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Review

On the value of seasonal mammals for identifying mechanisms underlying the control of food intake and body weight

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ABSTRACT

This article is part of a Special Issue "Energy Balance".

Seasonal cycles of adiposity and body weight reflecting changes in both food intake and energy expenditure are the norm in mammals that have evolved in temperate and polar habitats. Innate circannual rhythmicity and direct responses to the annual change in photoperiod combine to ensure that behavior and energy metabolism are regulated in *anticipation* of altered energetic demands such as the energetically costly processes of hibernation, migration, and lactation. In the last decade, major progress has been made into identifying the central mechanisms that underlie these profound long-term changes in behavior and physiology. Surprisingly they are distinct from the peptidergic and aminergic systems in the hypothalamus that have been identified in studies of the laboratory mouse and rat and implicated in timing meal intervals and in short-term responses to caloric restriction. Comparative studies across rodents, ungulates and birds reveal that tanycytes embedded in the ependymal layer of the third ventricle play a critical role in seasonal changes because they regulate the local availability of thyroid hormone. Understanding how this altered hormonal environment might regulate neurogenesis and plasticity in the hypothalamus should provide new insight into development of strategies to manage appetite and body weight.

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Introduction

Given the high international prevalence of obesity and the substantive costs of management of the associated co-morbidities, the need to develop pharmacological strategies to reduce appetite and support weight-control regimes has never been greater. As of 2013, there are no centrally-acting drugs that can be prescribed in the USA or Western Europe for this purpose, the most recently available compounds sibutramine (a monoamine reuptake inhibitor) and rimonabant (an endocannabinoid receptor antagonist) having been withdrawn because of adverse side effects (James et al., 2010; Rothman and Baumann, 2009). Clearly there is a huge need to understand better the complex behavioral mechanisms that underlie our motivation to eat in order to identify feasible drug targets, but our use of animals to achieve this is hugely skewed toward a few 'model' species. A brief analysis of the

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PubMed database in August 2013 using the search terms "appetite" OR "food intake" AND more specific mammalian species or genera revealed that only approximately 6% of all manuscripts were based on studies in seasonal species, of which sheep and hamsters were the most common (Fig. 1).

Of the remaining 94% of studies, approximately two-thirds were studies in rats, and about a quarter were studies in mice (Fig. 1). Even acknowledging the biases inherent in searching for studies utilizing seasonal species in a biomedical database, this simple analysis suggests that our understanding of the biology of appetite control is largely restricted to a few 'model' species. The limitations of using laboratory mice and rats as experimental models to understand human mechanisms or to predict drug efficacy has been reviewed in depth elsewhere; under standard conditions most strains are "sedentary, overweight, insulin resistant, hypertensive and prone to premature death" (Martin et al., 2010). There is no question that analysis of single gene mutations in mice and rats (e.g. *ob*/*ob*) that have arisen spontaneously or arising from genetic manipulation (e.g. the plethora of mutations of the melanocortin system) identify fundamental mechanisms involved in control of energy balance, but it is equally apparent that relatively few cases of clinical obesity reflect single gene mutations (Farooqi and O'Rahilly, 2006). The focus of this review is therefore to highlight how studies in mammals that undergo natural seasonal cycles of altered appetite and of fat deposition and catabolism have led to the identification of novel pathways that were missed in studies of intensively-bred conventional laboratory species. However, it is also interesting to consider the evidence that *Homo sapiens* is a seasonal species, particularly with regard to annual patterns of reproduction (Roenneberg and Aschoff, 1990a,b), mood and affect (Partonen and Lönnqvist, 1998), and immune function and susceptibility to illness (Nelson, 2004). While it is difficult to disentangle the relative contributions of social and cultural influences from the underlying true seasonal rhythmicity (Bronson, 2004; Mersch et al., 1999), increasing our understanding of the basic biological processes underlying seasonal rhythms is likely to have beneficial impact of human wellbeing where modern life styles conflict with our seasonal nature (Foster and Kreitzman, 2010).

Seasonal strategies

Seasonal cyclicity of reproductive and metabolic physiology coupled to complementary behaviors is almost ubiquitous among organisms that evolved in non-equatorial latitudes. Reproduction is an energetically costly process, and mammals have evolved strategies to give birth and raise young at times of year that favor survival and nutritional support of lactation and growth of the offspring. For terrestrial mammals this is usually spring, but as gestation lengths vary hugely between species, and because food availability and storage mechanisms also vary, a wide variety of different seasonal strategies are found. In mammals with short gestation periods of a few weeks such as hamsters, deer mice, shrews and voles, the neuroendocrine activation of the reproductive axis occurs in late winter/early spring at the time when day lengths are increasing. In larger species with longer gestation periods, for example sheep (5 months), goats and red deer, neuroendocrine activation occurs during the fall when day lengths are decreasing. Superficially, species can be divided into "long-day" and "short-day" breeders, but this nomenclature can be misleading, for example some species such as pine martens and stoats have short gestation periods but nevertheless breed in late summer when day length is decreasing because they then have a prolonged period of delayed implantation of the blastocyst, leading to births in the following spring (Amstislavsky and Ternovskaya, 2000). Despite different reproductive cycles between "long-day" and "short-day" breeders, there may be commonality of timing of other cycles. Almost all mammals studied to date show a summer rise in prolactin secretion which co-ordinates changes in growth and molting of fur and wool (Lincoln, 1990). Most species will also gain body weight in the summer as they store energy as fat depots (Bartness et al., 2002), and many use strategies such as torpor and hibernation to conserve energy in winter (Wilcox and Willis, in press), this may be combined with programmed winter hypophagia, thus only limited energy is spent on foraging for diminished food reserves (Heldmaier et al., 1989). However the precise timing and inter-relationship of seasonal cycles of appetite, fattening and reproductive activity is species specific, perhaps reflecting the trade-offs that have evolved between appetitive behaviors underlying acquisition of calories versus those promoting reproduction (Schneider et al., 2013). Moreover, even within species there may be polymorphisms in the inter-relationships of seasonal cycles of metabolic rate, feeding, activity and fertility [see White et al., in press for review].

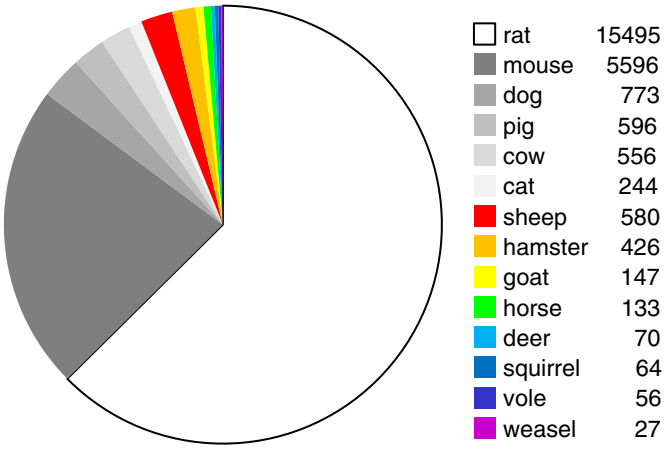

Fig. 1. Percentage of citations in PubMed (August 2013) using the search terms "appetite" OR "food intake" AND the animal group indicated. Absolute numbers of citations are indicated to the right of the animal group. Note that citations with "rat" or "mouse" as a search term comprise nearly 80% of the total, and seasonal mammals (in color) only constitute ~6% of the total. 28,895 citations using "human" or "man" with these search terms were also identified. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Leptin and seasonal body weight cycles

A classic series of lesion studies in the mid part of the 20th century identified the hypothalamus as a key homeostatic structure regulating feeding, satiety and energy balance (Anand and Brobeck, 1951; Hetherington and Ranson, 1940) as reviewed by Elmquist et al. (1999). Along with the brainstem, it detects circulating signals such as leptin and insulin relating to the condition of energy stores within the body, levels of energy metabolites such as glucose and fatty acids, and signals such as Ghrelin and cholecystokinin relating to the activity of the gastrointestinal tract, then integrates this information to affect both behavior and physiology. The cloning of leptin (Zhang et al., 1994) and the subsequent identification of leptin receptors initiated a huge leap forward in identifying specific hypothalamic pathways subserving these functions in mice and rats. Accordingly, under negative energy balance conditions, peripheral leptin concentrations are reduced, which promotes increased orexigenic gene expression in the mediobasal (e.g. NPY, AgRP) and lateral hypothalamus (e.g. orexin, MCH) and decreased anorectic gene expression (e.g. POMC, CART, TRH) (Friedman, 2009). Thus, in the short-term, decreased leptin production in response to reduced caloric availability or starvation engages food-seeking behaviors, and correspondingly promotes energy-saving adaptations such as decreased metabolic rate and torpor. Conversely, treatment of rodents in a leptin-deficient state with synthetic leptin suppresses food intake (Friedman, 2009). However, in seasonal mammals circulating leptin levels naturally decrease as intra-abdominal fat depots decrease in the short days preceding winter. Unlike the situation in rats and mice, there is a "leptin paradox (Morgan et al., 2006)"; that is, the seasonal decrease in leptin production is *not* perceived as a 'starvation' signal: it does not trigger a compensatory response, rather it is

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