Seasonal rhythms of energy metabolism

Most environments on our planet are highly seasonal, reflecting the tilt in the Earth’s axis relative to the sun. As a consequence, the majority of life forms have evolved profound seasonal variations in their behaviour and physiology that allow them to anticipate these patterns in food supply and to optimize their reproductive strategy. Reproduction is an energetically costly process in mammals, for example, in supporting pregnancy and then lactation in females. There has been strong selective pressure to ensure births occur in the optimal seasonal for survival. Terrestrial mammals indigenous to temperate and polar regions tend to give birth in spring, when the climatic conditions and food availability are conducive to survival. Seasonal cycles of reproduction also occur in equatorial regions, where they may be linked to wet and dry seasons. Only the species that have been domesticated by man or intensively bred, such as the laboratory strains of mice and rats, fail to display this seasonality. Given the intimate link between energy availability and reproductive success, it is no surprise that body systems regulating energy intake, storage and expenditure are themselves highly seasonal.

Photoperiod and circannual rhythmicity

Huge advances in our understanding of the mechanisms underlying the seasonal rhythms have occurred in the last few decades and thrown up quite a few surprises. The importance of the annual change in daylength as a proximate cue to synchronize seasonal rhythms in vertebrates was understood from the first half of the 20th century. Accordingly, sheep respond to the decreasing days in autumn to activate the hypothalamo-pituitary-gonadal axis, promoting spermatogenesis in males and follicular development in the ovary and ovulation in females, and consequently, sexual behaviour and copulation. Gestation is 147 days in sheep; therefore, lambs are born 5 months later in the following spring.

In a commonly studied laboratory rodent model for photoperiodic control of reproduction, the Siberian hamster, it is the long days of spring that promote activation of the reproductive axis, with the gestation being just 21 days. The seasonal cycle of energy balance is finely honed in these hamsters. Under spring–summer conditions that can be simply mimicked in the laboratory by keeping hamsters in long photoperiods of 16 hours of light and 8 hours of darkness, the hamsters display hyperphagic anabolic physiology, and so, they maintain an increased body weight (Figure 1a). However, exposing the hamsters to short photoperiods comprising 8 hours of light and 16 hours of darkness results in a winter survival strategy. Reproductive function ceases, and the animals display a markedly reduced voluntary food intake, whilst increasing lipolysis, resulting in catabolism of visceral fat reserves. This occurs to sustain life through winter. Daily torpor also occurs to preserve the caloric reserves. During 12 weeks in short days (Figure 1a), the body weight is reduced by up to 30%. Interestingly, this hypophagic catabolic state spontaneously reverts to the anabolic state after prolonged exposure to short days, resulting in a return to the spring–summer body weight. Thus, the seasonal changes in energy metabolism are not simply direct responses to the annual changes in daylength, but also reflect innate long-term timing mechanisms.

In vertebrates that have longer life spans, these mechanisms are truly circannual rhythms in that they persist in constant environmental conditions. An elegant study in chipmunks kept in the absence of changes in photoperiod and at constant ambient temperature demonstrated the persistence of a circannual rhythm in hibernation (Figure 1b), with innate periodicities slightly shorter than a year (227–367 days). There are some clear analogies between circannual and circadian timing systems; but whereas circadian timing relies upon intracellular transcriptional feedback loops, the mechanisms underlying circannual timing are not known. Current hypotheses revolve around cyclical histogenesis and tissue remodelling in the pituitary–hypothalamic network.

Melatonin

We now understand that for most mammals, it is the pineal gland that is key in transducing daylength information into a neurochemical signal – the nocturnal secretion of melatonin (Figure 2). Descartes considered
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The pineal to be the seat of the soul, and for many centuries, this gland was thought to be vestigial. However, the loss of response to changes in photoperiod in mammals such as Siberian hamsters, ferrets and sheep after surgical removal of their pineal gland confirms its importance in mediating the effects of photoperiod on reproductive and metabolic cycles. Although it was well known that the retina perceives the light–dark cycle in mammals, it was one of several recent surprises when Russell Foster and David Berson discovered in the early 2000s that a new class of photoreceptors in retinal ganglion cells use melanopsin rather than rhodopsin as the photopigment.

**Figure 1.**

a) Photoperiodic effects on the body weight of adult male Siberian hamsters maintained throughout on long days of 16 hours of light:8 hours of darkness (O), or transferred at week 0 to short days of 8 hours of light:16 hours of darkness (black filled circles). Note how the body weight declines substantially in short days, but after 20 weeks begins to revert back to the long-day phenotype. Data from Ebling, unpublished.

b) Persistence of circannual rhythms of hibernation in male chipmunks maintained at constant temperature (5°C) and constant photoperiod of 12 hours of light:12 hours of darkness. Note that cyclicity persists in all individuals, but the periodicity defined as the mean time between successive onsets of hibernation (values in red) varies between individuals. Data redrawn from Kondo et al. (2006) Cell 125, 161–172.

**Figure 2.** Pathway by which the change in daylength is perceived by mammals and transduced into a change in the duration of nocturnal melatonin secretion. Retinal ganglion cells expressing the photopigment melanopsin project directly via the retinohypothalamic tract (RHT) to the suprachiasmatic nucleus (SCN), a master circadian pacemaker. The SCN regulates sympathetic innervation via the brainstem and intermediolateral column of the spinal cord of the pineal gland, restricting melatonin synthesis and secretion to the dark phase.
photopigment (Figure 2). These then directly innervate the suprachiasmatic nucleus in the hypothalamus that in turn regulates pineal melatonin synthesis and secretion via the sympathetic nervous system (Figure 2).

Another surprise was that the identification of melatonin-sensitive structures in the brain and pituitary of mammals indicated that the pars tuberalis of the pituitary stalk is the common site of action across most mammalian species. The pars tuberalis likely communicates via paracrine signals to lactotrophs in the anterior pituitary, thereby regulating the seasonal patterns of prolactin secretion, the major determinant of annual cycles of coat growth and moulting (Figure 3). A final surprise is the pathway by which the energy balance is affected, because the influence of photoperiodic information encoded by melatonin is then relayed from the pars tuberalis back to the brain! The secretion of β-thyrotropin stimulating hormone (βTSH) is the main signal acting on tanycytes, and ultimately regulates the expression of deiodinases 2 and 3. These regulate the availability of tri-iodothyronine (T3), the active form of thyroid hormone. Intrahypothalamic T3 is a major determinant of seasonal cycles of energy intake and expenditure, and of reproduction.

**Tanycytes and thyroid hormone**

Although we are familiar with the metabolic importance of the influence of thyroid hormone in the periphery on the basis of the symptomology of hyper- and hypothyroidism, the notion that the thyroid hormone exerts actions on energy balance via processes within the central nervous system is relatively novel. Tanycytes express the TSH receptor and respond to seasonal alterations in the βTSH signal from the pars tuberalis by regulating local availability of thyroid hormone (tri-iodothyronine [T3]) in the surrounding hypothalamus. Their role in this is complex; they express thyroid hormone transporters such as MCT8 and OATP1C1, and therefore are a principal route by which the thyroid hormone in the bloodstream gets actively transported into the cerebrospinal fluid. In effect, tanycytes are a functional component of the blood–brain barrier. More importantly, they express deiodinase enzymes, as found in all target tissues of thyroid hormone. Deiodinase 2 converts the relatively inactive precursor thyroxine (T4) into the bioactive form T3, whereas deiodinase 3 inactivates T3 and T4 (Figure 4a) – an important protective mechanism in the developing brain. βTSH is secreted from the pars tuberalis in response to long-day patterns of melatonin secretion, and up-regulates DIO2 expression but down-regulates DIO3 expression, thus increasing local T3 concentrations. Experimental studies in sheep, hamsters and quail have demonstrated the functional importance of this seasonal change in hypothalamic thyroid hormone availability for both reproductive activity and control of energy balance. In the case of the Siberian hamster, for example, taking...
Figure 4. a) The regulatory roles of deiodinase 2 (DIO2) and deiodinase 3 (DIO3). DIO2 catalyses the conversion of thyroxine (T4) into the bioactive form of thyroid hormone, tri-iodothyronine (T3). DIO3 inactivates T4 to produce reverse T3 (rT3) and also inactivates T3. b) Experimental evidence that locally manipulating T3 concentrations in the hypothalamus by means of surgically placed microimplants affects energy balance. Adult male hamsters that had been maintained in short days for 13 weeks and therefore had a low body weight were either implanted with T3 and maintained on short days (red triangle) or received sham implants and were kept in short days (black circle) or long days (yellow circle). Note that the T3 implants induce a very rapid gain in body weight, even more swift than that in hamsters with sham implants but transferred to long days. Data redrawn from Murphy et al. (2012) Endocrinology 153, 101–112.

Animals in the short-day catabolic state but increasing the thyroid hormone locally by the surgical placement of microimplants directly within the hypothalamus induces the long-day hyperphagic and anabolic state (Figure 4b). Conversely, preventing the short-day–induced decline in hypothalamic thyroid hormone concentrations in hamsters using the same microimplant technology blocks the hypophagia and loss of body weight normally induced by short photoperiods.

**Perspectives: the relevance to man**

There are a number of reasons why an understanding of the mechanistic basis of seasonal cycles in energy balance has importance for the human condition. First, despite our evolutionary heritage as equatorial primates and our exposure to man-made environments where we can override the natural cycle in daylength, we still display elements of seasonality in many aspects of our lives. These tend to manifest as population-level changes in fertility rates or incidence of infectious diseases, but at an individual level, seasonal changes in mood and affect disorders are well documented. The prevalence of these symptoms increases at more northerly latitudes. The most recent diagnosis manual of the American Psychiatric Association defines seasonal affective disorder (SAD) as a recurring major depression that occurs usually in the autumn and winter and spontaneously remits in spring. SAD is an atypical depression in that it is usually associated with increased appetite, craving for carbohydrates and increased sleep, and hence is a further example of seasonal cyclicity in energy metabolism. In the UK, the Royal College of Psychiatrists considers around 3% of the population to have SAD, making it a substantive healthcare issue. Understanding the biological basis of SAD, which may be viewed as a type of hibernation strategy, has benefits for its treatment; for example, the use of bright light illumination to promote a return to the long-day/summer state.

The second reason is of perhaps even greater importance: by understanding the mechanisms by which long-term changes in appetite and energy expenditure are controlled in a seasonal context, we may gain new insights into the strategies to help people eat less, lose weight and, therefore, gain the associated health benefits. Unquestionably, obesity is a worldwide issue; yet, behavioural strategies rarely work in the long-term and pharmaceutical approaches have had almost no success. Genetic approaches in mice have identified a myriad of homeostatic pathways involved in the short-term development of satiety after meal ingestion. These encompass gut–brain signals, and downstream pathways in the hypothalamus and brain stem, but translation to clinically successful strategies has been disappointing. The observation that seasonal mammals can suppress appetite over a period of many months and correspondingly adjust their peripheral metabolism suggests that homeostatic mechanisms can be overruled by longer-term ‘rheostatic’ mechanisms. This article has highlighted the key role of hypothalamic thyroid hormone in the seasonal rheostatic process in hamsters, a finding that seems to apply to all vertebrate taxa. Some of the actions of thyroid hormone in regulating the seasonal cycles of appetite may be manifest through regulation of the pro-opiomelanocortin (POMC) mechanisms in the brain; but given the crucial role of thyroid hormone in initial brain development, it seems likely that some of its actions in adult seasonality are via plasticity and remodelling of neural circuits. The relatively recent appreciation of the plastic capabilities of the adult hypothalamus in seasonality and in pregnancy that encompasses altered neurogenesis, synaptogenesis and glial ensheathment should give us hope that the development of obesity is not a one-directional process. Perhaps better appreciation of the underlying mechanisms in seasonal cycles will lead to strategies to return the hypothalamic circuitry to a pre-obese state.
Finally, although the focus of this article has been the contribution of hypothalamic and pituitary mechanisms in seasonal cycles, study of the peripheral adaptations during the cycles of fat gain and loss might inform therapies to treat type 2 diabetes and obesity. One recent example relates to the actions of the hepatokine, fibroblast growth factor 21 (FGF21), an endocrine factor that has attracted the attention of multiple pharmaceutical companies. In preclinical studies in rodents, treatment with FGF21 was found to improve glucose homeostasis and induce weight loss. Our studies in the Siberian hamster suggest that increased production of FGF21 in the liver and brown fat may be part of the mechanism by which this species survives winter. Treatment of hamsters in the long-day anabolic state with FGF21 induces a number of features of the short-day state: reduced appetite, weight loss and catabolism of visceral fat depots. Studies using positron emission tomography (PET) scans reveal that white adipose tissue is a major target of FGF21, and so FGF21 promotes fat oxidation rather than carbohydrate oxidation, a key component of the winter survival strategy. Perhaps this seasonal biology of FGF21 could be exploited further in man? ■

Further reading

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