The TSH receptor in the pituitary and its clinical relevance
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SUMMARY

Aim of the thesis

When patients with Graves’ hyperthyroidism are treated with antithyroid drugs, they usually become clinically euthyroid within 1-3 months. Thyroid hormone levels normalise and the TBII titre usually declines. Remarkably, this restoration of euthyroidism is not always paralleled by normalisation of plasma TSH levels. These can remain suppressed for several months up to years, despite adequate antithyroid treatment. To date, the explanation for this phenomenon has been that TSH secretion by the pituitary thyrotrophs slowly recovers from the prolonged suppression of TSH production and secretion by excess thyroid hormone. However, experimental evidence supporting this hypothesis has been lacking so far. Thus, the aim of the studies described in this thesis was to provide a more plausible explanation for the long-term suppression of plasma TSH frequently seen in treated Graves’ disease patients that are otherwise euthyroid.

We hypothesised that in addition to the classic endocrine control mechanisms, provided by hypothalamic TRH and peripheral thyroid hormones, TSH secretion is also regulated through autocrine or paracrine mechanisms within the anterior pituitary. In this view, TSH secretion is directly monitored near its site of production. The most direct way of achieving such a control mechanism is by the expression of a TSH receptor in the pituitary; either by the thyrotrophs themselves or by one or more intermediate cell types. Ligand binding would then ultimately result in down regulation of TSH secretion. This additional control mechanism could enable fine-tuning of TSH secretion, with TRH and thyroid hormones as the most potent and main determinants of plasma TSH levels.

During Graves’ hyperthyroidism, autoantibodies directed against the TSH receptor (TSAb) might act as agonists that, like TSH, stimulate not only the thyroid but also the pituitary TSH receptor thereby causing down regulation of TSH secretion. Since TSAb can remain present for months up to years, they might well be the cause of the long-term suppression of TSH plasma levels in euthyroid Graves’ disease patients, even when thyroid hormone levels have been normalised by adequately treating these patients with antithyroid drugs and subsequent thyroid hormone replacement.
Summary of the results

In chapter 2 we showed that full length TSH receptor is indeed expressed in the human anterior pituitary. Using combined immunohistochemistry and in situ hybridisation, as well as double immunohistochemistry, we phenotypically characterised the cell types bearing this TSH receptor as a subset of folliculo-stellate cells. These cells make up approximately 10% of the anterior pituitary cell population and have been well recognised as paracrine mediators of anterior pituitary hormone secretion. Furthermore, this finding was supported by the functional expression of the TSH receptor in a murine folliculo-stellate cell line (chapters 5 and 6).

Chapter 3 describes that TSAb are indeed capable to suppress plasma TSH levels without the involvement of thyroid hormones. Hence, TSAb-containing immunoglobulins, in contrast to normal human immunoglobulins, induced a decrease in plasma TSH levels in rats that were unable to mount a thyroid response. Since the pituitary resides outside the blood brain barrier, this strongly suggests that this action of TSAb is mediated through stimulation of the pituitary TSH receptor.

The ability of TSAb to decrease plasma TSH levels through an extrathyroidal pathway was further supported in a prospective clinical study (chapter 4). Euthyroid Graves’ disease patients that were treated with antithyroid drugs showed significantly lower plasma TSH levels when they had a positive TBII titre, as compared to TBII-negative patients. Thyroid hormone levels did not differ between TBII-positive and TBII-negative groups. TSH plasma levels correlated quantitatively with TBII titres and not with fT4, fT3, duration of the thyroid disease, nor the L-T4 dose they received, further supporting the hypothesis that TSAb indeed act as a ligand for the pituitary TSH receptor, resulting in down regulation of TSH secretion.

In chapters 5 and 6 post-receptor effects through which the folliculo-stellate cells might down regulate TSH secretion in the thyrotrophs were studied. Using a murine folliculo-stellate cell line, we showed that in contrast to the TSH receptor in thyroid follicular cells, the pituitary TSH receptor does not signal through the classical adenylate cyclase/cAMP pathway, nor through the phospholipase C/intracellular calcium pathway. Instead, we provide evidence that TSH activates the JAK/STAT signalling cascade. However, instead of activating the transcription factor STAT3, as has been demonstrated by others in a rat thyroid follicular cell line and in Chinese hamster ovary cells transfected with the human TSH
receptor, stimulation of the pituitary TSH receptor induces up regulation of STAT5a transcripts.

TGF-β2 is identified as one of the target genes of TSH in the folliculo-stellate cell line (chapter 6). This indicates that this growth factor could be the paracrine mediator that provides the cross talk between TSH-stimulated folliculo-stellate cells and thyrotrophs. However, it remains to be elucidated whether TGF-β2 indeed down regulates TSH secretion by the thyrotrophs.

Folliculo-stellate cells not only expresses the TSH receptor. Transcripts of growth hormone receptor and adrenocorticotropic receptor were also detected (chapter 5). This suggests that folliculo-stellate cells might be involved in the paracrine control of other adenohypophyseal hormones too. Remarkably, receptors for follicle-stimulating hormone, luteinizing hormone and prolactin were not detected in the cell line. Apparently, hormones involved in reproductive functions escape paracrine regulation by folliculo-stellate cells.

Summarising, the studies described in this thesis strongly support the hypothesis that TSH secretion is regulated within the pituitary through an ultra-short negative feedback loop mediated by a TSH receptor on folliculo-stellate cells. By binding to this receptor, TSAb are responsible for the long-term suppression of TSH plasma levels in otherwise euthyroid Graves’ disease patients treated with antithyroid drugs. Stimulation of the TSH receptor activates the JAK/STAT signalling pathway and up regulates TGF-β2 in folliculo-stellate cells. TGF-β2 might be the paracrine factor that is secreted by the folliculo-stellate cells to cause down regulation of thyrotroph TSH secretion.