The pars tuberalis of the pituitary: a gateway for neuroendocrine output

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The pars tuberalis is a structurally distinct region of the adenohypophysis, the function of which has been unclear for decades. Recent studies, which demonstrate the localization of melatonin receptors on the pars tuberalis, suggest a photoperiodic function. The principal cell type of the pars tuberalis is morphologically distinct from others in the pituitary and is thought to secrete a specific product. In support of this, evidence is emerging that ovine pars tuberalis cells secrete a factor (‘tuberalin’) that exerts hormonal control over both gene expression and prolactin release from the pars distalis lactotrophs. These data in conjunction with physiological studies, which show that photoperiodically driven cycles in prolactin secretion can occur in the absence of an intact hypothalamic–pituitary axis, suggest that the function of the pars tuberalis is to act as an endocrine intermediate in the photoperiodic effects of melatonin on prolactin secretion. Studies of the cellular biochemistry of the ovine pars tuberalis suggest that the main function of melatonin is to prevent or terminate transcriptional and translational activation by an unidentified factor (Stim X). On the basis of these physiological and biochemical studies, a hypothetical model is proposed to account for the mechanism of photoperiodic regulation of prolactin secretion by melatonin.

The mammalian adenohypophysis has three discrete parts, based upon morphological, functional and developmental criteria. These are the pars distalis, the pars intermedia and the pars tuberalis (Fig. 1). While our understanding of the endocrine functions of the pars distalis and pars intermedia are well established, the role of the pars tuberalis has remained a conundrum. Its main function has long been thought to be as a support gland for the pars distalis, supplementing endocrine output during times of high demand (Stoeckel and Porte, 1984). However, recent findings that melatonin receptors are localized on the cells of the pars tuberalis, but are absent from the cells of the pars distalis of adult sheep, hamsters and rats, have prompted reassessment of its endocrine function (Morgan et al., 1994a). Such studies have confirmed the contention that the pars tuberalis has an endocrine role distinct from that of the pars distalis. This review considers the structure and function of the pars tuberalis, and reflects on its role as an endocrine mediator of the photoperiodic effects of melatonin.

Cytochemical features of the pars tuberalis and response to photoperiod

The pars tuberalis is composed of three cellular phenotypes (Dellman et al., 1974; Stoeckel and Porte, 1984). The first of these have been called ‘pars tuberalis-specific’ cells as they are ultrastructurally distinct from any of the cells found in the pars distalis. These cells contain well-developed rough endoplasmic reticulum and Golgi bodies, indicative of peptide or protein secretion, yet in almost all species, with the exception of mice, there is a notable paucity of dense core storage (secretory) granules. Another characteristic of the pars tuberalis-specific cells is the presence of variable amounts of glycogen particles, which appear ontogenetically before secretory granules. This diagnostic feature has enabled the unequivocal identification of the pars tuberalis during early development (Dellman et al., 1974; Stoeckel and Porte, 1984). The second type of cells are pars distalis-like cells, which are identical to the trophic cells of the pars distalis in terms of ultrastructure and immunocytochemical features. In general, these cells are a mixture of gonadotrophs and thyrotrophs, although the exact proportion of each is highly species specific (Gross, 1984). The occurrence of other trophic cell types from the pars distalis has been noted in some species, but they are much less common (Gross, 1984; Tillet et al., 1990; Bockers et al., 1996). The third cell type are follicular cells, which are generally smaller than either the pars tuberalis-specific or pars distalis-like cells, and are similar to the folliculo-stellate cells of the pars distalis (Dellman et al., 1974; Stoeckel and Porte, 1984). The morphology of the follicular cells shows no sign of secretory activity (Stoeckel and Porte, 1984). The pars tuberalis-specific cells are the most abundant of the cell types and are mainly concentrated in the rostral–dorsal region of the gland, whereas the pars distalis-like cells occur in the ventral region adjacent to the pars distalis (Fig. 1). The follicular cells are interdispersed throughout the gland (Dellman et al., 1974; Stoeckel and Porte, 1984; Bockers et al., 1996).
Attempts to characterize the pars tuberalis-specific cells by immunocytochemistry have further emphasized the difference between these cells and those of the pars distalis. Immunocytochemical studies on a number of species, including sheep, rabbits, mice, rhesus monkeys and guinea pigs, show that most secretory cells in the pars tuberalis do not contain hormones produced by the pars distalis (Gross, 1984; Bockers et al., 1996). While in rats and hamsters most of the pars tuberalis secretory cells are immunoreactive for thyrotrophin-stimulating hormone (TSH), closer analysis of their morphology indicates that these cells should not be classified as bone fide thyrotrophs (Wittkowski et al., 1992). The functional significance of this TSH-like immunoreactivity remains to be established.

A consistent feature of pars tuberalis-specific cells across different species is the presence of the glycoprotein hormone α-subunit (Stoeckel et al., 1993, 1994; Bockers et al., 1994; Bockmann et al., 1996). In situ hybridization and immunocytochemical studies reveal that both the mRNA and protein are expressed in pars tuberalis-specific cells of sheep, rats, mice and hamsters (Bockers et al., 1994; Stoeckel et al., 1994; Bockmann et al., 1996). The protein has also been detected in pars tuberalis-specific cells of guinea-pigs (Stoeckel et al., 1994).

These results suggest that pars tuberalis-specific cells synthesize and secrete glycoprotein hormones, although β-subunit has been identified (Bockers et al., 1994; Stoeckel et al., 1994). On the basis of immunocytochemical studies in sheep, it seems unlikely that this could be the β-subunit of LH, FSH or TSH, as these are almost absent from the pars tuberalis-specific cells. LHβ is localized to the caudal–ventral region of the sheep pars tuberalis where the pars distalis-like cells occur (Skinner et al., 1992; Bockers et al., 1996), and this distribution closely matches the localization of GnRH receptors, visualized using the radioligand 125I-labelled [Des-Gly10(Δ-Ala6)]-GnRH (Morgan et al., 1994b). The expression of the mRNA encoding LHβ and the protein in the specific cells of the ovine pars tuberalis remains contentious. While one study has reported that mRNA encoding LHβ is expressed throughout the ovine pars tuberalis and that its expression is influenced by photoperiod (Pelletier et al., 1992, 1995), another suggests that expression is restricted to the ventral–caudal region and is dependent on photoperiod (Bockers et al., 1996). The latter is consistent with the localization of LHβ protein, and suggests that LHβ expression is restricted to pars distalis-like cells within the pars tuberalis (Tillet et al., 1990; Bockers et al., 1996).

**Ontogeny of pars tuberalis and appearance of melatonin receptors**

The morphological and functional distinction between the pars distalis and the pars tuberalis is apparent at the earliest stages of embryonic development. The pars tuberalis originates specifically from the lateral lobes of Rathke’s pouch, the adenohypophyseal primordium (Stoeckel and Porte, 1984). Ultrastructural studies in mice and rats demonstrate that the pars tuberalis is the first region of the adenohypophysis to show morphological signs of secretory activity. In rats this occurs at
about days 14–15 of gestation (Stoeckel et al., 1973; Stoeckel and Porte, 1984) and in mice at about day 12 of gestation (Stoeckel et al., 1979). The gonadotrophic cells, which are components of the adult pars tuberalis, are not found before 10 days after birth in either rats or mice, and are considered, therefore, as invasive elements (Stoeckel and Porte, 1984). In rats the mRNA encoding the α-subunit can first be detected at embryonic day (E) 12 of gestation within Rathke’s pouch, and by E13 it is exclusively present within the pars tuberalis primordium (Stoeckel et al., 1993). By day 14 of gestation the α-subunit protein is identifiable in the pars tuberalis by immunocytochemistry. The appearance of the mRNA encoding α-subunit and the protein within the pars tuberalis pre-dates the onset of its expression within the pars distalis at E16–17, demonstrating the early differentiation of pars tuberalis-specific cells within the pituitary.

Melatonin receptors, detected by the binding of 2-[125I]iodomelatonin, have been localized to the pars tuberalis of all mammals studied thus far, with the possible exception of humans (Morgan et al., 1994a). Under the light microscope the binding of 2-[125I]iodomelatonin is seen to overlie the pars tuberalis-specific cells of the rostral–caudal region, characterized by their agranular arrangement (Fig. 2).

Melatonin-binding sites first appear over the fetal pituitary at day 15 of gestation in rats (Williams et al., 1991) and from day 12 of gestation in fetal Siberian hamsters, which have an embryology comparable with that of mice (Rivkees and Reppert, 1992). The hypophyseal–portal system of rats does not develop until 4 days after birth (Glydon, 1937). Similarly in sheep fetuses, melatonin receptors have been identified over the developing pituitary from day 31 of gestation onwards (Fig. 3) (term = 145 days) (Helliwell and Williams, 1994), although the hypophyseal–portal system is not fully developed until day 45 of gestation (Levdiotis et al., 1989). Thus it appears that the potential influence of melatonin over the pars tuberalis occurs early in fetal life, and precedes the existence of a functional hypothalamic–pituitary unit. These results support the overall contention that, within mammals, the pars tuberalis has an important function with respect to the transduction of the melatonin signal.

### Melatonin receptors and intracellular signalling

Pharmacological studies show that 2-[125I]iodomelatonin binding sites found in the pars tuberalis are functional membrane bound receptors of the G-protein coupled superfamily of proteins (Morgan et al., 1994a). This has been confirmed recently by the cloning of the melatonin receptor from the ovine pars tuberalis (Reppert et al., 1994). Melatonin receptors mediate the inhibition of forskolin-stimulated cAMP accumulation in the pars tuberalis of sheep, hamsters, rats and mice (Morgan et al., 1994a), but alone melatonin has no effect on basal cAMP concentrations. This is probably due to the low turnover of cAMP in these cells (Barrett et al., 1996). Similarly, melatonin has no independent effects on a number of other signal transduction pathways, including the mobilization of calcium, the stimulation of inositol phospholipid breakdown, the activation of phospholipase D, or the activation of mitogen activated protein kinase (MAPK) (Morgan et al., 1991a; McNulty et al., 1994a; Hazlerigg et al., 1996). A major inference from these studies is that an unidentified factor (Stim X) is able to stimulate...
cAMP and possibly other signal transduction events in pars tuberalis cells in vivo. The main function of melatonin is to counteract the effect of this stimulus (Morgan et al., 1994a). However, no ‘natural agonist’ has been identified to stimulate cAMP in melatonin-responsive pars tuberalis cells, although many candidate compounds have been tested (Table 1). Both an adenosine A2 receptor (Stehle et al., 1992) and a novel MSH receptor (Barrett et al., 1994) have been cloned from sheep pars tuberalis, yet neither mediate strong activation of cAMP in pars tuberalis cells or appear to have a role related to melatonin in this gland (P.J. Morgan and P. Barrett, unpublished). Similarly, insulin-like growth factor I (IGF-I) receptors have been localized to the pars tuberalis of sheep, but not rats (Williams et al., 1996), and have been shown to activate MAPK in ovine pars tuberalis cells. However, there is no functional interaction with melatonin (Hazlerigg et al., 1996).

Several lines of evidence support a primary role for the cAMP pathway in the cellular mode of action of melatonin within the ovine pars tuberalis. Activation of the cAMP-dependent protein kinase by forskolin is attenuated by physiological doses of melatonin (Hazlerigg et al., 1991), and this in turn affects the phosphorylated state of the transcription factor CREB (cAMP response element binding protein) (McNulty et al., 1994b). These responses suggest that cAMP-dependent pathways lead to the activation of gene transcription in the ovine pars tuberalis and that such activation can be silenced or attenuated by melatonin (Fig. 4). Direct evidence for this comes from a study of the regulation of the expression of early response genes of the fos and jun families, which heterodimerize to form the AP-1 complex that activates gene transcription through the binding site of the DNA encoding AP-1. Consistent with the hypothesis that melatonin acts primarily to attenuate the effects of a forskolin-stimulated cAMP signal transduction cascade, both c-fos and jun B gene expression were found to be induced by forskolin, and attenuated by melatonin (A. Ross, P. Barrett and P.J. Morgan, unpublished). Thus it appears that a major function of melatonin within the pars tuberalis is to act as a ‘valve’ to regulate a hypothetical stimulatory input to the cell (‘Stim X’), which determines intracellular cAMP concentration and hence gene expression (Fig. 4).

Recent studies indicate that the cAMP–PKA–CREB cascade may not be the only mechanism by which gene activation can occur in ovine pars tuberalis cells. Forskolin also activates MAPK in ovine pars tuberalis cells, and this activation is reversed by melatonin (Hazlerigg et al., 1996). This response seems to involve phosphoinositide-3-kinase (PI3K), and is particularly noteworthy as, with the exception of PC12 cells, cAMP has not been shown to inhibit MAPK activity (Hazlerigg et al., 1996). The ability to activate MAPK through increasing the concentration of intracellular cAMP, and thus the ability to modulate this pathway by melatonin, implies that melatonin may also modulate gene expression through a serum response element (SRE) via a MAPK-Elk-1 pathway (Fig. 4).

Melatonin and pars tuberalis function

Electrolytic lesioning and intracerebral microimplant studies in rodents suggest that the influence of melatonin on seasonal physiology is exerted through a hypothalamic target site (Morgan et al., 1994b; Maywood and Hastings, 1995). This consensus is further supported by the fact that the effect of a change in photoperiod upon the gonadotrophic axis is not simply dependent upon the absolute duration of the dark period (that is, melatonin), but also upon its direction of change, indicating that an animal retains a memory of its previous photoperiodic history (Robinson and Karsch, 1987; Hastings et al., 1989). These factors in combination have made the brain the favoured site of melatonin action to mediate its photoperiodic effects. However, several lines of circumstantial evidence now suggest a role for the pars tuberalis. First, the pars tuberalis in Djungarian hamsters shows ultrastructural and immunocytochemical changes in response to changing photoperiod (Wittkowski et al., 1992). Second, 2-[125I]iodomelatonin binding sites are found only in the pituitary and not in the brain of ferrets (Weaver and Reppert, 1990), seasonal breeders with a highly developed photoperiodic response.

In sheep micro-implants of melatonin, placed within the medial basal hypothalamus, but not in the preoptic area, cause premature activation of the reproductive axis and suppression of plasma prolactin concentrations (Lincoln and Maeda, 1992a,b;
Malpaux et al., 1993). These data support those from studies in rodents which also emphasize the importance of the medial basal hypothalamus in the influence of melatonin on the reproductive axis (Glass and Lynch, 1981, 1982; Hastings et al., 1988). Whether melatonin acts locally within the medial basal hypothalamus or diffuses to adjacent areas, one of which would be the pars tuberalis, was resolved elegantly in a study involving disconnection of the pituitary from the hypothalamus at the median eminence in Soay rams (Lincoln and Clarke, 1994). Despite a difficult surgical procedure, when these animals were exposed to alternating blocks of 16 weeks of long (16 h light: 8 h dark) and short (8 h light:16 h dark) days, they continued to show photoperiod-sensitive changes in prolactin secretion (Lincoln and Clarke, 1994). Furthermore, rams held under long days and given melatonin implants showed a decline in serum prolactin (Lincoln and Clarke, 1994). It was established that the central control of prolactin release had been abolished, as these hypothalamo–pituitary disconnected (HPD) sheep showed clinical evidence of diabetes insipidus, gonadal regression and enhanced obesity. They also failed to show increased plasma prolactin concentrations in response to a range of provocation tests (stressors), and so it could be concluded that photo-periodically driven cycles in plasma prolactin occurred independently of the brain (Lincoln and Clarke, 1994). This series of experiments provides the first unequivocal demonstration that photoperiod, via melatonin, regulates seasonal plasma prolactin concentration within the pituitary. Given that the distribution of melatonin receptors is confined to the pars tuberalis of the adult sheep pituitary (Hellwell and Williams, 1992; Skinner and Robinson, 1995), these data suggest that the pars tuberalis is involved in mediating the seasonal changes in prolactin concentration. As the central drive from the GnRH neurons is lost in animals with hypothalamic–pituitary disconnection, it was not possible to determine whether the pars tuberalis influences the gonadotrophic axis. However, in another study on female sheep, melatonin implants were directly apposed to the pars tuberalis, and were found to have no effect on plasma LH concentrations, although the effect on prolactin was confirmed (Malpaux et al., 1994, 1995). This finding indicates that in sheep the control of seasonal gonadotrophin and prolactin output is controlled independently at different sites. Experiments on Syrian hamsters show that lesioning of the medial basal hypothalamus blocks the ability of short day duration infusions of melatonin to induce gonadal atrophy and to decrease blood concentrations of LH, but has no effect on the decline in serum prolactin. (Maywood and Hastings, 1995). As for sheep, these data support the contention that melatonin modulates the prolactin and gonadotrophin endocrine axes through independent sites. It may be concluded tentatively that melatonin acts on the pars tuberalis to modulate the output of prolactin from lactotrophins within the pars distalis, whereas the gonadotrophin response involves regulation through a site in the medial basal hypothalamus.

### Protein secretion by the pars tuberalis

The hypothalamic–pituitary disconnection studies on sheep by Lincoln and Clarke indicate that the pars tuberalis releases a factor that acts in an endocrine manner to modulate the output of prolactin from the pars distalis. The polypeptides secreted by pars tuberalis-specific cells have been studied by [35S]methionine labelling of pars tuberalis cells and resolution of the products by denaturing gel electrophoresis over the molecular mass range 14–100 kDa. Such studies show that pars tuberalis-cells actively synthesize and release several proteins within this molecular mass range (Morgan et al., 1992). Consistent with the action of melatonin in inhibiting forskolin-stimulated cAMP accumulation, forskolin increases the synthesis and secretion of a number of these proteins, and melatonin reverses this response. The major protein detected is a 72 kDa protein of unidentified sequence, designated p72 (Morgan et al., 1992, 1994b). However, for a product of the pars tuberalis to mediate

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**Table 1. Compounds tested for ability to increase cAMP in ovine pars tuberalis cells**

<table>
<thead>
<tr>
<th>Neuropeptides (1 µmol l⁻¹)</th>
<th>Amines (100 µmol l⁻¹)</th>
<th>Prostaglandins (100 µmol l⁻¹)</th>
<th>Others (10 µmol l⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH</td>
<td>Noradrenaline (3–4x)</td>
<td>PGE₃ (7–8x)</td>
<td>Adenosine (3–4x)</td>
</tr>
<tr>
<td>TRH</td>
<td>Dopamine (2x)</td>
<td>PGE₃ (7–8x)</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>VIP</td>
<td>Histamine</td>
<td>PGF₂α (2x)</td>
<td>FSH (2 µg ml⁻¹)</td>
</tr>
<tr>
<td>NPY</td>
<td>Serotonin</td>
<td></td>
<td>LH (40 ng ml⁻¹)</td>
</tr>
<tr>
<td>Somatostatin</td>
<td></td>
<td></td>
<td>TSH (100 µU ml⁻¹)</td>
</tr>
<tr>
<td>AVP</td>
<td></td>
<td></td>
<td>T3 (1 mg ml⁻¹)</td>
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<tr>
<td>Angiotensin II</td>
<td></td>
<td></td>
<td>T4 (1 mg ml⁻¹)</td>
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<tr>
<td>β-Endorphin</td>
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<td>N-Acβ-endorphin</td>
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<td>CRF</td>
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<td>ACTH</td>
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<td>MIF</td>
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</tbody>
</table>

Unless indicated the compounds were without effect on cAMP concentrations in ovine pars tuberalis cells.

*Numbers in parentheses indicate the increase over basal concentrations in 10 min. Melatonin had no inhibitory effect on any stimulatory activity.

*Numbers in parentheses indicate concentrations used if different from one at head of column.

VIP: vasoactive intestinal peptide; NPY: neuropeptide Y; AVP: arginine vasopressin; CRF: corticotrophin releasing factor; MIF: melanocyte inhibitory factor.
an endocrine effect between the pars tuberalis and pars distalis, it is assumed that it must be selectively expressed in the pars tuberalis. As an identical profile of [35S]methionine labelled secretory proteins is obtained from pars distalis cells, it seems that the proteins detected by this method probably serve a general pituitary function rather than one specifically related to the pars tuberalis (Morgan et al., 1992).

**Hypothetical mode of action of melatonin in the pituitary**

The physiological effect of subcutaneous implants of melatonin given during long photoperiods is to reduce the concentration of prolactin in the blood (Lincoln and Clarke, 1994). This effect of melatonin does not involve dopamine (Lincoln and Clarke, 1995). Since melatonin acts to silence or attenuate both translational and transcriptional events within the pars tuberalis, this would suggest that the pars tuberalis produces a secretory product which can sustain high prolactin secretion. An extended duration of high plasma concentrations of melatonin, as occurs during short days, may inhibit the synthesis and output of this product from the pars tuberalis. This would reduce the stimulus to the pars distalis, resulting in a drop in plasma concentrations of prolactin. During a short duration of high plasma concentrations of melatonin (that is, long days) the
converse would occur, and prolactin concentrations would rise. If this hypothesis is correct then a product released from pars tuberalis cells should activate either the expression or release of prolactin from pars distalis cells. Recent evidence from our laboratory indicates that the pars tuberalis cells in primary culture release a factor that activates \textit{c-fos} gene expression in pituitary lactotrophs and stimulates the secretion of prolactin by primary cultures of pars distalis cells (Morgan \textit{et al.}, 1996). We have called this factor ‘tuberalin’. At present the nature of this factor is unknown.

One factor known to be produced by pars tuberalis-specific cells is the glycoprotein \textalpha-subunit, which is found throughout the pars tuberalis in several species (Bockers \textit{et al.}, 1994; Stoeckel \textit{et al.}, 1994; Bockmann \textit{et al.}, 1996). Free \textalpha-subunits can cause differentiation of lactotrophs from fetal rat pituitary, and this effect can be blocked by antibodies directed against intact LH, but not LHβ (Begeot \textit{et al.}, 1983). In addition, \textalpha-subunits stimulate the secretion of prolactin from human decidual cells (Blithe \textit{et al.}, 1991). The demonstration that changes in photoperiod influence the expression of \textalpha-subunit immunoreactivity in the pars tuberalis of sheep and hamsters, and also mRNA encoding the \textalpha-subunit in hamsters, further encourages consideration of the role of the \textalpha-subunit in relation to the photoperiodic function of the pars tuberalis. However, its role as an endocrine factor involved in the regulation of prolactin secretion by the pars distalis is not clear for the following reasons. Under long day conditions sheep express low concentrations of \textalpha-subunit, whereas hamsters exhibit high concentrations of \textalpha-subunit expression, in pars tuberalis-specific cells (Bockers \textit{et al.}, 1996; Bockmann \textit{et al.}, 1996). This situation is reversed under short day conditions (Bockers \textit{et al.}, 1996; Bockmann \textit{et al.}, 1996). Since the effect of either short

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**Fig. 5.** A hypothetical model of the endocrine regulation of prolactin (PRL) synthesis and secretion within the ovine pituitary. An undefined stimulus (Stim X) activates gene transcription of a secretory peptide, tuberalin, in pars tuberalis-specific cells through a cAMP/protein kinase A/cAMP response element binding protein cascade (see Fig 4); melatonin blocks this activation. A balance between synthesis and degradation determines the intracellular amount of mRNA encoding tuberalin, which in turn determines the amount of the tuberalin protein synthesized and secreted constitutively. Tuberalin activates prolactin gene expression in pars distalis lactotrophs. The graph illustrates how, through altered duration of melatonin, the balance of synthesis and degradation of the mRNA encoding tuberalin is changed, and how this leads to changes in the steady state concentrations of mRNA encoding tuberalin, and hence secretion. The kinetics of synthesis and degradation would undoubtedly be more complex than depicted in this simple model. L: light; D: dark.
photoperiod or melatonin implants or infusions is to suppress prolactin concentrations in the blood in both species (Lincoln and Clarke 1994; Maywood and Hastings, 1995), it would be difficult to reconcile direct effects of α-subunits on prolactin release in each of these species. It is not known whether pars tuberalis cells release free glycoprotein α-subunits, or whether there are receptors for free glycoprotein α-subunits in the pars distalis. At present the regulation of prolactin release from the pars distalis by free glycoprotein α-subunits can be considered only an interesting hypothesis. An alternative would be for glycoprotein α-subunits to associate with an as yet unidentified β-subunit, to form a secretary hormone of unique biological activity (Stoeckel et al., 1994).

We hypothesize that the mechanism through which melatonin modulates prolactin output from the pars distalis most probably involves a change in the amount of gene expression (Fig. 5). This may be a change in prolactin gene expression itself, or altered gene expression of transcription factors involved in the regulation of the prolactin gene, such as Pit-1. Our working hypothesis is illustrated (Fig. 5). The pars tuberalis-specific cells secrete a product, which we have called ‘tuberulin’, that is synthesized and released constitutively; this would account for the characteristic paucity of dense core secretory granules with the pars tuberalis-specific cells (Stoeckel and Porte, 1984; Morgan et al., 1991b). The release of tuberulin can be increased through the cAMP pathway in response to an unidentified factor (Stim X), and this effect can be reversed by melatonin (Fig. 4); this alters the rate of transcription of the tuberulin gene and the translation of its mRNA (Fig. 5). Thus the synthesis and release of tuberulin may be determined primarily through a balance of mRNA synthesis and degradation. In the absence of melatonin, pars tuberalis-specific cells are stimulated by Stim X, facilitating synthesis of mRNA encoding tuberulin. In the presence of melatonin, cellular activation would be prevented and mRNA encoding tuberulin would be degraded. Therefore, under long photoperiod conditions when the duration of exposure of the pars tuberalis to melatonin is short, there is a net synthesis of tuberulin. Conversely, during a short photoperiod the length of the melatonin signal is long and net degradation occurs, reducing the concentration of tuberulin. While this simple model reconciles many aspects of the physiological and biochemical observations that have been made about melatonin and the pars tuberalis, it must be recognized that it is only a working hypothesis and other explanations may emerge.

**Conclusion**

Recent studies on the pars tuberalis have shed light on its unique and distinct function in seasonal physiology. The challenge over the next few years will be to isolate and characterize the putative secretory product released by the pars tuberalis gland, and to understand its mechanism of action, particularly in relation to the endocrine regulation of prolactin. Given the special anatomical position of the pars tuberalis as a gateway to the neuroendocrine system, it will be important to establish whether secretions from the pars tuberalis can modulate or fine tune the output from the median eminence and thereby influence other endocrine axes.

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