REVIEW

What is the role of melatonin within the anterior pituitary?

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Abstract

The pineal hormone, melatonin, is uniquely defined by its role as hormonal time, but the processes whereby cells extract temporal information from the melatonin signal are not understood. Melatonin receptors are expressed in the pars tuberalis (PT) and, during fetal and perinatal life, in the pars distalis (PD). Functional studies suggest that the PT mediates the seasonal effects of melatonin on prolactin secretion, whilst the PD may be involved in photoperiodic programming of the developing gonadotrophic axis. To understand these effects at the cellular level we need to know the phenotype of melatonin-responsive cells. This review summarises current understanding in this area, and highlights present shortcomings. A case is presented for exploring the hypothesis that there is a functional association between melatonin receptor expression and cell differentiation in the anterior pituitary.


Introduction

Melatonin synthesis and physiological roles

The indole hormone, melatonin, is synthesised by the pineal gland in a strictly nocturnal pattern. Synthesis is directly coupled to secretion, and both begin at or shortly after dusk, continue through the night, and then terminate at or just before dawn. This rhythmic pattern of secretion is circadian in nature (i.e. recurs spontaneously, in the absence of exogenous cues, with a period of approximately 24 h), and depends ultimately on the master biological clock which resides in the suprachiasmatic nuclei (SCN) in mammals. Additionally, dependent on species and on time of year, direct inhibitory effects of light on pineal activity may contribute to phasing of the onset and termination of melatonin production. These mechanisms result in production of a melatonin signal whose duration reflects changes in daylength over the course of the year. For a comprehensive review of the biology of melatonin synthesis the reader is referred to Klein et al. (1997).

As a neurochemical representation of night length, the melatonin signal is put to multiple uses, dependent on the physiological requirements of the organism. Melatonin may participate in the co-ordination of circadian responses, reinforcing or complementing other entraining signals such as the light–darkness cycle or social cues. This role of melatonin is most evident in situations where the availability/utilization of other cues is reduced (e.g. in perinatal life in hamsters (Grosse & Davis 1999) or, in humans, during shift work (Arendt 1999) or neuropsychiatric illness).

A second major role of melatonin is to co-ordinate a variety of seasonal photoperiodic responses (e.g. seasonal changes in reproductive activity, appetite and energy metabolism, and the growth of fibre and horn) (Bartness & Goldman 1989). Whereas there is a high degree of redundancy built into circadian entrainment pathways, it appears that melatonin is both necessary and sufficient for entrainment of seasonal photoperiodic phenomena to the annual cycle of daylength. Removal of the pineal gland or ablation of circadian input to the pineal abolish both the normal pattern of melatonin synthesis and seasonal responses (Lincoln et al. 1989). Conversely, exogenous melatonin delivered by injection or infusion can mimic the seasonal effects of changing photoperiod (Elliott et al. 1989, Maywood et al. 1990, Bartness et al. 1993, Tamarkin et al. 1977).

The physiological actions of melatonin depend upon the expression of high-affinity G protein-coupled receptors, in melatonin-responsive cells and tissues (Reppert 1997, Barrett et al. 1999) (non-receptor-mediated modes of action for melatonin have been advanced, but their concentration dependence is too high to occur in response to circulatory titres of this hormone (Reppert & Weaver 1995, Vlkolinsky & Stolc 1999)). Two high-affinity melatonin receptor subtypes (mt1 and MT2) have been
identified in mammals (Reppert 1997); however, a number of observations support the view that mt1 is the functionally important subtype, particularly in the case of seasonal responses (Weaver et al. 1996, Liu et al. 1997).

In mammals, melatonin receptor expression has a restricted tissue distribution, with sites in the central nervous system (CNS), pituitary and cerebrovascular structures showing the highest levels of expression (Morgan et al. 1994b). In fetal and newborn animals, melatonin receptors are expressed more widely, both in the CNS and in the pituitary (Williams et al. 1991, Helliwell & Williams 1994), and in other tissues in which expression is absent in the adult (e.g. the developing renal cortex (Drew et al. 1998)). Physiological studies support the view that specific regions of melatonin receptor expression are responsible for mediating specific aspects of the overall response to melatonin. The SCN appears, unsurprisingly, to mediate the circadian effects of melatonin (Gillette & McArthur 1995), whilst other hypothalamic sites, notably the dorsomedial nuclei and the premammillary areas, appear to mediate effects on reproductive activation (Lincoln & Maeda 1992, Malpaux et al. 1998, Maywood et al. 1996). The effects of melatonin on seasonal prolactin (PRL) cycles appear to be mediated by sites within the anterior pituitary itself (Lincoln 1994, Lincoln & Clarke 1994, 1995). Despite this progress, our understanding of the cellular mechanisms of the action of melatonin within any of these sites is far from complete.

Response to melatonin within the anterior pituitary

This review considers one aspect of this problem, namely the role of melatonin-responsive cells in the mammalian pituitary. As a model tissue for understanding melatonin action, the anterior pituitary is advantageous in that it contains (in the pars tuberalis (PT)) the highest concentration of melatonin receptors of all mammalian tissues (Morgan & Williams 1989); moreover, compared with neurones, anterior pituitary cells are comparatively amenable to analysis at a cellular level. As well as modulating the PRL axis, melatonin-responsive cells within the pituitary are of biological interest because, in the pars distalis (PD) of both the rat and the sheep, a clear developmental loss of expression occurs over the perinatal period (Vanecek 1988, Williams et al. 1991, Helliwell & Williams 1994). This suggests that melatonin receptors are involved in the control of aspects of anterior pituitary function which are specific to the perinatal period.

In handling this topic, this review focuses on the phenotype of melatonin-responsive cells, rather than the intricacies of melatonin receptor biology and signal transduction which have been excellently reviewed elsewhere (Morgan et al. 1994b, Reppert 1997, Vanecek 1998). This review considers, first, the intrapituitary actions in the post-natal organism, beyond the immediate perinatal period. Secondly, intrapituitary actions of melatonin in fetal and perinatal life are considered. Finally, and speculatively, an attempt is made to synthesise these two lines of investigation into a general hypothesis for the role of melatonin within the anterior pituitary.

Melatonin-responsive cells in the post-natal pituitary gland

Beyond the perinatal period, melatonin receptor expression in the pituitary is confined to the adenohypophyseseal PT (Morgan et al. 1989), and to a projection from this region extending over the anteroverentral PD, known as the zona tuberalis (ZT) (Skinner & Robinson 1994). On cytological grounds, it is reasonable to consider these regions collectively (Skinner & Robinson 1995).

The role of PT in photoperiod/melatonin control of PRL secretion

There is strong evidence to implicate the PT in a specific aspect of melatonin responsiveness, namely the seasonal control of PRL secretion. This conclusion rests heavily on data from hypothalamo–pituitary–disconnected (HPD) Soay rams (Lincoln & Clarke 1994). In these animals, neuroendocrine communication between the hypothalamus and the pituitary is destroyed by extirpation of the median eminence (ME) – i.e. the region where neurosecretion into the primary plexus of the portal system occurs. Re-establishment of neuroendocrine communication through this route is prevented by insertion of a physical barrier beneath the lesion site. Importantly, this surgery leaves the descending portal supply to the PD and the associated PT tissue intact.

Under these conditions, a drastic loss of control of pituitary hormone secretion takes place but, remarkably, HPD animals continue to exhibit well-defined seasonal cycles in PRL secretion, closely resembling those in the intact animal (Lincoln & Clarke 1994). The non-involvement of hypothalamic input in this seasonal cyclicity is reinforced by the complete loss of acute control (e.g. in response to stress) of PRL in the HPD animal. The simplest interpretation of these data is that cells within the anterior pituitary itself mediate these seasonal effects of melatonin on PRL release. Given the highly restricted expression of melatonin receptors in the anterior pituitary (there is no evidence for melatonin receptor expression on lactotrophs) (Helliwell & Williams 1992, Skinner & Robinson 1994), this line of reasoning inevitably leads to the conclusion that the PT (and/or PT/ZT) may mediate the observed seasonal effects on PRL. Further support for this inference comes from the finding that hypothalamic melatonin implants exert potent effects on PRL release when placed close to the PT (Lincoln 1992).
**Structure and function in the PT**

How then might melatonin-responsive cells in the PT relay information to exert seasonal control on PRL secretion? Since PRL secretion by the PT is negligible (Hazlerigg et al. 1996), a strong hypothesis is that the PT produces unidentified molecules, so called ‘tuberalins’ (Stoeckel et al. 1994, Morgan et al. 1996), that modulate PRL release through mechanisms unknown.

In principle, a consideration of the functional anatomy of the PT and of its cytological composition might allow us to make firmer predictions about the chemical nature of such tuberalins, should they indeed exist. The PT sits at the interface between the ME and PD, and is the conduit through which the long portal vessels run from the primary capillaryplexus of the pituitary portal system into the PD. Within this region, neuroendocrine cell terminals release signals into the blood for carriage to the PD; conversely, blood-borne signals of peripheral or anterior pituitary origin may be transported to nerve-terminals in the ME, or into the CSF of the third ventricle (3V) through this region. On this basis, cells within the PT might modulate hypothalamo–pituitary function through several mechanisms; specifically they might:

1. Influence the rate of release of signals from neuroendocrine terminals into the portal blood
2. Influence the rate at which signals from the portal blood are transported into the ME/3V
3. Release signals into the brain to influence the behaviour of neuroendocrine cells involved in hypothalamo–pituitary communication
4. Release additional (possibly PT-specific) signals into the portal blood, which then act on target endocrine cells in the PD to directly influence the rate of anterior pituitary hormone secretion
5. Influence hypothalamic input or pituitary output by changing the rate of blood flow through the portal system – either by (anti)angiogenic actions or by affecting vasodilation/constriction
6. Influence pituitary output by affecting the rate of transport of released hormone into the blood supply

Since routes 1, 2 or 3 depend upon maintained hypothalamo–pituitary communication they cannot have any relevance to the intrapituitary control of the PRL secretion seen in the HPD animal (Lincoln & Clarke 1994). Rather, if the PT mediates the effects of melatonin on PRL release, then it must do so either by directly regulating lactotrophs (i.e. by production of a PRL-releasing factor (PRF), or release-inhibiting factor (PRIF), route 4), or by changing PRL secretory output indirectly, e.g. through blood flow or hormone uptake rates in the capillary beds surrounding lactotrophs (i.e. routes 5 and 6).

In general terms, the very extensive list of potential intra- and extra-pituitary PRFs/PRIFs (comprehensively reviewed in Freeman et al. (2000)) supports the idea that the PT may produce such a molecule. Furthermore, co-culture and media-conditioning experiments have demonstrated that ovine PT cells produce unidentified factor(s) which promote PRL release from ovine PD cells (Hazlerigg et al. 1996, Morgan et al. 1996). Alternative, indirect mechanisms of modulating PRL release are also possible, have precedents in the literature, and cannot be discounted. For example, vascular-cast methods have been used to demonstrate a positive association between enhanced tumour vascularisation and hyperprolactinaemia in rats bearing pituitary adenomas (Elias & Weiner 1984). Alternatively, local effects on capillary permeability (and thus rate of uptake of endocrine signals), through the actions of factors such as vascular endothelial growth factor (VEGF), itself strongly expressed in the PT (Ferrara et al. 1991), remain a possibility.

**PT cytology**

Having established that routes 4–6 above are the most likely ways through which the PT might mediate the effects of melatonin on PRL secretion, it is worth asking whether the known characteristics of PT cells are suggestive of a specific mechanism out of these three possibilities through which PT modulation of PRL secretion might occur. At the same time, it is obviously necessary to identify which cell types present in the PT are melatonin responsive. The PT contains a mixture of cell types including classical granular secretory cells, ‘PT-specific’ cells and folliculo-stellate cells (Stoeckel & Porte 1984).

**PT-specific cells** The major parenchymal cell type in the PT tissue are agranular or contain many fewer secretory granules than classical granular endocrine cells; nevertheless, they contain an extensive rough endoplasmic reticulum, indicative of a putative secretory function (Stoeckel & Porte 1984). These cells are of unknown function. It is not clear whether these, so called, ‘PT-specific’ cells constitute a homogenous or mixed population but, collectively, they may be distinguished from folliculo-stellate cells by their ultrastructure and by their non-expression of immunogenic markers for this latter cell type (in particular S100 protein). PT-specific cells are potentially of particular interest, since, based on the correlation between the proportional representation of PT-specific cells in ovine PT cell cultures and the proportion of forskolin-induced cAMP production that can be suppressed by melatonin, it has been argued that this cell type is the major melatonin–responsive cell type in the ovine PT (Morgan et al. 1991).

Immunological characterisation of PT-specific cells indicates that species differences exist in their expression of the known glycoprotein hormones. In the Syrian hamster, glycoprotein hormone α-subunit (αGSU) and thyrotrophin-stimulating hormone β (TSH-β) subunit are present in PT-specific cells, and undergo photoperiod-dependent changes in expression (Bockmann et al. 1996, 1997). In contrast, ovine PT-specific cells do not express
any of the known β subunits for the glycoprotein hor-
mones, although αGSU expression is observed, and is
apparently also photoperiod sensitive (Bockers et al. 1994).
The consequences of this expression and its relationship to
melatonin action are unknown.

There have, additionally, been two recent reports that
PT-specific cells may be identified by the presence of
novel immunological features. The first, in the rat, reported
that PT-specific, S100-negative cells express
guanylin (D’este et al. 2000). Guanylin is a peptide
of approximately 12.5 kDa weight, which is thought to be
the endogenous ligand for the surface membrane-
associated guanylate cyclase C (Currie et al. 1992). The
function of guanylin is as yet unknown but it is thought
that it may be involved in the regulation of electrolyte/
water secretion in ion-transport epithelia (e.g. in the
intestine and kidney) (Hamra et al. 1995). On this basis,
the expression of guanylin by PT-specific cells warrants
further investigation, and it is tempting to speculate that
expression of guanylin might relate to effects on uptake or
permeability in the context of endocrine traffic into the
microvasculature. It is of tangential interest to note that a
pronounced circadian variation in guanylin expression in
the intestine has recently been reported (Sheving &
Jin 1999).

The second report of PT-specific cell immuno-
characterisation derives from earlier reports that the syn-
thesis of specific, unidentified secretory proteins by ovine
PT cells is melatonin sensitive (Morgan et al. 1992, 1994a).
Lately, 21 and 72 kDa proteins were purified from
media conditioned by bovine PT explants and used to
raise antisera (Guerra & Rodriguez 2001). Subsequent
immunohistochemistry at the light and electron micro-
scope level suggested that these recognised antigens are
preferentially expressed in PT-specific cells. The identity
of the antigens involved is unresolved, as is the issue of
whether any of these immunogens are regulated by
melatonin or photoperiod.

**Folliculo-stellate cells** These cells are characterised by a
stellate morphology (expression of cytoplasmic processes),
and association with intercellular follicular spaces that are
filled with unidentified colloidal material (Inoue et al.
1999). Folliculo-stellate cells are also characterised by the
expression of a number of antigens, notably S100 protein,
glial-fibromatous acidic protein and basic fibroblast growth
factor (bFGF) (Inoue et al. 1999). Folliculo-stellate cell
cultures from the bovine hypophysis were the original
sources from which both bFGF and VEGF were isolated
(Gospodarowicz et al. 1987, Ferrara et al. 1991), and it is
worth noting that the PT contains a higher proportion of
folliculo-stellate cells than does the PD. The function of
folliculo-stellate cells both within the PT and in the
anterior pituitary in general remains obscure, but the
expression of factors such as bFGF and VEGF might
reflect undefined trophic actions on endocrine cells, or
possibly involvement of a role in maintaining the pituitary
micro-vasculature (Inoue et al. 1999).

From the perspective of melatonin action, the relevance
of PT folliculo-stellate cells is unclear. Jabbour et al. (1997)
examined the expression of VEGF in the highly seasonal
Soay sheep, and found enriched expression in the PT,
which was independent of hypothalamic input (i.e. similar
in HPD and intact animals). There are no published data
on whether PT VEGF expression is photoperiod or
melatonin sensitive. Melatonin has been reported to in-
fluence bFGF RNA expression in ovine PT cells, although
no effect on bFGF peptide secretion was observed in the
same study (Graham et al. 1999). This, and the lack of
effect of recombinant bFGF on PRL secretion from ovine
PD cells cultures (Graham et al. 1999), suggest that any
role for bFGF – presumably of folliculo-stellate origin – as
a mediator of melatonin action in the PT must involve
local actions within the PT itself.

**Granular endocrine cells** Immunological and in situ
hybridisation analyses of the granular endocrine cells
present in the PT suggest that thyrotrophs and gonado-
trophs are the main defined endocrine cell type present in
this tissue; nevertheless, they constitute a minority popu-
lation, both relative to the overall composition of the PT to
the wider luteinizing hormone (LH)/TSH positive pool in
the anterior pituitary as a whole. Two studies, one in the
rat (Nakazawa et al. 1991) and one in the sheep (Skinner
& Robinson 1997), have reported that gonadotrophin-
releasing hormone (GnRH)-induced LH release from PT
explants is melatonin sensitive (albeit at supraphysiological
concentrations of the hormone). The significance of this is
unclear; it is unlikely that these cells significantly influence
peripheral circulating TSH or gonadotrophin titres, but the
possibility that these cells act locally – e.g. in short loop
feedback on terminals in the ME – cannot be completely
excluded. Skinner et al. (1997) found no evidence for this
in the sheep, however. Moreover, such a model cannot
explain the effects on PRL seen in the HPD sheep.
Similarly, a model in which PT-derived gonadotrophin
influences PD PRL release is difficult to envisage, since
any PT-derived signal would surely be swamped by LH
levels within the PD itself. To overcome this difficulty, a
model implicating these cells in melatonin regulation of
PRL would have to invoke specificity, either in terms of
production of a distinct chemical form of LH/TSH by PT
thyro/gonadotrophs, or in terms of delivery of signals from
these cells to lactotrophs in the PD. We cannot exclude
such complexity, but should exclude simpler mechanisms
first.

**Perspectives on PT cytology in relation to melatonin
responsiveness** Overall, the foregoing summary of our
cytological knowledge of the PT reveals one major diffi-
culty: there is no consensus as to exactly which of the cells
discussed is the key melatonin-responsive phenotype.
There is some evidence for melatonin responsiveness in each of the cell types discussed, but in no case is the evidence so compelling as to focus attention on that cell type alone. Whether the true picture is indeed one in which melatonin regulates multiple cell types in the PT can only be determined with further work. In particular, efforts to co-localise melatonin receptor expression against phenotypic markers, either by in situ hybridisation or using the recently developed melatonin receptor specific antisera (Brydon et al. 1999, Williams et al. 2001) must be a priority.

Intrapituitary actions of melatonin in the fetal and perinatal animal

Melatonin-responsive gonadotrophs

In addition to the PT itself, which appears early in adenohypophyseal organogenesis, melatonin receptors are expressed in fetal and perinatal gonadotrophs in the PD (Vanecek 1998). The most extensive characterisation of melatonin-responsive gonadotrophs has been undertaken in the newborn rat. This transient sensitivity is evident in vivo and in vitro, and takes the form of an acute antagonism of GnRH-induced increases in LH release, by physiological concentrations of melatonin (Martin & Klein 1976). Approximately half of total gonadotrophin secretion from 4- to 8-day-old rat pituitary glands is melatonin sensitive, but by day 21 almost no response to melatonin can be seen (Vanecek 1998); over the same period a dramatic decline in melatonin-binding site density is also observed (Vanecek 1988). Based on single cell analysis of the effects of melatonin on GnRH-induced calcium release in PD cells (Vanecek & Klein 1993), it is likely that approximately 50% of gonadotrophs are melatonin responsive in the newborn rat.

Functional relevance of perinatal melatonin responsiveness in gonadotrophs

It is well established that the onset of puberty in mammals can be sensitive to photoperiod experienced in utero, and that this depends upon the maternal melatonin signal at this time (Ebling & Foster 1989, Horton & Stetson 1992). Very little is known about the sites of action in the fetal brain through which this programming occurs, although it is assumed that hypothalamic areas associated with the GnRH system are likely candidates. Additionally, it has been speculated that the transient expression of melatonin-responsive gonadotrophs is specifically concerned with fetal programming of the reproductive axis (Vanecek 1998). Despite its plausibility, the experimental support for this hypothesis remains limited. In early studies, repeated melatonin administration to newborn Sprague–Dawley rats had no significant effect on the onset of puberty, despite causing a pronounced decline in circulating LH levels in the neonatal period (Aubert et al. 1989). Possibly, this reflects compensatory effects occurring in the interval between loss of neonatal melatonin responsiveness and the onset of puberty, and the general photoperiodic insensitivity of the strain of rat used. More recently, studies have shown that pubertal activation is melatonin sensitive in Fischer 344 rats (Heideman et al. 2001), and it would be interesting to determine whether perinatal programming effects of melatonin are detectable in this strain.

Are melatonin receptor expressing cells fully differentiated?

The transitory nature of melatonin receptor expression on gonadotrophs and the ambiguous literature on the phenotype of melatonin-responsive cells in the PT raise a fundamental question about the nature of melatonin-responsive cells in the pituitary: are such cells of defined terminally differentiated phenotypes, or are they in partially differentiated states? This distinction has major implications for how we should view the role of melatonin in the pituitary. If melatonin-responsive cells are terminally differentiated (i.e. of PT-specific or gonadotrophic phenotype), then it is reasonable to suppose that melatonin acts by up- or down-regulating specific outputs/activities of specific cell types (e.g. tuberoinfundibular production/LH secretion). If, on the other hand, melatonin-responsive cells are in the process of differentiation towards a future (and ultimately melatonin-unresponsive) terminal phenotype, then melatonin might act in an entirely different manner (e.g. accelerating, delaying or redirecting the process of differentiation). These two alternative (but not mutually exclusive) scenarios are summarised in Fig. 1, and discussed further below.

In considering the general plausibility of an alternative, differentiation-based model for melatonin action, the first general point to make is that photoperiodic responses to melatonin (in which it is most likely that pituitary melatonin-responsive cells participate) typically occur over comparatively long time-scales (weeks to months). Hence, one cannot simply exclude control of cell differentiation as a mode of melatonin action on temporal considerations. The second point to make is that transient expression of melatonin receptors is observed during development of tissues beyond the pituitary – for example, in the nephrogenic region of the developing human kidney around week 20 of fetal life (Drew et al. 1998). Thirdly, it is worth noting that, in songbirds, seasonal control of changes in the capacity for birdsong has been linked with melatonin-dependent changes in the volume of central regions concerned with this function, presumably through melatonin effects on cell recruitment/turnover (Bentley et al. 1999).
Figure 1 Actions of melatonin within the anterior pituitary. Melatonin input reaches the adenohypophysis through the circulation, and the profile of secretion reflects the environmental photoperiod. Two possible modes of melatonin action are indicated: direct effects on endocrine or paracrine cells (expressing βLH, αGSU or tuberulin (Tub.)), and effects on incompletely differentiated precursor (Prec.) cells. Solid and stippled grey shading, respectively, indicate known and putative melatonin receptor expressing regions (PT/ZT) or cell types. Solid and stippled blue arrows, respectively, indicate known and putative differentiation processes leading to the expression of specific cell-types from percursor populations. Solid orange arrows indicate the endocrine output pathways known to be ultimately sensitive to intrapituitary effects of melatonin. N.B. a significant intrapituitary effect of melatonin on circulatory LH titres has only been observed in perinatal rodents. The stippled orange arrow indicates putative paracrine communication between the PT/ZT and the PD through which intrapituitary effects of melatonin on PRL release are thought to be mediated.
Returning to the melatonin-responsive PD gonadotroph, two possibilities exist to account for the developmental disappearance of melatonin receptors: either receptors may disappear as these cells become ‘mature’ gonadotrophs, or separate pools of melatonin-sensitive and -insensitive gonadotrophs are initially present in the fetal PD, and programmed cell death selectively removes the former subset. The speed with which these cells disappear in the rat argues against the latter possibility, however. Best estimates of general PD cell turnover rates in young rats suggest that, in general, cells die or divide once every 60–70 days (Nolan et al. 1998); this would be too slow to account for the rate of loss of melatonin-responsive gonadotrophs post partum. Thus, developmental loss of melatonin receptors from rat gonadotrophs depends either on selective loss of this cell type, at rates much higher than those for general PD cell turnover, or on further differentiation of these cells, making them indistinguishable from melatonin-unresponsive cells.

A second line of evidence supporting the idea that melatonin receptor expression is a feature of differentiating cells derives from the fact that the only region in which expression persists beyond fetal/perinatal life is the PT/ZT. During fetal development, differentiation of the stomedeal ectoderm gives rise to Rathke’s pouch and subsequently to the hypophysis. During this process, adrenohypophysal differentiation can be plotted in terms of expression of specific transcription factors which are associated with particular cell lineages (Kioussi et al. 1999). Of these, the homeobox transcription factor Ptx1 is notable because its appearance precedes terminal differentiation of all pituitary cell lineages (Szeto et al. 1996, Tremblay et al. 1998).

Comparison of melatonin receptor and Ptx1 distributions in the adenohypophysis reveals a striking parallel. In the mouse, Ptx1 appearance in the PT (embryonic day 12) coincides with the first evidence of pituitary differentiation occurring in this region (αGSU expression and transient, Pit1-independent thyrotrophin β subunit expression) (Lanctot et al. 1999). Melatonin receptor expression also appears as early as embryonic day 15 in the rat, and, from as early as anatomical resolution is possible, it is clear that expression is higher in the PT/ZT than in the adjacent PD (Williams et al. 1991). Against this background, it is interesting to note that whilst Szeto and colleagues indicate that αGSU and (Pit-1 independent) TSH-β expression is a transient phenotype in the rostral tip of the developing mouse adenohypophysis (=primordial PT), in the hamster, both αGSU and (Pit-1 independent) TSH-β are expressed in the PT of adult hamsters, and are sensitive to photoperiod/melatonin (Bockmann et al. 1996, 1997).

Beyond embryonic day 12-5, Ptx1 begins to appear in the developing mouse PD but, except on its ventral surface (perhaps equating to the ZT), is expressed at lower levels than in the PT (Lanctot et al. 1999). This has led to the proposal that high Ptx1 expression is a marker for zones of proliferation in the developing anterior pituitary, whilst moderate Ptx1 expression in conjunction with other tissue-specific transcription factors (e.g. SF1, Lim3, Pit1) promotes the expression of terminal phenotypes in the PD (Lanctot et al. 1999). Extending this idea, together with the data from Bockman and colleagues, and the melatonin receptor distribution work, an intriguing possibility is that cell proliferation/differentiation is a feature of the PT/ZT in post-natal life and that, by influencing these processes, melatonin affects the recruitment of cells to specific differentiated pools.

There are a number of comparatively straightforward ways in which this hypothesis can be tested initially. In particular, co-localisation studies would allow the distribution of melatonin receptor gene expression to be compared with that for Ptx1, and other factors known to determine pituitary cell fate. The same approach would also allow the turnover of melatonin-responsive cells in the PD and PT to be evaluated. If such preliminary studies encourage further consideration of a differentiation-based model for melatonin action, then a gamut of questions will follow concerning the ultimate fate of cells from the PT/ZT.

The value of any model for biological action depends upon its ability to account for the available data and to make testable predictions for further investigation. The hypothesis that melatonin acts in the PT to regulate the production of as yet unidentified ‘tuberalin(s)’ remains to be proven. Although it is clear that PT-conditioned media contain PRL-releasing activity (Hazlerigg et al. 1996, Morgan et al. 1996), evidence for acute regulation of such activity by melatonin has not been forthcoming. One attraction of the alternative model argued for here is that it might account for this difficulty: melatonin-responsive cells may feed into a pool of differentiated cells, which are responsible for the PRL release observed in vitro. Conversely, this comparatively indirect mode of action may have difficulty accounting for the initial rapidity with which detectable changes in PRL occur in HPD rams following a change in photoperiod (within 1 week, Lincoln & Clarke 1994). Nevertheless, the time required for a maximal PRL response to develop in these animals (approximately 6 weeks) is certainly by no means too fast to exclude consideration of melatonin effects on cell recruitment/differentiation. More generally, a merit of the ontogenic view put forward here is that it provides a context through which melatonin actions in the PT and in the perinatal PD may be viewed collectively. Of course, a differentiation based model for melatonin action may prove false; the author’s hope is that approaching melatonin receptor expression in terms of pituitary ontogeny may provide useful insights into the cellular actions of melatonin.
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