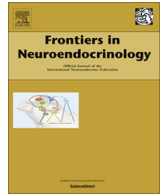




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Review

Hypothalamic control of seasonal changes in food intake and body weight

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ABSTRACT

Seasonal cycles of fattening and body weight reflecting changes in both food intake and energy expenditure are a core aspect of the biology of mammals that have evolved in temperate and arctic latitudes. Identifying the neuroendocrine mechanisms that underlie these cycles has provided new insights into the hypothalamic control of appetite and fuel oxidation. Surprisingly, seasonal cycles do not result from changes in the leptin-responsive and homeostatic pathways located in the mediobasal and lateral hypothalamus that regulate meal timing and compensatory responses to starvation or caloric restriction. Rather, they result from changes in tanycyte function, which locally regulates transport and metabolism of thyroid hormone and retinoic acid. These signals are crucial for the initial development of the brain, so it is hypothesized that seasonal neuroendocrine cycles reflect developmental mechanisms in the adult hypothalamus, manifest as changes in neurogenesis and plasticity of connections.

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1. Introduction: seasonal rhythms of neuroendocrine function

Seasonal cycles in physiology, morphology and behavior are very common in mammals that have evolved in temperate and arctic environments. Overt examples include growth, cleaning and shedding of antlers of deer (Lincoln et al., 1982), molt of the dark summer fur to white winter pelage in arctic foxes, hares and mustelids (Martinet et al., 1992), and onset of rutting and estrus behavior in wild sheep in autumn such that lambs are born the following spring (Lincoln, 1998). More covertly, many terrestrial mammals increase food intake and increase body fat in spring/summer, but then survive winter by reducing appetite, reducing energy expenditure through daily torpor or hibernation, and by catabolizing stored adipose tissue (Bartness et al., 2002). Seasonal cyclicity can be objectively recorded in animals kept in semi-natural field conditions; some elegant examples include studies of cycles of food intake, hair growth, and body weight in red deer maintained at Whipsnade Zoo (Loudon et al., 1989), studies of horn growth and reproductive function in Mouflon sheep kept at Auchtertool, Scotland (Lincoln, 1998), and remote telemetry studies of hibernation cycles in free-living alpine marmots in Switzerland (Arnold et al., 2011). However, the majority of mechanistic studies tend to use small mammals or domesticated species that can be kept under controlled conditions.

An exemplar of the value of a large domesticated species that has substantially improved our understanding of the mechanisms underlying seasonal cycles is the Soay sheep. This *Ovis aries* breed has been living feral since the Bronze Age in the Outer Hebrides off the coast of Scotland (Grubb and Jewell, 1973), and shares many seasonal characteristics with wild Mouflon sheep (*Ovis musimon*) (Lincoln, 1989), but can be maintained indoors under controlled conditions. Whilst many domesticated breeds of sheep retain a degree of seasonality in the timing of reproduction, Soay sheep have a very precise timing of the rut and estrus when observed in the wild (Grubb and Jewell, 1973), that is reflected by high amplitude cycles of testicular activity and regression when kept under alternating photoperiods (Fig. 1 top). Soay sheep also display major cycles in appetite (Fig. 1, bottom) and body weight in such conditions, and in many other parameters, for example horn and wool growth (Ebling and Lincoln, 1987; Lincoln, 1990).

An exemplar of a small rodent that can be maintained under laboratory conditions but still express clear changes in seasonal physiology is the Siberian hamster, *Phodopus sungorus*. A breeding colony derived from wild-captured individuals from Kazakhstan was established in the late 1960s in the laboratory of Klaus Hoffmann in Germany. The effects of season and photoperiod on somatic growth and reproduction were readily evident in this species (Hoffmann, 1973, 1978), and because of the generosity of this laboratory in making hamsters available to other researchers, colonies of this species now exist in multiple research groups in the USA and Europe. The profound nature of the seasonal variation in

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body weight is illustrated in Fig. 2. Hamsters maintained in laboratory conditions of constant temperature and ad libitum diet nevertheless decrease appetite by approximately 20% when exposed to short photoperiods that mimic winter (Fig. 2, bottom), and consequently lose up to a third of their body weight (Fig. 2, top). The weight loss predominantly reflects catabolism of abdominal fat depots (Bartness et al., 1989; Bartness, 1995), but lean tissue mass also decreases (Klingenspor et al., 2000). The loss of lean tissue includes decreases in the mass of the liver, kidney and testes (Petri et al., 2014), but it is still not clear whether there is significant bone or skeletal muscle loss in hamsters exposed to short days (Rousseau et al., 2005).

A much debated question is whether the seasonal decrease in appetite is a response to the decrease in body weight or a cause of it. Some studies in the Siberian hamster have found that body weight loss upon exposure to short days slightly precedes a decrease in food intake (Wade and Bartness, 1984). It may be postulated that the primary action of short days is to increase fat oxidation in anticipation of increased thermoregulatory needs, and that consequently appetite decreases. In support of this view, certain drugs such as the PPAR α agonist fenofibrate that promote mitochondrial fatty acid oxidation result in decreased appetite (Ji et al., 2005). Moreover, we have recently observed that levels of FGF21 increase in plasma, liver and fat in hamsters exposed to short photoperiods (Murphy et al., 2013; Samms et al., 2014). FGF21 is known to promote fat oxidation (Coskun et al., 2008). As there is now evidence that the brain can directly regulate energy metabolism in the liver, white and brown fat via sympathetic outflow (Bamshad et al., 1999; Klieverik et al., 2009;

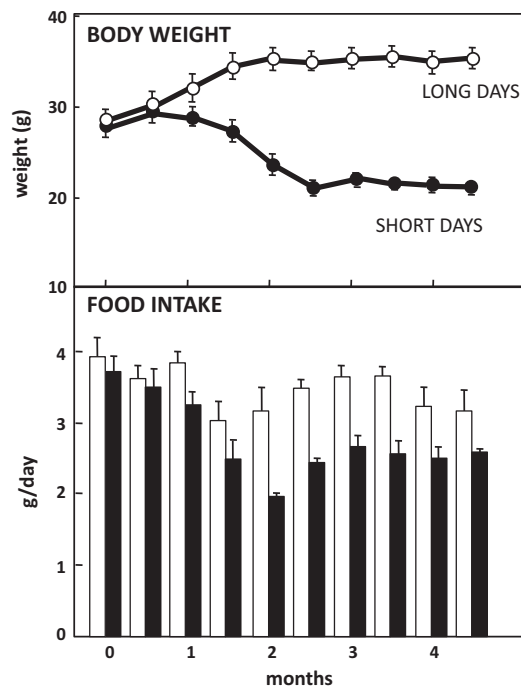


Fig. 2. Photoperiodic regulation of body weight and food intake in male Siberian hamsters. Hamsters were initially raised on long days of 16 h light: 8 h dark, then moved to short days (8 h light: 16 h dark, $n = 6$) at 2 months of age or maintained in long days ($n = 10$). Note that food intake gradually declined in short days even though the hamsters were maintained on ad libitum diet, and that this was mirrored by a decline in body weight. Data are the control animals redrawn from Ebling et al. (1998).

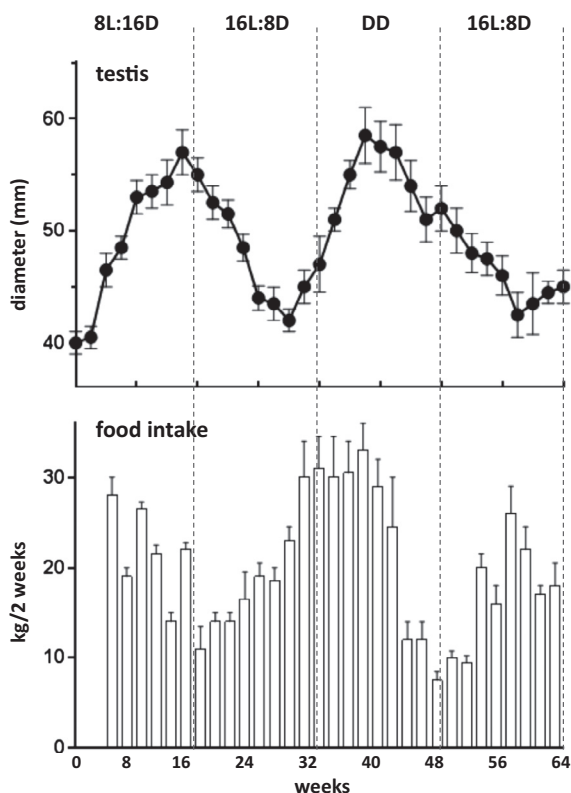


Fig. 1. Photoperiodic regulation of voluntary food intake in male Soay sheep ($n = 8$). Adults rams were maintained indoors on alternating 16-week periods of long days (16 h light: 8 h dark) then short days (8 h light: 16 h dark) or at week 32–48 constant dim red light, DD). Note that short days synchronized testicular recrudescence (top panel) but a decrease in food intake occurred (bottom panel). Testis data are redrawn from Ebling and Lincoln (1987); food intake data are from the same study (Ebling, 1984).

Bartness et al., 2014) it is plausible that this provides a mechanism whereby the brain drives seasonal cycles in adiposity and body weight. However, other studies have not been able to discriminate the time course of weight loss and changes in appetite in the Siberian hamster (eg Fig. 2). Detailed studies of energy expenditure using metabolic cages (Knopper and Boily, 2000; Warner et al., 2010) underpin the alternative view that the primary response to short photoperiods is to change behavior. Thus, as daylength shortens, there is a decreased motivation to forage and eat, thereby anticipating the likelihood of reduced food availability in winter. This programmed decrease in appetite is the primary driver for weight loss, rather than increased energy expenditure (Morgan et al., 2006).

2. Broad significance

We should appreciate three important points when considering seasonal cycles. First, they are caused by changes in neuroendocrine function. Seasonal changes in the occurrence of estrus cyclicity or spermatogenic function reflect cyclical activity of the GnRH-gonadotropin axis, and many of the accompanying behavioral and morphological changes are secondary to altered secretion of sex steroids (Lincoln and Short, 1980; Karsch et al., 1984). Likewise, annual changes in hair follicle activity underlying altered fur and wool growth predominantly reflect altered prolactin secretion (Duncan and Goldman, 1984). Seasonal changes in growth and in energy metabolism reflecting torpor, altered lipolysis, and increased thermogenic capacity of brown fat involve more complex interactions of pituitary [eg β -endorphin (Ebling and Lincoln, 1987)] and peripheral hormones [eg leptin (Tups et al., 2004), FGF21 (Samms et al., 2014)] and the autonomic nervous system (Bamshad et al., 1998, 1999), but the salient point is that the

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