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Endocrine drivers of photoperiod response

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Abstract

Life in a seasonally variable environment has evolved to interpret the time of year through day length (photoperiod) which is translated into a neurochemical signal. In mammals, the pars tuberalis is a key site where seasonal time signal (melatonin) interfaces and relays photoperiodic information to the hypothalamus via thyrotropin. Recent work has elucidated a potential circannual clock in 'calendar cells' of the pars tuberalis. In the hypothalamus, tanycytes are an integral part of the hypothalamic network. Previous studies show the importance of local synthesis of thyroid hormone and retinoic acid in tanycytes. Recently novel downstream neuroendocrine signals, e.g. VGF, FGF21 and chemerin, were identified to govern seasonally appropriate phenotype. Additionally, the hypothalamic-pituitary-growth axis has been implicated in seasonally bodyweight and torpor regulation. Here, we will focus on the endocrine drivers of photoperiod response and highlight novel downstream effects on bodyweight and growth focusing on recent findings from seasonal rodent studies.

Keywords

photoperiod, seasonal, hypothalamus, bodyweight, appetite, growth

Abbreviations

DIO2: deiodinase enzyme type 2
DIO3: deiodinase enzyme type 3
EYA 3: eyes absent 3
FGF21: fibroblast growth factor 21
LP: long photoperiod, summer day length (typically 16 h light : 8 h dark in experimental settings)
NMU: neuromedin U
POMC: pro-opiomelanocortin
PT: pars tuberalis
SCN: suprachiasmatic nucleus
SP: short photoperiod, winter day length (typically 8 h light : 16 h dark in experimental settings)
T3: tri-iodothyronine
T4: thyroxine
T2: di-iodothyronine
TSH: thyroid stimulating hormone, thyrotropin

1. Introduction

Life on earth has evolved for temporally variable environments, and in temperate regions this not only means the environmental influence of the daily light cycle, but the seasonally variable pressures that come with this. Consequently, many species have adapted seasonal plasticity in many life history traits, including energy balance, growth and reproduction. In terms of energy balance, in times of low food availability, some species gain weight, such as the Golden hamster (*Mesocricetus auratus*), or lose weight, such as the Siberian hamster (*Phodopus sungorus*); and many species time their reproductive capacity so that offspring are born during plentiful food supply [1]. These processes are under neuroendocrine regulation and have many upstream pathways in common, and thus understanding the processes by which seasonal species regulate such pathways (which also exist in human) will help understand physiology and will help to develop novel interventions for

human disease. This review will focus on the endocrine drivers of photoperiod response and the downstream effects on energy balance and growth, in particular focusing on recent insights from seasonal rodent studies.

2. Regulators of bodyweight change

2.1 Melatonin is the seasonal cue

As the most consistent indicator of circannual timing, day length (photoperiod) is the seasonal cue, translated neurochemically by the release of melatonin from the pineal gland during darkness. In mammals, this is mediated by light input through the eye and via the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) in the hypothalamus [reviewed extensively in [2, 3]. Briefly, melatonin acts on the *pars tuberalis* (PT), a thin sheath of vascularised tissue connecting the base of the brain with the anterior pituitary, to regulate thyrotropin (thyroid stimulating hormone, TSH) release to the third ventricle of the hypothalamus. In short photoperiod (SP, winter day length) the duration of melatonin signal effectively abolishes secretion of TSH from the PT, whereas in long photoperiod (LP, summer day length) the short duration of melatonin signal is permissive for TSH release [4-6] (Figure 1). Despite this key role, after a prolonged period of exposure to SP, seasonal animals begin to recover from their winter state and reverse the SP phenotype, deemed the photorefractory response [e.g. 7, 8], and indicative of a circannual clock. Work in sheep demonstrates transcriptional regulation by a D element in the promotor of *TSH* which is activated by the circadian transcription factor thyrotroph embryonic factor (TEF) and the rapid induction of eyes absent 3 (*Eya3*) in the PT under LP [9]. This circannual regulation has further elucidated thyrotrophic so-called calendar cells in the PT appearing to be under long-term transcriptional regulation, with a binary switch in expression of EYA3 [10], together indicating that the PT may be the site of an endogenous circannual clock [reviewed in 11]. Pinealectomised European hamsters (*Cricetus cricetus*) can entrain to photoperiod in the absence of melatonin [12] and recent work demonstrates that in these hamsters, TSH rhythm and photoperiod appropriate phenotype remains intact; likely receiving input from the SCN to entrain circannual rhythm in the PT in the absence of melatonin [13]. Together this demonstrates that although key to signalling time of year, the melatonin-TSH pathway may have evolved redundancy in order to prepare for return to LP summer conditions.

2.2. Hypothalamic thyroid hormone is the gatekeeper for photoperiod regulated phenotype

Studies in a variety of seasonal species have demonstrated that TSH regulates availability of thyroid hormone in the hypothalamus by driving expression of deiodinase enzyme *Dio2* in LP, to catalyse conversion between biologically active (triiodothyronine, T3) and inactive thyroid hormones (thyroxine, T4) [4, 14-19]. Species-specific differences exist [2], for example in photoperiod-sensitive F344 rats, TSH not only increases *Dio2* expression, but also decreases *Dio3* expression, which converts T4 or T3 to its biologically inactive form T2 (diiodothyronine) [20]. Key loci for *Dio2* and *Dio3* expression in the hypothalamus are the tanycytes, specialised glial cells that line the third ventricle of the hypothalamus and extend into appetite regulating nuclei (Figure 1). Tanycytes have been characterised as important structural and supporting cell types with their proliferation and differentiation contributing to long-term regulation of energy balance [21]. Tanycytes are a diet-responsive stem cell niche and we have recently discussed how they might contribute to increased hypothalamic cell proliferation and neurogenesis in SP, a common response amongst seasonal species [2].

Interestingly, a new study has shown that T3 also suppresses torpor, a controlled hypometabolic state during the normal rest phase, in Siberian hamsters [22]. It is well established that Siberian hamsters (among many small mammals) lose bodyweight and exhibit daily torpor to reduce appetite in anticipation of low food availability in winter [23, 24]. However, the mechanism by which appetite reduction is mediated is still debated. An exciting new development is the genome sequencing of *P. sungorus* [25], and subsequent transcriptomic analysis comparing hamsters adapted to LP and SP [26]. Many differentially expressed transcripts in the hypothalamus of Siberian hamsters housed in either LP or SP were found. Of note was pro-opiomelanocortin (*Pomc*), the precursor for α-melanocyte-stimulating hormone (α-MSH), a key appetite suppressing peptide. Bao and colleagues identified thyroid-receptor 1b binding motifs in the proximal promotor of *Pomc,* suggesting that T3 regulates *Pomc* expression through this thyroid hormone response element. However, *in vitro* assays did not show altered transcriptional activation on treatment with T3, suggesting it is only part of the multiple downstream effects of altered hypothalamic thyroid axis tone.

2.3. Changes in downstream pathways are required to regulate physiological response to photoperiod

Amongst these downstream pathways, the retinoic acid signalling pathway is a key intermediate in the effects of photoperiod with retinoic acid signalling genes localised in tanycytes and adjacent hypothalamic areas [27-29]. In F344 rats, Golden and Siberian hamster, retinoic acid signalling genes are upregulated in LP in a melatonin-dependent manner [27, 29]. Retinoic acid signalling is downstream of thyroid signalling, given that *in vivo* and *ex vivo* experiments in rats have shown that *Raldh1*, encoding the rate limiting enzyme for retinoic acid synthesis, increases in response to T4 [30]. It is important to note here that a recent RNAseq study in LP, SP and thyroidectomised sheep failed to detect changes in retinoic acid signalling genes in response to photoperiod [31] thus this might be a feature exclusive to rodents.

Other pathways also profoundly respond to photoperiod in the hypothalamus. A microarray analysis of photoperiod-regulated genes in the hypothalamus of F344 rats provided first evidence of the complexity of the photoperiodic response in mammals [32]. In F344 rats and Siberian hamsters, the Wnt/β-Catenin pathway has been identified as part of the photoperiodic response with high levels of Wnt signalling genes in LP and low levels in SP [27, 33, 34]. However, these changes seem to be independent of TSH but are regulated by NMU in F344 rats [20]. Recent advances in hypothalamic Wnt signalling are discussed in detail elsewhere [35].

Recent studies have highlighted VGF nerve growth factor as a critical signal downstream of thyroid hormone signalling. VGF is a neuropeptide precursor involved in energy metabolism and synaptic plasticity. In non-photoperiodic rats and mice, fasting increases hypothalamic expression of *Vgf* mRNA and this effect is blocked by leptin [36]. T3 decreases *Vgf* expression *in vitro* and in SP Siberian hamsters [37] and over expression of VGF in the hypothalamus reduces bodyweight accompanied with a decrease in energy expenditure [38]. Furthermore, a new study focusing on the VGF-derived peptide TLQP-21 demonstrates reduced food intake and increased energy expenditure in SP but not in LP Siberian hamsters after peripheral injections [39]. Whether it has a photoperiodic role in other species remains to be confirmed, but if substantiated it might provide a novel link to seasonal regulation of adiposity.

A metabolic hormone that has gathered recent interest in the field of seasonal biology is fibroblast growth factor 21 (FGF21) which is a fasting stimulated hormone produced largely by the liver, adipose tissue and the pancreas, as well as skeletal muscle and testes to a lesser extent [40, 41]. FGF21 has been implicated in a PPARα-FGF21 pathway to enhance torpor in mice [42]. There is evidence that FGF21 can both inhibit and stimulate lipolysis [43], and recent work has implicated tanycyte FGF21 in the central regulation of whole body lipid homeostasis [44]. In Siberian hamsters, FGF21 is suppressed in SP, and increased with access to a running wheel [45] and FGF21 treatment causes weight loss in LP hamsters, likely through increased energy expenditure, while leaner SP hamsters are protected from excess weight loss [46], and this appears to be due to lowered adiposity rather than photoperiod effects [47].

A promising candidate linking photoperiod-mediated changes in the hypothalamus to energy balance is the adipokine chemerin, demonstrated in studies in F344 rats. Chemerin is an inflammatory chemokine, encoded by the gene *Rarres2*, involved in inflammation, adipogenesis, angiogenesis and energy metabolism [48]. Administration of retinoic acid to the third ventricle increases *Rarres2* expression in tanycytes [49]. Chemerin is strongly regulated by photoperiod and importantly, intracerebroventricular administration causes process extension and proliferation of tanycytes accompanying increased bodyweight and food intake. Current evidence suggests that tanycytes release chemerin since *Rarres2* mRNA is locally expressed in tanycytes [49]. Given that chemerin is linked with energy homeostasis [48], understanding chemerin signalling will help further elucidate the role of tanycytes linking photoperiod and metabolic phenotype. This might include additional inflammatory markers since photoperiod regulation of NFκB, the master regulator of inflammation, is higher in SP F344 rats [50].

Taken together recent data indicate that early events in the photoperiodic response in the hypothalamus involve are range of pathways. Downstream of these events are changes in inflammatory signals [49, 50] and neurogenesis [2]. However, a gap in our knowledge is how the changes in these pathways in tanycytes link to the pathways regulating energy balance and growth in the hypothalamus and how they regulate physiological output such as energy balance and growth.

3. Implication of the hypothalamic-pituitary-growth axis in seasonally appropriate bodyweight and torpor regulation

Recent work has implicated the role of the growth axis in regulation of seasonally appropriate bodyweight and torpor induction in the Siberian hamster [51-53]. Seasonal rhythms of growth hormone exist in many species [54-56], and in the Golden hamster, growth axis regulation of photoperiod appropriate bodyweight has been suggested since the 1990s [57-59]. Altered expression of growth axis components within the hypothalamus has been demonstrated many times in Siberian hamsters and F344 rats [17, 45, 60, 61]. The release of growth hormone from the pituitary is regulated by growth hormone-releasing hormone and somatostatin, which are produced in the hypothalamus and stimulate and inhibit secretion of growth hormone, respectively. Siberian hamsters housed in SP have reduced fat and lean mass [51, 62, 63], and administration of the somatostatin antagonist pasireotide causes loss of both lean and fat mass in LP hamsters and inhibits LP stimulated growth in hamsters previously housed in SP [51]. Pasireotide does not alter tanycyte expression of *Dio2* and *Dio3* or photoperiod appropriate pelage, which is regulated at pituitary lactotrophs by melatonin [64], indicating intact photoperiod perception. This is in keeping

with the exercise stimulated growth that SP Siberian hamsters demonstrate with free access to a running wheel [45, 65]. This growth effect is inhibited by pasireotide treatment [52], demonstrating a key role for the growth axis in regulating exercise stimulated weight gain. In each of these studies, food intake was not measured, but it is reasonable to speculate an increase to drive weight gain. An unexpected result of these experiments was the action of pasireotide to enhance likelihood to enter torpor and torpor bout length [53], and treatment with selective somatostatin agonist octreotide suggests torpor effects at the $SSTR_5$ receptor which is highly expressed in the pituitary.

4. Conclusion

Despite considerable progress in the last decade identifying multiple pathways underlying the neuroendocrine driven changes in seasonal physiology, little is known about how these pathways drive downstream physiological functions. Novel markers recently identified in seasonal rodents shine new light on the complexity of photoperiod control of energy balance and growth. Without doubt, recent advances in gene editing will provide the molecular tools to dissect the pathways further and decipher their relevance in seasonal physiology. Studies of seasonal animals will provide new perspectives of the neuroendocrine regulation of energy metabolism and will help to explain long-term appetite and bodyweight cycling even in humans.

Figure legend

Figure 1: Neuroendocrine drivers of photoperiod. In short photoperiod (winter), the long duration of pineal melatonin signal inhibits the release of thyroid stimulating hormone (TSH) in the pars tuberalis. In long photoperiod (summer) thyroid stimulating hormone (TSH) is released into the median eminence (ME), a process which is coordinated by the photoperiod-responsive transcription factor EYA3. TSH increases the expression of Dio2 in the tanycytes lining the third ventricle to catalyse the conversion of inactive thyroid hormone T4 to biologically active thyroid hormone T3. Increased T3 regulates key downstream pathways resulting in appropriate seasonal phenotypes.

Conflict of interest statement

Nothing declared.

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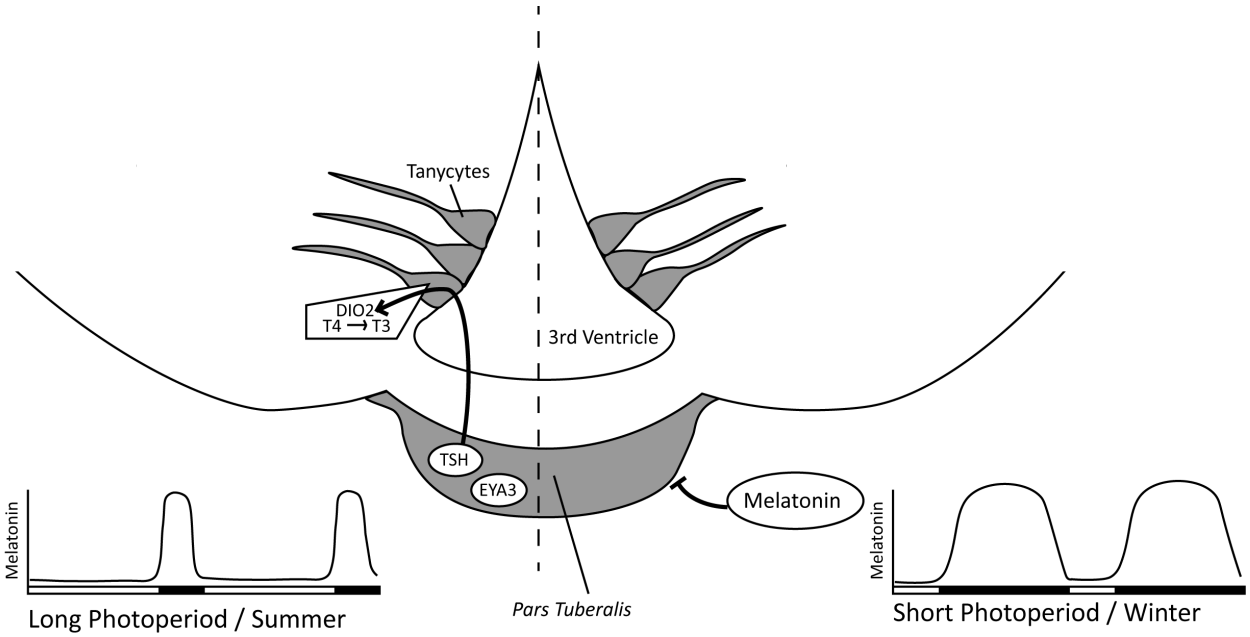

Conflict of Interest statement

We have no competing interests to declare.

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