MINI REVIEW

The pars tuberalis of the hypophysis: a modulator of the pars distalis?

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The pineal hormone melatonin is known to influence circadian systems. Melatonin is also ascribed to mediate photoperiodic effects on the regulation of the hypothalmo-hypophysial-gonadal axis. Other endocrine actions, especially a thyrotropic influence, have been postulated. Site and mechanism of action of melatonin, however, are still matters of speculation. In search of a functional cascade of (i) photoperiodic stimuli, (ii) their hormonal messenger melatonin, and (iii) endocrine targets, the pars tuberalis has gained a key position. The recent discovery and characterization of melatonin receptors located in the pars tuberalis of several species support such a functional significance. Earlier results point to a functional connection of the pars tuberalis with the pineal gland: the pars tuberalis is known for a pattern of differentiation distinctly different from other parts of the adenohypophysis. It contains a specific cell population with a morphology typical of peptide secreting cells. Like the hypothalamic nerve endings of the median eminence, they are in close contact with the primary plexus of the portal system. In contrast to secretory cells of the pars distalis, the specific cells of the pars tuberalis do not respond with morphological alterations to functional changes of peripheral endocrine glands. Yet, photoperiodic stimuli obviously influence morphology and functional activity of the pars tuberalis-specific cells. Investigations during recent years have led to the tentative conclusion that the pars tuberalis represents the hypophysial "receptor" for melatonin as the chemical messenger of photoperiodic stimuli. Depending on melatonin secretion pattern and melatonin receptivity, the pars tuberalis seems to modulate at least gonadotrophic and thyrotropic activity of the pars distalis via a peptide hormone distributed in the pars distalis by the portal plexus. Such an intrahypophysial regulatory concept may explain the widespread actions of melatonin on endocrine targets.

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Topography and anatomy

The pars tuberalis (PT) constitutes a well-defined part of the vertebrate adenohypophysis (1-4). In mammals it consists of strands of a bilayered to multilayered glandular epithelium surrounding the hypophysial stalk and extending along the ventral surface of the median eminence (Figs. 1, 2).

The secretory cells of the PT are in close contact with the capillaries of the primary plexus of the portal vessel system, as are the nerve endings of the median eminence (5). Because of these spatial relations, secretory products of the PT as well as neuropeptides of the hypothalamic nerve endings are released into the portal system and are spread throughout the pars distalis (PD) by the secondary capillary plexus. These neuropeptides may also directly influence the activity of PT cells via the common perivascular space lined by nerve endings on the one side and PT cells on the other (Fig. 1). On the contrary, the release of neuropeptides by nerve endings of the median eminence may be influenced by the PT cell products.

Cell composition

Morphological studies have shown that the PT consists of several types of cells (6): (i) PT-specific cells: secretory cells with an ultrastructural appearance different from that of PD cells; (ii) follicular cells: cells lacking signs of secretory activity, resembling folliculo-stellate cells of the PD; (iii) PD cell types: secretory cells known from the PD, especially gonadotropes and thyrotropes.

(i) PT-specific cells

PT-specific cells exhibit all the characteristics of peptide-secreting cells but are different from any cell type of the PD (Fig. 3). Ultrastructurally, they are defined by a small number of secretory granules (with a diameter of 100–150 nm), peculiar cup-shaped lysosomes, and often long ribbons of endoplasmic reticulum (6-9). Exocytotic release of secretory granules could be shown using tannic acid (Fig. 3; Merks, Schulze-Bonhage & Wittkowski, unpublished results). PT-specific cells were not
observed to react immunohistochemically with antibodies against PD hormones in a number of species. Only in rats and djungarian hamsters do varying percentages of PT-specific cells show a weak TSH-like immunoreactivity (7, 10) (Fig. 4). Consequently, PT-specific cells were considered to be thyrotropes in these species. Their morphological appearance, however—cell size, cytoplasmic characteristics, and number and distribution patterns of granules—does not support this assumption (7, 11). Furthermore, the intensity of TSH-like immunostaining does not necessarily correspond to their content of secretory granules (12, 13) indicating that variable amounts of secretory products of the PT-specific cells do not bind TSH antiserum. Morphological and immunohistochemical results (in rats and hamsters) suggest that there is only one type of PT-specific cells regardless of their TSH-like immunoreactivity. Although it is unlikely that TSH is the major product of PT-specific cells, changes in TSH-like immunoreactivity in rat and hamster have been shown to occur depending on experimental conditions (11, 12, 14).

(ii) Follicular cells
These small cells with irregularly shaped nuclei are often seen in groups bordering central cavities filled with electron dense material. Follicular cells are devoid of secretory characteristics (6).

(iii) PD cell types (sometimes called “invasive cells”)
PD cell types are secretory cell types known from the PD which are found predominantly in the caudal PT, especially around the hypophysial stalk. They usually differ from PT-specific cells by their abundance of secretory granules (15).

Immunohistochemical investigations have demonstrated that gonadotropes regularly occur in the mammalian PT (16–20). Ultrastructural immunocytochemical studies have confirmed their morphological identity with PD gonadotropes (15, 21). Moreover, their secretory activity is GnRH-dependent (17, 22–24).

Thyrotropes are the other PD cell type found in the caudal PT of most species. They occur in low number compared to the other cell types (5).

A differentiation between thyrotropes and PT-specific cells which exhibit TSH immunoreactivity is difficult at
Fig. 3a. PT-specific cell with characteristic cytological features, especially small groups of secretory granules and of lysosomes; neonatal rat; bar = 1 μm. 3b: Typical exocytotic release of a secretory granule (arrowhead) from a PT-specific cell; C, capillary of the primary plexus; TARI-method (55); adult djungarian hamster (Phodopus sungorus); bar = 0.5 μm.

Fig. 4a, b. TSH-immunoreactivity of PT-specific cells lining the median eminence (a) and of thyrotropes in the PD (b); rat, 20 day: bars = 50 μm.

Development and differentiation

The PT as a part of the adenohypophysis originates from the anteroventral part of Rathke's pouch (for details see 3). Bilateral paramedian processes grow rostrally along the median eminence, fuse, and surround the hypophysial stalk. The processes are clearly separated from the Anlage of the PD by the so-called Atwell's recess, a connective tissue space through which portal vessels penetrate into the PD. Developmental characteristics of the PT are original and distinct (6, 25, 26). Prenatally,
the rat PT consists of two cell types only: PT-specific cells with all signs of secretory activity, and some interspersed follicular cells (6, 14). An early sign of differentiation is the occurrence of glycogen, which is not observed in other parts of the adenohypophysis. Besides glycogen storage, a well-developed Golgi apparatus, rough endoplasmic reticulum and secretory granules are found in rat fetal PT cells (15th day of gestation) when PD cells are still immature. Also in the human fetal PT a differentiated cell type exists which closely resembles PT-specific cells known from other species (26). Studies on postnatal development have shown a characteristic pattern of age-dependent changes of ultrastructure and TSH-like immunoreactivity of PT specific cells in the rat (13).

Functional relations

Experimental interference such as thyroidectomy, hypophysectomy or gonadectomy failed to provide convincing evidence for a functional significance of the PT (6, 8, 27, 28). There are, however, some findings indicating the role played by the PT. Changes in the morphology of the PT cells have been related to the periods of the annual life cycle in submammalian species (29). Demailmann et al. (8) suggested first that a seasonal influence on the PT may exist in mammals, too. Recent experiments on the djunugarian hamster have shown that changes in the morphology and immunoreactivity of PT cells can be induced by altering the lighting conditions (7, 11). Signs of secretory activity are markedly reduced under short photoperiods. Similar cytological differences were found comparing active and hibernating hedgehogs (9). These results substantiated the suggestion of characteristic circannual variations in the activity of the mammalian PT. As concomitant gonadal involution is associated with seasonal rhythmicity, a connection of PT function with the neuroendocrine gonadal axis may be assumed.

Also, antithyrotrophic effects of pineal melatonin are discussed to be mediated by the PT. A coupling between thyroid function and PT activity was concluded from experiments showing marked cytological and immunohistochemical alterations of fetal PT cells following maternal application of T3 and propylthiouracil (14, 30). In various experiments, Vriend (31), Vriend and Wasserman (32), and Hoffmann (33) postulate that short photoperiods exert an inhibitory influence on the neuroendocrine thyroid axis. These new approaches to a functional significance of the PT are supported by recent results concerning melatonin binding sites.

PT as a site of melatonin receptors

Melatonin is well known for its influence on the circadian and seasonal timing of several physiological processes (34–37). Its profound influence on reproductive functions is generally accepted. As mediator of photoperiodic signals, melatonin is believed to exert ant gonadotrophic and—in some species—progonadotropic effects which are closely related to the absolute and relative duration of its secretion (37). The functions of target cells are not completely understood nor are the mechanisms mediating the actions of melatonin (38, 39).

Circadian rhythm of melatonin secretion by the pineal gland in mammals depends on circadian oscillators within the suprachiasmatic nucleus of the hypothalamus (40). During recent years, investigations using the high affinity ligand 2 125 [iodomelatonin (41) for the localization and characterization of melatonin receptors have specified evidence for target sites of melatonin in the mammalian brain, the retina and the pituitary. Iodomelatonin binding sites found within the suprachiasmatic nucleus probably point to a role of the hormone in circadian systems. "Perhaps pineal melatonin serves as temporal feed-back on oscillators within the suprachiasmatic nucleus regulating circadian phase and maintaining rhythm stability" (40). In several seasonally responsive animals, however, [125]iodomelatonin binding sites could not be detected in the suprachiasmatic nucleus (42–44) or at best only in relatively low density (45). Williams and Morgan (46) were the first to demonstrate the presence of high affinity binding sites for the ligand [125]iodomelatonin on the PT of the adenohypophysis of the adult rat. Further autoradiographic studies showed specific and intense labelling of the PT in various mammalian species (47). Pharmacologically, these PT-binding sites fulfill the criteria of receptors (48). Other sites of putative melatonin receptors in the brain seem to be species-specific (42, 49). Age-dependent differences of receptor localization and density may play a role, too. For instance, specific melatonin receptors are reported to occur in the PD of fetal and newborn rat and appear to be absent in the adult (50). Stanton et al. (45) have found a significant decrease in iodomelatonin binding sites in the PT of hibernating ground squirrels compared to those of awake, euthermic animals. In hamsters exposed to short photoperiods the number of melatonin binding sites in the PT was also markedly reduced (43).

The physiological relevance of binding sites which can be labelled with melatonin has been shown in several studies. Morgan et al. (51) have found some evidence that PT-specific cells are the melatonin responsive ones. Melatonin inhibits forskolin-stimulated cAMP production in the PT (hamster, 52; rat, 53; sheep, 48). In neonatal rats, melatonin is effective in a picomolar range and inhibit cAMP and cGMP accumulation in PD tissue of rats stimulated in vitro with GnRH (53). Inhibition of LH release from neonatal rat hemipituitaries was found to be potentiated after pretreatment with melatonin (54).

During rat fetal development, melatonin binding sites were first found in the pituitary on the 15th day of gestation (50). This coincides with the observation of
secretory differentiation of PT-specific cells. In newborn rats, the PT is more intensely and more homogeneously labelled than the PD. The authors conclude that the fetal pituitary may have the potential of responding to maternal melatonin signals from day 15 of gestation. Thus, as the suprachiasmatic nucleus may mediate prenatal entrainment of circadian rhythms, the PT is a likely site for mediating photoperiodic information to the fetus.

Conclusions

The topography of the PT is characterized by close spatial relations to the primary capillary plexus of the portal system and to the hypothalamic nerve endings of the median eminence (Fig. 1). Special features of fetal differentiation confirm that the PT is a unique part of the adenohypophysis. The PT-specific secretory cells differ from cell types of the PD. Using the highly specific ligand 

\[ ^{125} \text{I}} \text{iodomelanotin the PT has been demonstrated to contain receptors of this hormone mediating an inhibitory influence on cAMP accumulation. These results have raised the question concerning which physiological effects ascribed to melatonin could be mediated by the PT as target organ. Specific seasonal changes in cytological and immunohistochemical parameters of the PT in hamsters and hedgehogs suggest a reduction in cell activity during short photoperiods or hibernation. As demonstrated in hibernating ground squirrels (45) seasonal changes of number or affinity state of melatonin binding sites have also been taken into account. In addition to secretion patterns of melatonin, the receptivity for melatonin may play an important role in the response of the PT to melatonin.

Thus earlier hypotheses (4, 6, 8) concerning PT function are revived and can be elaborated in the following way: PT cells may exert a modulating effect on the PD which may be influenced by melatonin. This could be effected by a PT peptide hormone released into and distributed by the portal vessel system. Gonadotropic and thyrotropic functions, in particular, may be modulated in this way. Thus, gonadotropic and thyrotropic effects of the pineal gland could be explained by the PT as melatonin target mediating neuroendocrine effects. Alternatively, endocrine effects of PT secretory products on hypothalamic or peripheral endocrine tissues via general circulation may occur.

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