

# Seasonal food intake and energy balance: Neuronal and non-neuronal control mechanisms

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## ABSTRACT

Animals inhabiting temperate and high latitudes undergo drastic seasonal changes in energy storage, facilitated by changes in food intake and body mass. Those seasonal changes in the animal's biology are not mere consequences of environmental energy availability but are anticipatory responses to the energetic requirements of the upcoming season and are actively timed by tracking the annual progression in photoperiod.

In this review, we discuss how photoperiod is used to control energy balance seasonally and how this is distinct from energy homeostasis. Most notably, we suggest that photoperiodic control of food intake and body mass does not originate from the arcuate nucleus, as for homeostatic appetite control, but is rather to be found in hypothalamic tanycytes. Tanycytes are specialized ependymal cells lining the third ventricle, which can sense metabolites from the cerebrospinal fluid (e.g. glucose) and can control access of circulating signals to the brain. They are also essential in conveying time-of-year information by integrating photoperiod and altering hypothalamic thyroid metabolism, a feature that is conserved in seasonal vertebrates and connects to seasonal breeding and metabolism.

We also discuss how homeostatic feedback signals are handled during times of rapid energetic transitions. Studies on leptin in seasonal mammals suggest a seasonal shift in central sensitivity and blood-brain transport, which might be facilitated by tanycytes.

This article is part of the Special Issue on "Food intake and feeding states".

## 1. Seasonality and photoperiod

Due to the Earth's orbit around the Sun and the relative tilt of the Earth's axis, habitats of temperate and high latitudes experience annual cycles in day length, temperature, and energy availability. These cyclic changes are known as the seasons. Animals living in seasonal environments time their life cycles in a fashion in which they take advantage of the energetically favourable seasons while periods of unfavourable conditions are met with behavioural and physiological quiescence and other survival strategies. Most seasonal animals, for example, time their reproduction so that birth and offspring sustenance coincide with favourable conditions, and apart from those 'breeding windows' seasonal animals are reproductively inactive and have underdeveloped gonadal systems. The activity and inactivity of the reproductive axis on a yearly scale is a prime example of a seasonal rhythm. Many seasonal animals also exhibit increased food intake and accumulation of energy stores in times of plenty while reduced food intake and catabolizing of energy stores ensures survival during times of scarcity.

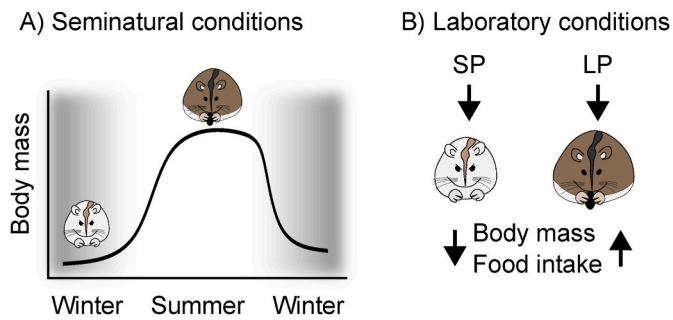
Seasonal change in energy balance spans across the animal kingdom and is especially pronounced in inhabitants of high latitudinal environments. The Siberian hamster (*Phodopus sungorus*), Svalbard ptarmigan (*Lagopus muta hyperborea*) and Arctic charr (*Salvelinus alpinus*) are

individual examples from three different classes (mammals, birds, and fishes, respectively). Siberian hamsters accumulate fat stores during the summer and deplete them during the winter (Fig. 1A) (Barrett et al., 2007; Figala et al., 1973; Heldmaier and Steinlechner, 1981; Petri et al., 2016; Zysling et al., 2009). The Svalbard ptarmigan, a sub-species of the rock ptarmigan that lives permanently on the high Arctic archipelago of Svalbard, feeds extensively in the autumn, accumulating fat reserves ensuring winter survival (Lindgård et al., 1995; Mortensen et al., 1983). Anadromous Arctic charr feed extensively during their relatively short sea trips in the summer (few weeks each year), resulting in sharp increases in body mass, and express inappetence during winter (Jørgensen et al., 1997). These are three prime examples of species combining clear expression of seasonal cycles in energy metabolism in the wild as well as in the lab. In our discussion, we highlight research insights from the above-mentioned species as well as other models that have substantially contributed to seasonal research.

Seasonal rhythms in feeding behaviour are not just consequences of the environmental availability of resources, in fact, the above-mentioned examples can display their seasonal food intake and body mass cycles in captivity under *ad libitum* food conditions (Heldmaier and Steinlechner, 1981; Lindgård et al., 1995; Tveiten et al., 1996). Instead of being mere responders to the prevailing environmental conditions,

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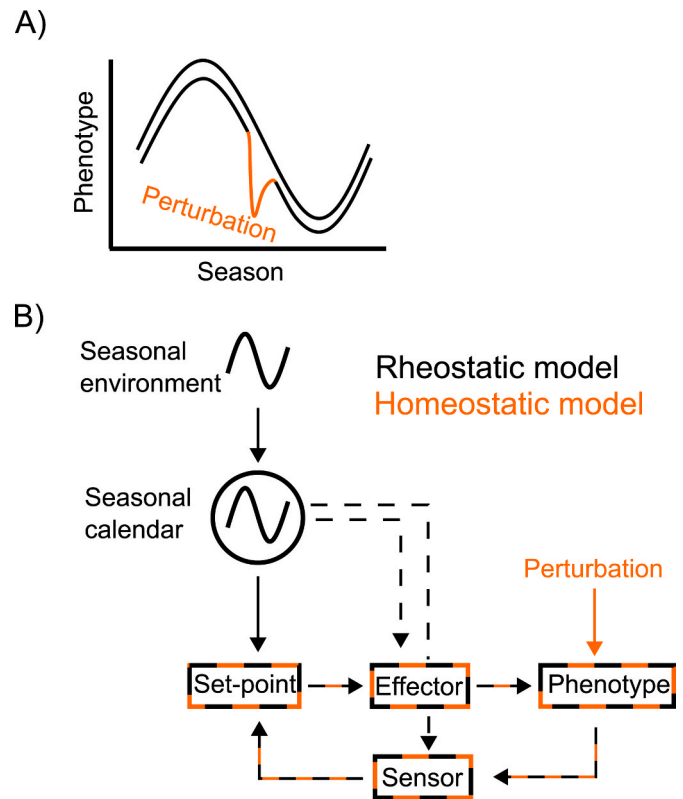
**Fig. 1.** Photoperiodic control of energy balance in seasonal animals A) Siberian hamsters under natural photoperiod express clear changes in energy balance despite being fed *ad libitum*. The figure is based on published data (Heldmaier and Steinlechner 1981; Figala et al. 1973; Barrett et al., 2007; Zysling et al. 2009)

B) The seasonal changes in food intake and body mass can be triggered by transitions between artificial photoperiods, as exemplified by responses in Siberian hamsters under either short photoperiod or long photoperiod. The figure is based on published data (Ebling et al., 1998; Knopper and Boily, 2000; Warner et al., 2010; Masuda and Oishi, 1988). SP, short photoperiod; LP, long photoperiod.

most seasonal animals rely on an internal calendar that uses the annual change in photoperiod to time the expression of an appropriate phenotype in anticipation of the upcoming season. For example, Siberian hamsters in summer-like long photoperiods (LP) exhibit hyperphagia and increases in fat stores, while under winter-like short photoperiods (SP) they exhibit decreased food intake and loss in body mass despite *ad libitum* food supply (Fig. 1B) (Ebling et al., 1998; Knopper and Boily, 2000; Masuda and Oishi, 1988; Warner et al., 2010).

While the annual change in day length is the main synchronizing agent of this internal seasonal calendar, in some species the expression of the appropriate seasonal phenotype can occur in the absence of photoperiodic changes (Gwinner, 1986). This phenomenon is known as circannual rhythmicity and describes the occurrence and termination of a seasonal phenotype with a period of approximately one year in an artificially constant environment. For example, Eastern chipmunks (*Tamias striatus*) express annual food intake and body mass cycles for over six years despite being kept under constant ambient temperature and a constant photoperiod of 12 h light and 12 h dark (Gwinner, 1986; Richter, 1978). Experiments of this sort are indicative of the endogenous time-keeping property of the internal calendar, but much is still unknown about circannual rhythms and the exact nature of the seasonal calendar. Furthermore, the expression of a true circannual rhythm must be confirmed over several cycles/years and their expression depends on the species and the experimental conditions (Gwinner, 1986). Hence, most studies on seasonal body mass and food intake focus on the comparison between photoperiod-induced seasonal phenotypes, and this review does likewise.

The seasonal/photoperiodic response in feeding and body mass is distinct from the response in feeding as a mechanism of homeostasis. Sliding set-point experiments (Fig. 2A) illustrate this distinction elegantly and have been conducted in several seasonal mammals and birds (Berthold, 1975; Canguilhem and Marx, 1973; Mercer et al., 2001; Mortensen and Blix, 1985; Mrosovsky and Fisher, 1970; Mustonen et al., 2005; Steinlechner et al., 1983; Stokkan et al., 1995). The design is similar between these different studies: One experimental group is kept under *ad libitum* food conditions and is left to express its body mass cycles under simulated natural photoperiod, while a second group is kept under the same photoperiod but is starved and subsequently re-fed at various stages of the body mass cycle. In these experiments, starvation always leads to body mass decline with subsequent hyperphagia and body mass regain after re-introducing food. However, body mass does not recover to the pre-starvation level but to a level determined by the



**Fig. 2.** Graphical presentation of a sliding set-point experiment and the distinction between the homeostatic and rheostatic model.

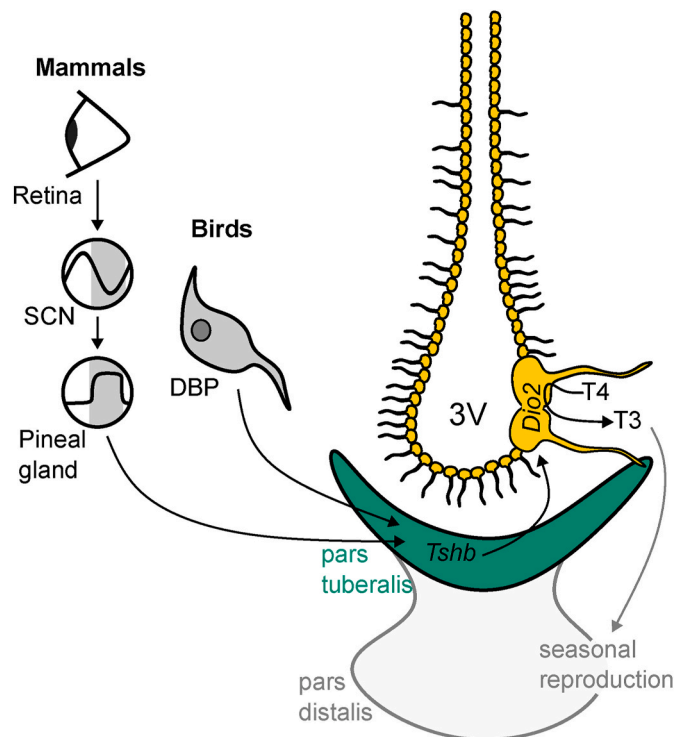
A) Two experimental groups are exposed to seasonal changes in photoperiod and are recorded for body mass (seasonal phenotype). One group is then starved (perturbation) and re-fed, which leads to body mass loss and regain respectively. Importantly, body mass is not recovered to the pre-starvation set-point but to the seasonal appropriate set-point. Sliding set-point experiments distinguish empirically between the rheostatic and homeostatic model. B) The homeostatic model (orange) describes body mass as a set-point to be defended via effectors which includes appetite. Sensors, such as hormonal signalling, reflect the phenotype and feedback to the central system. Perturbations, such as starvation, lead to compensatory responses via the effector, such as changes in food intake. In the rheostatic model, the homeostatic set-point is described to be adjustable and to be under the control of the seasonal calendar which synchronizes to the environmental photoperiod. Experimental data on golden hamsters, Siberian hamsters and field voles suggest the effector and sensor element to be under seasonal control in addition to the set-point (Canguilhem and Marx, 1973; Król et al., 2006; Rousseau et al., 2002; Tups et al., 2004). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

changing seasonal state (as displayed by the non-starved control group). It is not only negative energy balance challenges that can be reversed: positive net energy balance caused by high-fat feeding increased body mass in golden hamsters (*Mesocricetus auratus*) with a subsequent return to the seasonal set-point once high-fat feeding has stopped (Wade and Bartness, 1984). Hence, we see two processes acting in synergy, one which can be summarized in the homeostatic model, in which a set-point of body mass is defended, and the other which can be summarized in a rheostatic model (Mrosovsky, 1990; Stevenson, 2023), in which this set-point is shifted seasonally (Fig. 2B). In the homeostatic model, a set-point is implemented by the effectors, e.g. food intake achieving a certain body mass. Sensors, e.g. peripheral hormones such as leptin and insulin, feedback to the system which compares the phenotype to the actual set-point, which then again implements changes through the effectors. In the seasonal rheostatic model, we assume the very same set-point under the control of the animal's seasonal calendar which synchronizes to the season using the prevailing photoperiod. The

seasonally adjusted set-point then causes a change in phenotype via the effectors, which conceptually overlap with the homeostatic model but may not necessarily do so mechanistically. Sliding set-point experiments in European hamsters (*Cricetus cricetus*) further showed that the rate of body mass recovery after starvation was different depending on the season, suggesting that the effector is under seasonal control as well (Canguilhem and Marx, 1973). Most research on food intake uses laboratory mice and rats, which express no seasonal changes in physiology, therefore this review focuses on seasonal models of appetite regulation. We aim to distinguish mechanisms involved in seasonal (or rheostatic) control of feeding and the associated body mass cycle from those involved in short-term homeostatic control of appetite. For this purpose, we describe how photoperiod is perceived and processed by seasonal animals. We discuss how the photoperiodic signalling pathway connects to feeding control and how the homeostatic centre for appetite control might contribute to seasonal changes. We consider how peripheral feedback signalling is handled during periods of fast changes in the animal's internal energy storage. Finally, we highlight other aspects of seasonal feeding behaviour, e.g. food hoarding.

## 2. Photo-neuroendocrine cascade

The most complete understanding of how photoperiod is perceived by seasonal animals and ultimately leads to the expression of a seasonal



**Fig. 3.** Graphical presentation of photoperiodic responses in reproduction and its possible connection to seasonal food intake.

Photoreception in mammals is accomplished by the retina. The photoperiodic information is then signalled to the circadian master clock, the suprachiasmatic nucleus, and to the pineal gland, where the external photoperiod is translated into an internal melatonin signal. The melatonin signal is received by the pars tuberalis. In birds, photoperiodic information is received and signalled to the pars tuberalis by deep brain photoreceptors. Long photoperiod triggers increased *Tshb* in the pars tuberalis. TSH triggers the expression of *Dio2* in tanycytes lining the third ventricle. DIO2 converts T4 into T3 by outer ring deiodination. The bioactive form of thyroid hormone, i.e. T3, ultimately affects the reproductive axis. SCN, suprachiasmatic nucleus; DBP, deep brain photoreceptors; 3V, third ventricle; *Tshb*, thyroid stimulating hormone subunit b; T3, triiodothyronine; T4, thyroxine; *Dio2*, deiodinase 2.

phenotype, has been achieved in relation to seasonal breeding (Fig. 3). However, different seasonal traits likely share the same core mechanisms and the photoperiodic pathway controlling reproduction probably also controls seasonal feeding and body mass cycles (Ebling, 2014, 2015; Helfer et al., 2019).

To use photoperiod, the animal first needs to perceive light. In mammals, the major light-sensing tissues are the eyes and retinas. Photosensitive ganglion cells within the retina signal to the mammalian circadian master clock, the suprachiasmatic nucleus (SCN) (Berson et al., 2002; Hattar et al., 2002). The SCN controls the synthesis and secretion of pineal gland-derived melatonin (Perreau-Lenz et al., 2003; Pevet and Challet, 2011). Melatonin is secreted during nighttime leading to high levels in circulation during darkness and low levels during light periods. Hence, the melatonin signal is an internal representation of the prevailing environmental photoperiod. While melatonin controls various mechanisms and sustains circadian synchronisation of peripheral tissue with the SCN (Pevet and Challet, 2011), it is also important to relay photoperiodic information in a seasonal context (Goldman and Nelson, 2020).

The pars tuberalis (PT), which is part of the anterior pituitary gland, is a key recipient of the melatonin signal (Bittman, 1993; Messenger et al., 1997) and triggers a localised thyroid hormone conversion cascade in the mediobasal hypothalamus ultimately leading to activation of the reproductive axis (Nakane and Yoshimura, 2014). Therefore, the transfer of photoperiodic mammals from SP to LP triggers, via melatonin, high expression of thyroid stimulating hormone beta subunit (*Tshb*) in the PT (Hanon et al., 2008, 2010; Nakao et al., 2008; Ono et al., 2008). Specialized ependymal cells lining the 3rd ventricle, known as tanycytes, express TSH receptors and the binding of PT-derived TSH triggers a cAMP cascade ultimately leading to an increased expression of the Type II iodothyronine deiodinase (*Dio2*) (Bolborea et al., 2015; Hanon et al., 2008, 2010; Ono et al., 2008; Revel et al., 2006b; Watanabe et al., 2004). DIO2 converts locally available thyroxine (T4) into triiodothyronine (T3) (Yoshimura et al., 2003) and T3, being the active form of thyroid hormone, exerts its effects on the hypothalamic parenchyma ultimately affecting seasonal breeding via the classical hypothalamic–pituitary–gonadal axis (Dardente et al., 2014; Dardente and Simonneaux, 2022; Henson et al., 2013; Klosen et al., 2013; Quignon et al., 2020; Revel et al., 2006a; Yamamura et al., 2004, 2006).

Conversely, under SP, low expression of *Tshb* and *Dio2* coincide with high expression of the thyroid-deactivating type III iodothyronine deiodinase (*Dio3*) in tanycytes, leading to low levels of bioactive T3 and reversal of the reproductive state compared to LP (Milesi et al., 2017; Yasuo et al., 2005).

The photoperiodic switch in hypothalamic thyroid conversion is a core feature of seasonal breeders, which not only includes mammals but also birds and fishes in which this trait is remarkably conserved (Hanon et al., 2008; Hazlerigg and Loudon, 2008). The major difference in the avian system is the decoupling of melatonin from the photoperiodic response. Instead of light transmission via the retina, SCN and pineal gland, birds use deep brain photoreceptors to directly relay environmental photoperiod to the PT (Fig. 3) (Halford et al., 2009; Nakane et al., 2010; Pérez, 2022). In fact, this decentralised and more localised photoreception is the norm in photoperiodic animals, with mammals forming the exception (Menaker et al., 1997). In fish, the neuroanatomical system differs from the mammalian and avian systems but still seems to employ photoperiod-driven changes in *Tshb* and *Dio2* transcripts (Fleming et al., 2019; Nakane et al., 2013; Nishiwaki-Ohkawa and Yoshimura, 2016). Yet, despite the general conservation of the TSH-DIO cascade in the mediobasal hypothalamus, species-specific variation does exist. For example, in a comparison between Siberian and golden hamsters housed under the same conditions, temporal expression patterns of *Tshb*, *Dio2* and *Dio3* vary significantly relative to the same changing photoperiod (Milesi et al., 2017). Besides variation in the temporal patterns, *Dio2* expression also shows pronounced anatomical variation between the two hamster species (Milesi et al.,

2017).

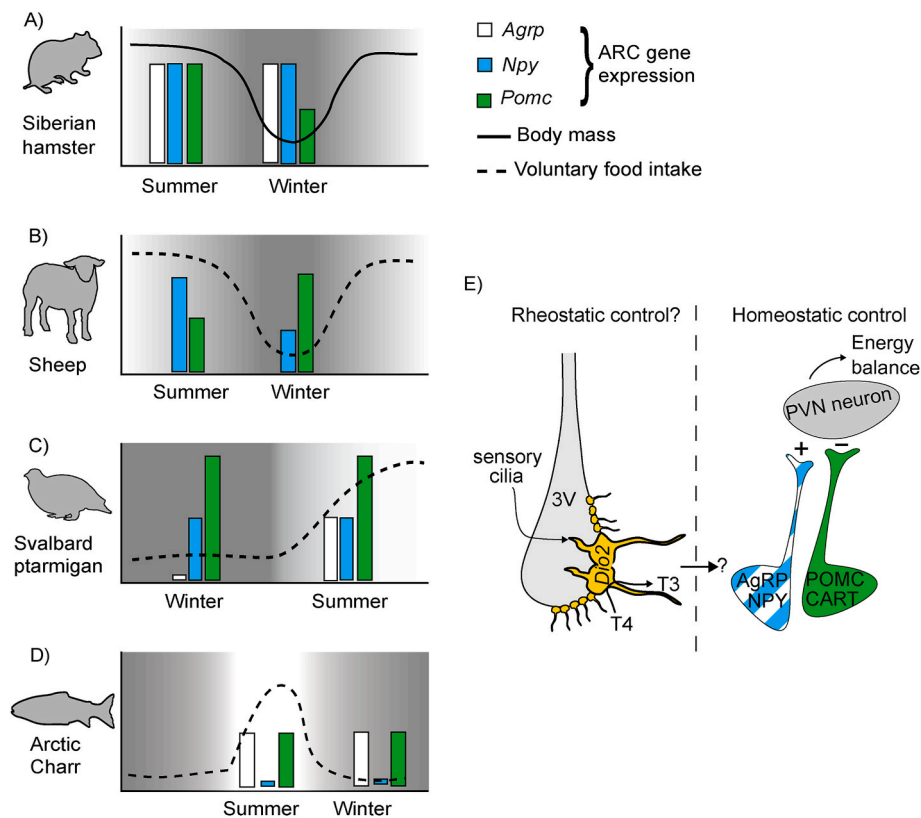
How exactly the above-described photo-neuroendocrine pathway links to photoperiodic control of food intake and body mass is still under debate, but much of the attention has focused on the homeostatic appetite centre, i.e. the arcuate nucleus (ARC).

### 3. The melanocortin system and seasonal food intake

Homeostatic food intake control is tightly regulated in the central melanocortin system of the hypothalamic ARC and paraventricular nucleus (PVN). The ARC contains two subpopulations of neurons that when active increase (orexigenic) or decrease (anorexigenic) food intake via the expression of Agouti-Related Peptide/Neuropeptide Y (*Agrp/Npy*) and Proopiomelanocortin/Cocaine- and Amphetamine- Regulated Transcript (*Pomc/Cart*), respectively. The ARC neurons exert their effect through the melanocortin 4 receptor (MC4R) expressed in neurons of the PVN. POMC/CART neurons use alpha-melanocyte stimulating hormone ( $\alpha$ -MSH), which derives from the POMC peptide by post-translational modification and binds the receptor as an agonist leading to appetite inhibition, while AgRP and NPY inhibit the anorexigenic effects of POMC/CART neurons thus exerting an antagonistic effect (Kalra and Kalra, 2004; Lu et al., 1994). Due to their privileged location with almost direct contact with the blood-brain barrier and the median eminence, the ARC neurons can sense hormones and metabolites signalling the

body's energy status. Changes in the messages coming from the periphery such as glucose, leptin, or insulin, are sensed and integrated by the ARC neurons and relayed to other brain structures such as the PVN (Ahn et al., 2022). The role of the ARC for homeostatic appetite control is undisputed, however, its role for seasonal/rheostatic regulation of feeding is less clear, and in seasonal studies the gene expression data on the key neuropeptides, i.e. *Agrp*, *Npy* and *Pomc*, is often inconsistent (Fig. 4).

Female and male Siberian hamsters (Fig. 4A) show no photoperiodic variation in *Npy* and *Agrp* (Adam et al., 2000; Mercer et al., 2000, 2001) and *Pomc* expression is, counter-intuitively, down-regulated in lean hamsters under SP compared to their fat counterparts under LP (Mercer et al., 2000). However, the discrepancy between *Pomc* gene expression and the hamster's phenotype could be explained by post-translational modifications. The post-translational modifications of POMC, from which  $\alpha$ -MSH derives, include prohormone convertases 2 and Carboxypeptidase E, both of which were upregulated in hamsters under SP compared to hamsters under LP, which further correlated with higher  $\alpha$ -MSH content in SP hamsters (Helwig et al., 2006, 2013). While the post-translational modification of POMC might suggest a role of the ARC in seasonal appetite and body mass control in Siberian hamsters, other experimental findings suggest otherwise (Ebling, 2014; Schuhler and Ebling, 2006). Neurotoxic knockdown of ARC-neurons (ca. 80% of neurons) in neonatal male Siberian hamsters did not disrupt



**Fig. 4.** Seasonal expression of hypothalamic neurotransmitters in the arcuate nucleus in four different animal models is variable whereas hypothalamic thyroid hormone control is maintained.

**A)** Siberian hamster (*Phodopus sungorus*) housed either in long photoperiod or short photoperiod. The figure is based on gene expression data from Mercer et al. (2000) and body mass data from Petri et al. (2016). **B)** Female sheep (*Ovis aries*) housed in outdoor natural photoperiods across the year. The figure is based on data from Clarke et al. (2000). **C)** Svalbard ptarmigan (*Lagopus muta hyperborea*) kept indoors and transferred from constant darkness into constant light. The figure is based on data from Melum (2018). **D)** Arctic charr (*Salvelinus alpinus*) under simulated natural photoperiod. The figure is based on data from Striberny et al. (2015). **E)** Model proposing the different components for a rheostatic vs a homeostatic control of seasonal food intake. Rheostatic control involves the conserved pathway of hypothalamic thyroid hormones common for all seasonal animal models and the homeostatic control involves the melanocortin ARC/PVN communication with variable regulation depending on the species by coupling to each metabolic needs. NPY, Neuropeptide Y; AgRP, Agouti related peptide; POMC, proopiomelanocortin; CART, cocaine and amphetamine related transcript; MCR4, melanocortin receptor type 4; ARC, Arcuate Nucleus; PVN, paraventricular nucleus of the hypothalamus; T3, triiodothyronine; T4, thyroxine; Dio2, deiodinase 2.

photoperiodic responses in appetite and body mass (Ebling et al., 1998) and hypothalamic overexpression of *AgRP* did not block the catabolic response to SP even though it blocked a photoperiodic response in food intake (Jethwa et al., 2010). Furthermore, pharmacological manipulations of the MC4R via intracerebroventricular administration of an agonist and an antagonist impacted food intake but the effect was similar between Siberian hamsters under LP and SP, suggesting that the endogenous state of the melanocortin system is unaltered between photoperiods (Schuhler and Ebling, 2006).

Comparing data across species and classes further undermines the ARC's potential role in seasonal appetite control. While the homeostatic role of the melanocortin system seems conserved across mammals, birds and fishes (Boswell et al., 2002; Boswell and Dunn, 2015; Cornelius et al., 2013; Kalanathan et al., 2020; Lin et al., 2000; Phillips-Singh et al., 2003; Rønnestad et al., 2017; Volkoff et al., 2005), the seasonal impact is variable.

In seasonal sheep breeds (*Ovis aries*), expression patterns of *Npy* and *Pomc* agreed broadly with seasonal feeding patterns (Fig. 4B) but there were strong sex differences (Clarke et al., 2000, 2003; Skinner and Herbison, 1997). In photoperiodic male rats (F344 strain of *Rattus norvegicus*), long photoperiod triggered an increase in food intake which correlated with an increase in *AgRP* expression, however, *Npy* expression was counter-intuitively decreased in LP compared to SP, and *Pomc* in the ARC was unchanged by photoperiod (Ross et al., 2009). In captive male and female Svalbard ptarmigan, *AgRP* expression was high after 10 weeks under LP compared to SP values which correlated with increased food intake, but *Npy* and *Pomc* were relatively unaltered (Melum, 2018) (Fig. 4C). In Arctic charr, attempts to directly connect the strong seasonal feeding cycles to expression of genes with orexigenic or anorexigenic roles in mammals (i.e. *Npy*, *AgRP* and *Pomc*) have altogether failed (Fig. 4D) (Striberny et al., 2015).

#### 4. Tanycytes and food intake control

The inconsistency of the seasonal and photoperiodic data in the ARC has led to the conjecture that seasonal appetite control might be found outside the ARC (Ebling, 2014). Tanycytes are an important hub connecting many aspects of not only metabolism but also food intake, body weight regulation and glucose metabolism (Prevot et al., 2018). Their position around the third ventricle allows them communication with various systems: they extend cell processes into hypothalamic nuclei, including the ARC (Bolborea and Dale, 2013; Dale, 2011), they respond to nutrients, like glucose, in the cerebrospinal fluid (CSF) (Benford et al., 2017; Elizondo-Vega et al., 2019; Frayling et al., 2011; Orellana et al., 2012), and they control access of bloodborne substances to the brain (Balland et al., 2014; Langlet et al., 2013a, 2013b).

As outlined above, the photoperiodic expression of deiodinases (*Dio2* and *Dio3*) in tanycytes controls T3 availability in the hypothalamus. In contrast to neuropeptide expression in the ARC, the deiodinase expression pattern within tanycytes is a conserved pattern among seasonal animals, including those that display strong annual cycles in appetite (Helfer et al., 2019; Helfer and Stevenson, 2020). Furthermore, intra-hypothalamic T3 administration increased body mass and food intake in Siberian hamsters under SP connecting the hypothalamic thyroid conversion to energy balance (Fig. 4E) (Barrett et al., 2007; Murphy et al., 2012).

In non-seasonal rodents, tanycytes increased expression of *Dio2* after 48 h of fasting (Fontes et al., 2017; Lazcano et al., 2015) and optogenetic activation of tanycytes caused hyperphagia through activation of ARC neurons (Bolborea et al., 2020), which together suggests that tanycytes can react to energetic signals and can recruit ARC neurons to exert effects on appetite (Fig. 4E). Work by Melum et al. (2024) showed further that tanycytes underwent a photoperiodic regulation in their capacity to sense signals in the CSF with a higher number of sensory cilia in male Siberian hamsters raised under LP than in hamsters raised under SP (Melum et al., 2024).

All of this makes tanycytes a prime candidate for seasonal/rheostatic control of energy balance.

#### 5. Hormonal feedback system

Besides central rheostatic control, peripheral feedback signalling is a key component to understand seasonal feeding behaviour. In the homeostatic model, these peripheral signals function as feedback to control appetite and cellular metabolism to ultimately maintain a steady state. Leptin is the major peripheral signal relaying information about the fat stores in mammals (Coleman, 1973; Halaas et al., 1995; Zhang et al., 1994). Leptin is primarily expressed in adipocytes of white adipose tissue and levels in the circulation correlate strongly with fat mass (Friedman and Halaas, 1998). Disruption in leptin signalling such as the mutation in either the leptin gene (as in *ob/ob* mice) or its receptor (as in *db/db* mice) leads to severe hyperphagia and obesity (Hummel et al., 1966; Ingalls et al., 1950). Consequently, leptin injections have a clear and dose-dependent negative effect on food intake and body mass (Campfield et al., 1995; Friedman and Halaas, 1998; Halaas et al., 1995) and the anorexigenic effect of leptin seems to be mediated by inhibition of NPY/AgRP neurons and stimulation of POMC neurons within the ARC (Friedman, 2011; Korner et al., 2001; Williams et al., 2010).

This raises the question of how seasonal mammals handle leptin signalling in periods when its anorexigenic effect would be averse to the seasonal phenotype. For example, Siberian hamsters show a rapid increase in fat stores when they are transferred from SP to LP, this increase in fat stores correlates with an increase of the anorexigenic factor leptin in the circulation (Klingenspor et al., 1996; Mercer et al., 2000; Tups et al., 2004). Therefore, Siberian hamsters must be able to 'ignore' the increased leptin levels otherwise the compensatory anorexigenic feeding response would surely offset the desired increase in body mass. This is called the 'leptin paradox' (Ebling, 2014; Morgan et al., 2006; Rousseau et al., 2002). Seasonal rodents and sheep resolve this paradox through photoperiodic changes in leptin sensitivity (Adam et al., 2006; Atcha et al., 2000; Król et al., 2006, 2007; Miller et al., 2002; Tups et al., 2004). In Siberian hamsters and field voles (*Microtus agrestis*) this is mediated by changing expression of the Suppressor Of Cytokine Signaling 3 (*Socs3*) in the ARC (Król et al., 2006, 2007; Tups et al., 2004), which inhibits the anorexigenic effect of leptin by inhibiting phosphorylation of the major leptin mediator 'Signal transducer and activator of transcription 3' (STAT3) (Auernhammer and Melmed, 2001). Siberian hamsters were not responsive to leptin administration in LP and *Socs3* was higher expressed under LP than under SP, strongly suggesting increased leptin resistance under LP in this species (Atcha et al., 2000; Tups et al., 2004), an observation also seen in male field voles (Król et al., 2006, 2007).

Several studies on Siberian hamsters and field voles favour a direct effect of photoperiod on leptin sensitivity rather than being indirectly driven by changes in fat mass and leptin levels. Food restriction in Siberian hamsters under LP caused a decline in fat mass and leptin levels to SP levels but LP hamsters still remained leptin insensitive (Rousseau et al., 2002). In another study, post-weaning female Siberian hamsters initially increased in body mass both under SP and LP, but from week 3 post-weaning onwards hamsters under LP increased body mass more rapidly and significantly diverged from the SP trajectory (Tups et al., 2004). Importantly, *Socs3* expression diverged one week before the body mass trajectory did with higher expression in LP hamsters. The same study showed also that juvenile female hamsters kept under LP with restricted food access resembled SP hamsters in terms of body mass and serum leptin concentration but *Socs3* expression of those food-restricted LP hamsters did not differ from LP hamsters with *ad libitum* food access (Tups et al., 2004). Furthermore, a study on male field voles shows that LP triggers an increase in body mass accompanied by increased expression of *Socs3* in the ARC (Król et al., 2007). However, *Socs3* expression does only differ from SP values during the transitional period, i.e. during rapid body mass increase, but not after body mass plateaued after which *Socs3* expression returns to SP values. The authors

argue that leptin resistance is only necessary to transit between steady states, i.e. a low or high body mass plateau (Król et al., 2007).

Besides shifting leptin sensitivity via *Socs3* expression, leptin signalling might also be photoperiodically modulated via changing blood-brain transport of circulating leptin as seen in seasonal male sheep (Adam et al., 2006), a process which might be facilitated by the choroid plexus or the tanycytes (Balland et al., 2014; Prevot et al., 2021).

Insulin is another prominent peripheral feedback signal, with the role of controlling glycaemic levels by cellular glucose uptake. Seasonally, insulin plasma levels are lower in lean SD-adapted male and female Siberian hamsters (Cázarez-Márquez et al., 2019; Korhonen et al., 2008) and insulin administration has a stronger effect on blood glucose levels in male Siberian hamsters under SP than under LP (Garcia et al., 2010). Besides its role in glucose regulation, insulin acts as a lipostatic hormone (i.e. correlates with fat mass) with an anorexigenic effect mediated via the ARC (Niswender and Schwartz, 2003) and in male Siberian hamsters, insulin injection influenced food intake in SP but not in LP (Garcia et al., 2010). Contrary to the finding by Garcia et al. (2010) that SP-adapted hamsters show increased insulin sensitivity, Tups et al. (2006) showed decreased insulin receptor expression in the ARC of SP-adapted juvenile female Siberian hamsters compared to their LP counterparts. Despite this contradiction, these results collectively highlight changing insulin sensitivity as a seasonal trait of the Siberian hamster.

In summary in seasonal mammals, altered sensitivity to circulating signals of energetic state and/or blood-brain transport of those signals, possibly facilitated by tanycytes, seems a key component of seasonal feeding and body mass cycles.

Little is known about shifting sensitivities in non-mammalian models, which is further aggravated by functional deviation of peripheral hormones in birds and fishes. In birds, leptin is barely/not expressed in adipose tissue, is barely measurable in the circulation and leptin administration has contradictory results in a range of avian species, all of which suggest a general loss of leptin's lipostatic function in birds (Friedman-Einat and Seroussi, 2019). In fish, leptin seems to act as a glucostat rather than a lipostat but retains a general anorexic role in feeding behaviour with direct or indirect action of leptin on the appetite neurons in the hypothalamus (Blanco and Soengas, 2021). Due to the strong variation in peripheral signalling between taxonomic classes, exemplified by leptin, it becomes evident that a convincing framework for seasonal control of feeding in birds and fishes cannot rely on a mammalian blueprint.

## 6. Sex differences in seasonal appetite control

In addition to taxa and species-specific differences in the seasonal control of food intake and body mass, sex-specific differences are worth noting. Seasonal sheep, as already mentioned, have sex-specific differences in seasonal neuropeptide expression (Clarke et al., 2000, 2003; Skinner and Herbison, 1997). They also show seasonal changes in leptin sensitivity (leptin resistant in autumn, leptin sensitive in spring) with clear variation between the sexes, i.e. stronger anorexigenic effect of leptin in females than in males in the early spring season (Clarke et al., 2001). Those variations naturally reflect different seasonal energy requirements of the sexes: female sheep might rely on increased sensitivity to their energetic state to better handle the metabolic demands linked to birth, which occurs in spring, and subsequent lactation (Clarke, 2001; Clarke et al., 2001). Similarly, pre-breeding fattening in grey seals (*Halichoerus grypus*) occurs earlier and to a greater extent in females than in males to sustain pregnancy and lactation (Beck et al., 2003). Furthermore, in Siberian hamsters, short photoperiod exposed males and females showed spatial differences during fat depletion, i.e. males displayed different degrees of weight decrease between distinct anatomical fat pads while females showed a more uniform depletion pattern (Bartness et al., 1989).

More generally, sex-specific differences are also known in the ARC

architecture (Leal et al., 1998; Urban et al., 1993), in body composition (Bredella, 2017) and in the general effect of sex hormones on appetite and body mass (Hirschberg, 2012; Shi and Clegg, 2009).

These differences emphasise the need for more holistic studies in which both sexes are represented; unfortunately, such studies presently remain in the minority.

## 7. Other seasonal feeding behaviour

Seasonal feeding behaviour has more facets than the mere consumption of food as we have discussed so far. Food hoarding, for example, is a common phenomenon in seasonal mammals and birds and is a supplementary or alternative strategy to store energy reserves for the winter months. For example, Pika (*Ochotona princeps*) in North America accumulate hay piles during the summer, which sustain them during the winter (Dearing, 1997); male Arctic ground squirrels (*Urocitellus parryi*) carry food in their pouches to their burrows in late summer to accumulate a food store used to fuel mate competition in the spring after hibernation (Gillis et al., 2005), and black-capped chickadee (*Poecile atricapillus*) remember the locations of thousands of food caches to sustain them through the winter (Hall et al., 2014; Hitchcock and Sherry, 1990).

While food hoarding is clearly a seasonal trait the external factors stimulating it are variable: photoperiod, ambient temperature and food availability are factors that can trigger food hoarding in several species (Bartness et al., 2011; Wood and Bartness, 1996). In Siberian hamsters, food scarcity seems the most potent stimulator for hoarding (Bartness et al., 2011; Wood and Bartness, 1996). Manipulation of the hormonal feedback system can also alter food hoarding behaviour despite opposite food availability, for example, leptin administration inhibited food hoarding behaviour in food-deprived male Siberian hamsters (Bartness et al., 2011; Keen-Rhinehart and Bartness, 2005, 2008). Other species show photoperiodic dependency such as deer mice (Barry, 1976) and black-capped chickadees (MacDougall-Shackleton et al., 2003).

Other aspects of feeding behaviour include food foraging and voluntary diet choice, both of which seem to be under photoperiodic control in Siberian hamsters, as determined by 'working for food' experiments (Teubner and Bartness, 2009) and diet selection experiments (Fine and Bartness, 1996).

## 8. Conclusions

According to the WHO, in 2019 39% of the world's population adults were overweight (1.9 billion adults). Obesity is a global health crisis and the WHO links more deaths to overweight than underweight. Obese individuals suffer from cardiovascular diseases, diabetes, musculoskeletal impairments and cancer, and to recover from obesity, affected people need to undergo radical behavioural and nutritional changes and might even require medical intervention. On the other hand, numerous seasonal animals undergo self-induced 'obesity' accompanied by hyperphagia every year and subsequently 'recover' from it in a matter of weeks. The question arises if we can compare human obesity with 'obesity' in seasonal animals and what we can learn from that.

Photoperiodic-induced obesity differs from diet-induced obesity. For example, in seasonal male Brandt's voles (*Lasiopodomys brandtii*), photoperiod-induced adiposity did not lead to adverse effects in glucose homeostasis and fat accumulation in muscles, while diet-induced adiposity did (Yang et al., 2023). Furthermore, while seasonal fluctuations in body mass and food intake were observed in humans (De Castro, 1991; Kuzmenko et al., 2021; Ma et al., 2006; Stelmach-Mardas et al., 2016; Westerterp, 2020), the main cause of obesity in humans is most likely not a seasonal effect. Hence, human obesity is distinct from seasonal 'obesity' in photoperiodic animals. Yet, studies of the mechanistic differences between seasonal- and diet-induced obesity may yield valuable knowledge for potential pharmacological treatments in humans.

At the time of writing, however, the central mechanisms controlling seasonal feeding behaviour and body mass remain under much debate. It is well established how seasonal animals receive and transduce changes in photoperiod within the PT and tanycytes, a process that involves a photoperiodically controlled change in hypothalamic thyroid hormone levels which ultimately leads to changes in seasonal life traits such as breeding and energy balance. How exactly this conserved photoperiodic pathway links to seasonal control of feeding is less clear. Much attention has focused on the neighbouring melanocortin system of the ARC but the data in seasonal animals is conflicting.

Tanycytes sitting at the intersection of metabolic and photoperiodic gatekeeping might be better candidates to understand the heart of seasonal appetite control, which does not imply that the melanocortin system does not partake in seasonal appetite regulation. Furthermore, photoperiodic shifts in hormonal feedback signalling are key components of seasonal appetite control and while the hormonal blood-brain transport might be facilitated by tanycytes, changes in sensitivity are still likely integrated via the melanocortin system.

## Funding

D.A. and F.C.M. are supported by the Arctic Seasonal Timekeeping Initiative (ASTI), awarded by UiT - The Arctic University of Norway.

## CRediT authorship contribution statement

**Daniel Appenroth:** Writing – review & editing, Writing – original draft, Conceptualization. **Fernando Cázarez-Márquez:** Writing – review & editing, Writing – original draft, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

## Acknowledgements

We, the authors, thank David Hazlerigg and Shona Wood for their feedback and support. Thanks also to Yoshi.

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