in Siberian hamsters. Of those that have been reported there are no changes in either orexin or MCH gene expression related to food deprivation or in relation to seasonal changes in body weight (Reddy *et al.* 1999, Mercer *et al.* 2000). This suggests that in the Siberian hamster the peptides of the

LH are not primarily involved in seasonal regulation of energy homeostasis. Nevertheless given the reciprocal relationship between the ARC and LH and the inputs from the circadian system involving neural projections from the suprachiasmatic nucleus (SCN) to the LH neurons (Kalra *et al.* 1999, Abrahamson *et al.* 2001), there is clearly potential for temporal input to, and modulation of, the energy balance via the LH.

Thus while it seems that the known hypothalamic regulators of energy balance could contribute to seasonal body weight regulation, it is unlikely that they have a primary role. This is for two reasons. First, it has been shown that monosodium glutamate lesions which destroy at least 80% of the NPY-immunoreactive neurons of the ARC, do not prevent short photoperiod-induced changes in body weight in Siberian hamsters (Ebling *et al.* 1998). Secondly, Siberian hamsters continue to lose body weight even in the face of declining peripheral leptin concentrations (Atcha *et al.* 2000, Klingenspor *et al.* 2000, Mercer *et al.* 2001). Moreover hamsters are more sensitive to leptin injections or infusions, in terms of body weight and fat loss, when held on short photoperiod than on long photoperiod (Klingenspor *et al.* 2000, Rousseau *et al.* 2002). This suggests that the normal responses to leptin and energy deficit are being overridden by photoperiod, and implies that there is a distinct system of regulation through which photoperiod exerts its effects on the energy balance.

Melatonin receptors and sites of action

Since seasonal regulation of body weight is not readily explained through the known hypothalamic regulators of energy balance, it is necessary to understand how photoperiod regulates activity of the neuroendocrine system.

It has been known for a long time that photoperiod is perceived through the eye and is converted into a hormonal signal, melatonin, which is produced and secreted by the pineal gland (Morgan *et al.* 1994). A critical question in terms of understanding the neuroendocrine activities of photoperiod has been to identify where melatonin acts. Receptor mapping studies using *in vitro* autoradiography have revealed target sites for melatonin in the brains of a variety of species. What is remarkable is the wide degree of species diversity in the distribution of melatonin receptors (Morgan *et al.* 1994). For example, while both the sheep and the Siberian hamster are highly seasonal species, the extensive expression of receptors in the sheep brain contrasts with the more restricted distribution observed in the brain of the Siberian hamster. Nevertheless there are a few target sites common across species, and these have been the focus of attention to explain how melatonin exerts its photoperiodic effects.

One of these sites is the pars tuberalis (PT) of the pituitary, which has been implicated in the regulation of seasonal prolactin secretion (Lincoln & Clarke 1994),

possibly through the secretion of an unidentified prolactin-releasing factor, called tuberulin (Morgan 2000). From work performed in both sheep and hamsters it is clear that a pituitary site of action cannot explain the reproductive effects of melatonin, and is unlikely to explain the effects on body weight. Instead a hypothalamic site of action is favoured. Studies using lesions to discrete areas of the brain of the Syrian hamster have implicated the DMN of the hypothalamus, where melatonin receptors are expressed, in the reproductive effects of this species (Maywood *et al.* 1996). Within the Siberian hamster melatonin receptors have been localised on the SCN, the DMN, anterior hypothalamic area (AHA) of the hypothalamus and the stria medullaris (Morgan *et al.* 1994, C Ellis, JG Mercer & PJ Morgan, unpublished observations). Lesions to the SCN of the Siberian hamster have been associated with loss of body weight response to timed infusions of short-day melatonin, suggesting that the SCN may be important to photoperiodic regulation of body weight (Bartness *et al.* 1991). Within the DMN the level of receptor expression is extremely low, with receptors expressed on only a few neurons (Song & Bartness 2001, C Ellis, JG Mercer & PJ Morgan, unpublished observations). In addition, Song & Bartness (2001) have shown that a direct connection is made between melatonin receptor-expressing neurons of the DMN of the Siberian hamster and the adipose tissue, supporting the view that melatonin receptors in the DMN may be involved in the regulation of energy balance in this species. This view is further strengthened by the fact that the DMN has been implicated as an important site in the regulation of energy balance in other rodent species. The DMN is therefore a potential site of action through which melatonin could control body weight in the Siberian hamster. The expression of melatonin receptors in the AHA makes this a plausible site through which melatonin could regulate seasonal body weight in the Siberian hamster. Thus at the present time it is not possible to define precisely which of the known melatonin target sites are key to the seasonal regulation of body weight.

Decoding photoperiod

The unique feature about photoperiod is that through the relative durations of light and darkness over a 24 h period, an animal determines time of year. This information is converted into a hormonal signal, melatonin, which is produced solely at night and for a duration directly related to the length of darkness. The mechanism by which this temporal information is decoded is not yet fully clear. Nevertheless some interesting insights have recently been revealed by examining gene expression patterns over 24 h cycles in the PT in hamsters held under either long or short photoperiod (Messenger *et al.* 1999, 2000). The PT is a pituitary site of melatonin action, with the highest density of melatonin receptor expression. It has proved to

be a particularly useful tissue for the study of the basic signalling mechanisms of melatonin and its receptor. From some of these studies it has been demonstrated that the clock gene *Per1* and the inducible cAMP early repressor gene are expressed in diurnal rhythms (Messenger *et al.* 1999, 2000). However, these rhythms are characterised by the photoperiodic background upon which the hamsters are held. Under long photoperiods (short nocturnal melatonin signal) there is a large amplitude peak in expression at Zeitgeber time 3 h, whereas this peak is either greatly attenuated or absent in short photoperiods (long nocturnal melatonin signal) (Messenger *et al.* 1999, 2000). It seems that it is the decline in nocturnal melatonin which allows the peak expression to occur; yet it is the duration of the melatonin signal that defines the amplitude of the peak (Messenger *et al.* 1999, 2000). These changes in *Per1* gene expression also result in corresponding changes in PER1 protein levels (Nuesslein-Hildesheim 2000). From this it appears that the duration of the melatonin signal may be decoded at the cellular level and translated into amplitude of early response gene and protein expression.

It is also known that, in addition to *Per1*, most of the other members of the clock gene family of proteins are expressed in the PT (D Hazlerigg, personal communication). However, at present it is unclear whether, or how many of, these may contribute to the mechanism of decoding photoperiodic time. More importantly the potential mechanisms being discovered for the PT are different for the SCN, which also expresses melatonin receptors (Morgan *et al.* 1994). The SCN does show sensitivity to a change in photoperiod, although it is a change in the duration, rather than the amplitude of *Per1* gene and protein expression that is observed (Messenger *et al.* 1999, 2000). This change is related to the altered period of induction by light rather than any effect of melatonin. This apparent lack of effect of melatonin on the SCN in relation to photoperiod is perhaps not surprising since light has such a powerful influence on clock gene expression and function. It also implies that the SCN may have no direct role in the photoperiodic effects of melatonin, including the seasonal regulation of body weight, even though a small number of the total melatonin receptor expressing neurons in the SCN may be connected to adipose tissue (Song & Bartness 2001, Bartness *et al.* 2002). Thus an important question is whether the observations made in the PT can be extrapolated to other melatonin-sensitive tissues such as the DMN and AHA as an index of photoperiodic sensitivity to melatonin, or is it unique to the PT.

While it is clear that the *Per1* gene is expressed widely in the DMN of the Siberian hamster, and there is a diurnal rhythm of expression, the peak is late in the dark phase, and not early in the light phase as in the PT (C Ellis, JG Mercer & PJ Morgan, unpublished observations). However, given the sparse expression of melatonin receptors on only a few neurons of the DMN, it is possible that any

Figure 3 Schematic figure showing the hypothalamic nuclei involved in energy balance and biological timing, and their interrelated connections. (O) and (A) respectively, represent the orexigenic (NPY and AgRP) and anorexigenic (α -MSH and CART) projections from the ARC and PVN, which have a primary role in the regulation of energy balance. Also shown are the reciprocal connections between the LH and the ARC, which serve to modulate energy balance. Melatonin acts on the SCN and the DMN, which express melatonin receptors, and it is through these sites that photoperiod and melatonin may influence the tone of energy balance. The connections between these sites and the energy balance pathways are not known. It is known that there are connections between the SCN and LH, and the DMN and the PVN. However, as the action of photoperiod and melatonin appears not to be mediated through the well-characterised orexigenic and anorexigenic pathways between the ARC and PVN, it seems likely that other sites may be involved in the interface between biological timing and energy balance.

rhythm of *Per1* expressed in neurons that also express the melatonin receptor will be masked by the more generic expression of *Per1* in this nucleus. Nevertheless, tissues such as the DMN and AHA remain important sites for further investigation of their potential role in the seasonal regulation of body weight.

In search of new genes

From the above it is clear that a system distinct from the known regulators of energy balance is involved in the progressive resetting of defended body weight in the Siberian hamster. This involves an interface between the neural pathways involved in biological timing and those involved in energy balance regulation (Fig. 3). The location of this system is unknown, although it must involve target sites expressing melatonin receptors.

Another characteristic feature must be the ability to respond to different durations of melatonin with an appropriate cellular response, such as a change in *Per1* gene amplitude. Since genes other than the known regulators of energy balance seem to be involved in the seasonal regulation of body weight, a strategy for identifying these genes is required. The rationale being taken is that any genes involved in the photoperiodic resetting of body weight will change progressively with time, and thereby will be at their maximal difference in expression at the extremes of the body weight differences (i.e. hamsters in long days for 12–14 weeks vs hamsters in short days for 12–14 weeks). To identify these genes a combination of subtractive hybridisation together with gene arrays is being used. We have identified several genes which change in expression in response to photoperiod in distinct hypothalamic nuclei and regions (PJ Morgan, AW Ross, P Barrett & JG Mercer, unpublished observations). The challenge is

now to show that these genes are causative of, and not simply associated with, the seasonal cycles in body weight.

While there is still a long way to go in identifying all the hypothalamic genes that change with photoperiod, and more importantly in demonstrating a functional consequence to the changes observed, the initial work looks promising. If this optimism is realised then the relationship between biological timing and the regulation of energy balance will lead to fundamental advances in understanding of neuroendocrine integration and regulation.

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