COMMENTARY

Photoperiodic regulation of prolactin secretion: changes in intra-pituitary signalling and lactotroph heterogeneity

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Abstract

Many mammalian species utilise day-length (photoperiod) to adapt their physiology to seasonal changes in environmental conditions, via secretion of pineal melatonin. Photoperiodic regulation of prolactin secretion is believed to occur via melatonin-mediated changes in the secretion of a putative prolactin secretagogue, tuberalin, from the pituitary pars tuberalis. Despite the *in vivo* and *in vitro* evidence in support of this intra-pituitary signalling mechanism, the identity of tuberalin has yet to be elucidated. This paper reviews recent advances in the characterisation of tuberalin and the regulation of its secretion. Furthermore, the hypothesis that pituitary lactotroph cells display heterogeneity in their response to changing photoperiod and tuberalin secretion is examined.

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Introduction

Regions of extreme latitude are subject to marked changes in environmental conditions. In order to maximise survival, many mammalian species utilise changing annual day-length (photoperiod) to adapt their physiology in anticipation of these environmental changes. The master circadian clock, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, integrates photoperiodic information (reviewed in Schwartz *et al.* 2001) and continues to reflect ambient day-length even after many months of exposure to constant photoperiod (Carr *et al.* 2003). The SCN innervates the pineal gland via a polysynaptic neural pathway to drive rhythmic, nocturnal secretion of melatonin, the duration of which varies in proportion to the length of the night. Altered melatonin signal duration is then interpreted by target tissues to drive downstream changes in physiology.

In seasonal mammals, photoperiod drives robust rhythms of prolactin secretion from the pars distalis (PD) region of the adenohypophysis. Prolactin secretion peaks during the summer months and reaches a nadir during the winter. Circulating prolactin concentration primarily regulates seasonal changes in pelage, but also has important effects on reproductive status, along with other aspects of physiology and behaviour (reviewed in Lincoln 1989). It was initially thought that melatonin might regulate prolactin secretion via altered release of hypothalamic factors (e.g. dopamine, noradrenaline). However, this mechanism is now not believed to be a major contributory factor (Steger & Bartke 1991, Badura & Goldman 1992, Lincoln & Clarke 2002).

Compelling *in vivo* evidence for a novel, intra-pituitary mechanism of prolactin regulation came from the hypothalamo–pituitary disconnected (HPD) ram, which bears a surgical lesion of the neural connection between pituitary and hypothalamus, leaving the pituitary circulation intact. Photoperiodic prolactin regulation persists in these animals, suggesting that melatonin acts directly at the level of the pituitary gland to drive changes in prolactin secretion (Lincoln & Clarke 1994). It was subsequently demonstrated that hamsters bearing hypothalamic lesions exhibited normal prolactin rhythms, despite loss of their reproductive response to photoperiod (Maywood & Hastings 1995). These key studies formed the basis of the 'dual site' hypothesis, whereby melatonin acts at the level of the hypothalamus to drive reproductive rhythms, but directly within the pituitary to regulate changes in prolactin secretion (Fig. 1).

The pars tuberalis (PT) and tuberalin

The pituitary PT is a thin layer of the adenohypophysis that surrounds the pituitary stalk and extends rostrally along the ventral surface of the median eminence. It therefore lies in close proximity to the primary plexus of pituitary portal vasculature, an ideal position from which

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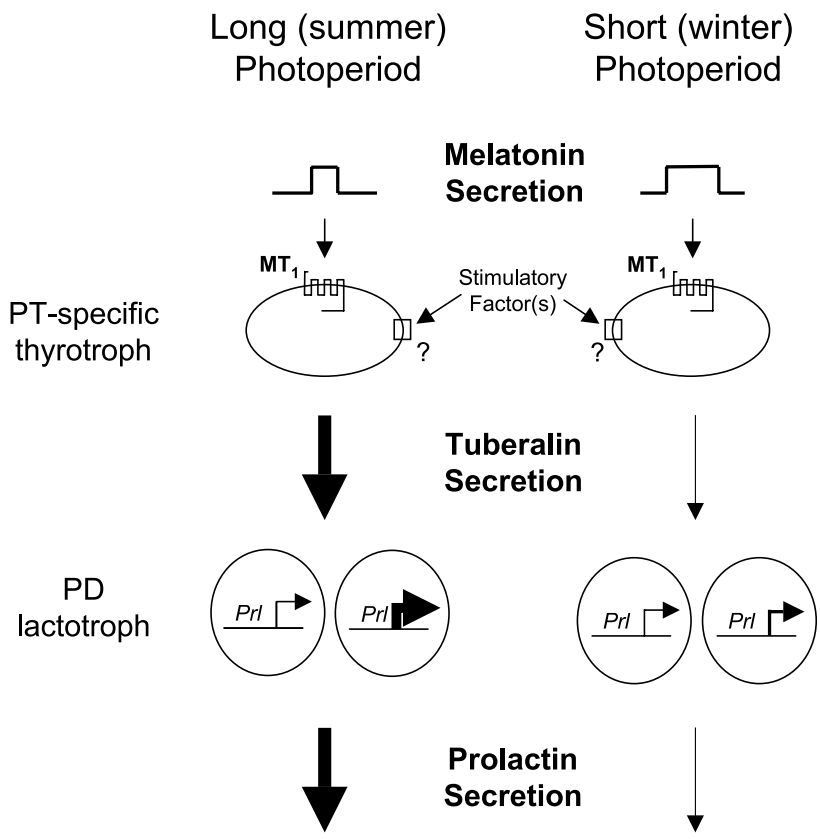

Figure 1 A model of intra-pituitary mechanisms driving photoperiodic prolactin secretion. Melatonin binds to MT_1 receptors expressed on PT-specific thyrotrophs. The duration of the nocturnal melatonin signal is decoded, through the regulation of circadian clock genes and/or sensitisation, to modulate the stimulation of PT by an endogenous agonist (e.g. adenosine or PACAP). This mechanism regulates the secretion of tuberalin, which stimulates prolactin promoter activity in a subpopulation of lactotrophs, leading to an increase in mRNA expression and hormone secretion. PRL, prolactin.

to modulate the activity of cells in the distal pituitary gland. The PT consists of three main cell types; PD-like endocrine cells, follicular cells and 'PT-specific' cells, which are thyrotrophs morphologically distinct from those found in the PD (reviewed in Wittkowski *et al.* 1999). Seasonal changes in the physiology of PT-specific cells (e.g. Merks *et al.* 1993) are also induced by melatonin administration (Bockers *et al.* 1995), suggesting that the function of the PT is dependent on photoperiod-driven melatonin signal duration (additional references in Wittkowski *et al.* 1999).

High affinity binding sites for the radioligand [^{125}I]iodomelatonin have been detected in the PT of most species examined (reviewed in Morgan *et al.* 1994), suggesting that it is an important melatonin target tissue. There are two major subtypes of mammalian melatonin receptor, termed MT_1 and MT_2 (previously Mel_{1a} and Mel_{1b}; reviewed in Reppert *et al.* (1996)), of which MT_1 is the dominant pituitary subtype (Weaver *et al.* 1996, von Gall *et al.* 2002). Despite transient expression of MT_1 receptors in neonatal pituitary gonadotrophs (Johnston *et al.* 2003*b*), co-localisation studies have shown that MT_1 is only expressed in the PT-specific thyrotroph cells in adult rodents (Klosen *et al.* 2002, Dardente *et al.* 2003).

The restriction of melatonin receptor expression to the PT in the adult pituitary (Morgan *et al.* 1994), together with the inability of melatonin to directly regulate either prolactin gene expression or secretion in PD cultures (Stirland *et al.* 2001), is consistent with the hypothesis that melatonin drives seasonal changes in prolactin secretion via altered secretion of a PT-derived prolactin secretagogue(s). This hypothesis was supported by the demonstration that ovine PT cells secrete a peptide(s), termed tuberalin, that stimulates prolactin secretion from primary cultures of PD cells (Hazlerigg *et al.* 1996, Morgan *et al.* 1996). Tuberalin secretion was subsequently demonstrated from bovine (Lafarque *et al.* 1998) and hamster (Stirland *et al.* 2001) PT cells, indicating conservation of this PT function between

species. Two key challenges that arose from these observations were to identify tuberalin and also understand the cellular and molecular mechanisms that regulate its secretion.

The extensive list of secretory molecules expressed in PT-specific cells (reviewed in Wittkowski *et al.* 1999) has recently been extended (D'Este *et al.* 2000, Guerra & Rodriguez 2001). However, the ability of many of these molecules to fulfil the putative physiological role of tuberalin has not been rigorously examined. In order to partially characterise the chemical nature of tuberalin, different groups have utilised size fractionation of PT-conditioned medium. It has been suggested that bovine tuberalin is >30 kDa, based on Percoll gradient separation (Lafarque *et al.* 1998). By contrast, exclusion filtration studies indicate that ovine tuberalin is <1 kDa in size (Graham *et al.* 2002). This discrepancy may be due to interspecies differences in tuberalin identity, or contamination of PT-conditioned medium by factors of hypothalamic or serum origin present in primary PT cell cultures. Irrespective of this, the identity of tuberalin remains elusive and to date no candidate molecules have been identified that are both regulated by melatonin and able to stimulate prolactin secretion.

Regulation of tuberalin secretion

In the PT, melatonin acutely inhibits the stimulation of cAMP-dependent signal transduction (reviewed in Hazlerigg *et al.* 2001). Furthermore, melatonin also acutely inhibits the ability of forskolin, a pharmacological stimulator of adenylyl cyclase activity, to increase tuberalin secretion *in vitro* (Morgan *et al.* 1996, Stirland *et al.* 2001, Graham *et al.* 2002). Together, these data suggest that cAMP-mediated pathways play an important role in regulating tuberalin secretion.

Critical to the model described in Fig. 1, tuberalin secretion from the hamster PT is dependent upon prior photoperiod exposure (Stirland *et al.* 2001, Johnston *et al.* 2003*a*). However, the mechanisms by which melatonin signal duration drives PT physiology are poorly understood. Prolonged (6–24 h) incubation of PT cell cultures with melatonin sensitises subsequent stimulation of cAMP (Hazlerigg *et al.* 1993, von Gall *et al.* 2002), probably resulting from changes in tyrosine phosphorylation of adenylyl cyclase (Barrett *et al.* 2000). This had fuelled speculation that melatonin signal duration may modulate the induction of cAMP by stimulatory factor(s), such as pituitary adenylyl cyclase-activating polypeptide (PACAP) or adenosine (Barrett *et al.* 2002, von Gall *et al.* 2002). Over a range of melatonin signal duration that mimics change from long to short photoperiod, the sensitisation of PT cells *in vitro* increases in proportion to the duration of melatonin incubation (Hazlerigg *et al.* 1993). However, decreased tuberalin secretion and amplitude of cAMP-responsive gene expression on short days suggests that longer melatonin signals result in decreased cAMP levels *in vivo*. This apparent paradox has yet to be resolved.

A separate avenue of research has provided evidence that altered phasing and/or amplitude of circadian clock gene expression within the PT decodes melatonin signal duration (Messager *et al.* 1999, Lincoln *et al.* 2002, Johnston *et al.* 2003*a*). This topic is the subject of a recent review (Lincoln *et al.* 2003).

Unmasking the enigma: how might tuberalin be identified?

Despite these recent advances in the understanding of PT physiology, the identity of tuberalin remains unresolved. Due to the small size of the rodent PT, previous attempts to identify this enigmatic factor(s) have relied upon studies of secretory products from the PT of larger ungulate species. However, even in these animals, PT explants contain median eminence nerve terminals, and therefore it is likely that PT-conditioned medium will be contaminated by hypothalamic factors (Graham *et al.* 2002). In order to progress with this line of research, it would thus be preferable to first generate a population of PT cells that is independent of hypothalamic input. One solution to this problem would be to generate a PT-derived cell line by one of a number of established *in vivo* and *in vitro* immortalisation techniques (e.g. Mellon *et al.* 1991, Katakura *et al.* 1998). PT secretion from these cells could then be compared in various experimental conditions, such as the presence of forskolin with or without melatonin. However, a major drawback of this approach is the uncertainty that the immortalised cells will retain the same physiology as PT cells *in vivo*. An alternative solution would be to compare PT secretory products from primary PT cells derived from HPD rams exposed to appropriate photoperiodic conditions. However, the generation of HPD animals requires complex surgery and therefore can only generate a finite number of PT cells for experimentation.

Rather than analysis of secreted products from the PT, future experiments could take advantage of more recent molecular techniques, such as differential display and microarray technology, to identify genes expressed in the PT in a photoperiod-dependent manner. To be successful, these experiments would rely upon photoperiodic tuberalin regulation occurring at the level of mRNA expression and not merely secretion. Furthermore, if tuberalin is a low molecular weight molecule, as predicted from recent studies of the ovine PT (Graham *et al.* 2002), it is possible that such an approach would not identify mRNA for tuberalin itself. In this instance, one might hypothesise that the gene(s) identified would instead encode enzyme(s) involved in tuberalin biosynthesis.

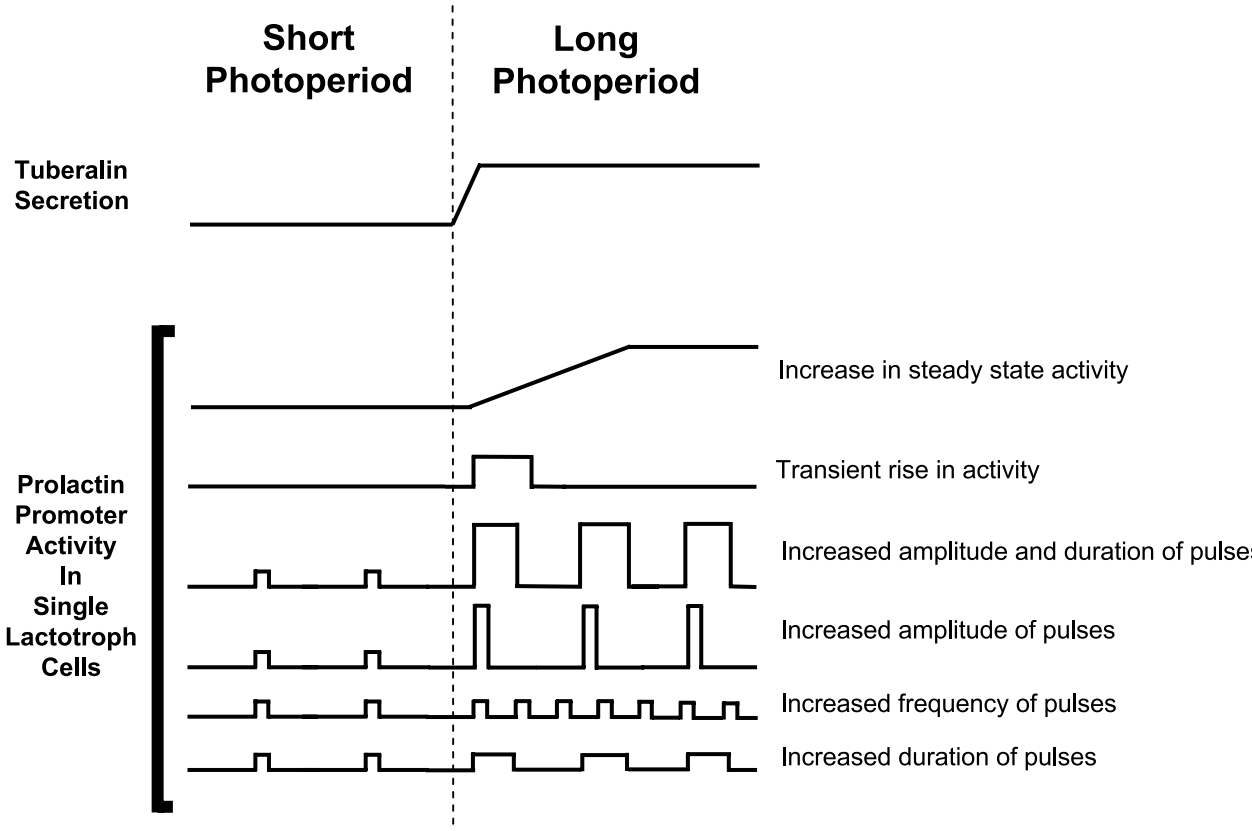

Figure 2 Schematic representation of putative heterogeneity in prolactin promoter stimulation by tuberalin. It is hypothesised that some lactotroph cells will be unresponsive to tuberalin, while others will show altered steady-state or phasic prolactin promoter activity.

The identification of tuberalin will provide the opportunity for a number of additional studies. Within the field of seasonal endocrinology, it would be of interest to determine whether the identity of tuberalin is conserved amongst photoperiodic mammals. Since the photoperiodic regulation of prolactin secretion is regarded as an 'ancient' aspect of physiology (Lincoln 1999), it might be predicted that the identity of tuberalin would be conserved between species. Additionally, a specific assay for tuberalin synthesis/secretion would provide an important endocrine endpoint to aid studies attempting to understand the decoding of melatonin signal duration by the PT. Such experiments would enable direct examination of the hypothesis that the photoperiodic changes in circadian clock gene expression are directly associated with the endocrine activity of the PT. This line of experimental analysis is currently under active consideration. Finally, in a wider endocrine context, one might also determine if tuberalin is secreted from, or acts upon, any other regions of the neuroendocrine system, distinct from the intra-pituitary regulation of prolactin secretion. The ability of PT-conditioned medium to stimulate c-*fos* expression in non-lactotroph cells (Morgan *et al.* 1996) suggests that tuberalin may play a role in multiple neuroendocrine pathways.

Photoperiodic changes in prolactin transcription and lactotroph heterogeneity

Photoperiodic changes in prolactin secretion are accompanied by robust changes in pituitary prolactin mRNA expression (Hegarty *et al.* 1990, Stirland *et al.* 2001), which may result from changes in either gene transcription or mRNA degradation (Khodursky & Bernstein 2003). Recent studies have shown that both ovine and hamster PT-conditioned media stimulate a prolactin-luciferase reporter construct transfected into lactotroph cells (Stirland *et al.* 2001, 2003, Johnston *et al.* 2003*a*), suggesting that transcriptional regulation may be a key factor driving photoperiodic prolactin mRNA expression.

Heterogeneity of lactotroph physiology is well established (reviewed in Lamberts & MacLeod 1990). However, the cellular mechanisms underlying the regulation of individual endocrine cells by photoperiod are poorly

understood. A study of freshly dispersed hamster PD cells revealed heterogeneity of prolactin mRNA expression in animals housed under both long and short photoperiod (Johnston *et al.* 2003*c*). Despite a large overall change in the frequency distribution of prolactin mRNA expression per cell, a similar number of low-expressing cells were observed in both photoperiods suggesting that there may be heterogeneity in the response of lactotrophs to photoperiod. This hypothesis is consistent with the observation that tuberalin is only able to activate c-*fos* expression in a subpopulation of ovine lactotroph cells (Morgan *et al.* 1996). Additional heterogeneity may result from regional differences in tuberalin secretion into the portal vasculature, as has been previously reported for hypothalamic dopamine (Reymond *et al.* 1983). Together, these findings suggest a novel dimension to lactotroph heterogeneity in seasonal mammals.

Individual lactotroph cells exhibit phasic, temporal variation in prolactin gene expression (Takasuka *et al.* 1998, Villalobos *et al.* 1999, Shorte *et al.* 2002, Stirland *et al.* 2003). Individual cells exhibited heterogeneous temporal profiles of promoter activity and also qualitative differences in promoter regulation by prolactin secretagogues; some cells exhibit gradual changes in promoter activity whereas others respond with bursts of transient promoter activity (Takasuka *et al.* 1998, Villalobos *et al.* 1999, Stirland *et al.* 2003). Given these findings, it is therefore plausible that some hamster pituitary cells reported as expressing low levels of prolactin mRNA (Johnston *et al.* 2003*c*) are actually in a stimulated state, but responded to changing photoperiod with altered temporal patterns of gene expression. In this instance, the timing of pituitary collection and dispersion would influence the mRNA expression profiles obtained. Use of viral transfection technology now permits the efficient transfection of reporter constructs into primary cells (Stirland *et al.* 2003). Pituitary cell transfection, coupled with real-time promoter analysis, could therefore greatly extend our understanding of the regulation of lactotroph physiology by photoperiod and more accurately define the heterogeneity of response of lactotroph cells to changing photoperiod and tuberalin secretion (Fig. 2). Such studies, coupled with the identification of tuberalin and its regulatory mechanism(s), would fully substantiate the 'dual site' hypothesis and also reveal how a novel intra-pituitary signalling mechanism can alter lactotroph cell heterogeneity.

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