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Extrathyroidal expression of TSH receptor

Expression thyroïdienne du récepteur de TSH

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Résumé

Le récepteur de TSH s'exprime à la surface des cellules folliculaires de la thyroïde et possèdent un rôle crucial dans la régulation de la fonction et de la croissance de la glande thyroïde. Ces dernières années, il est apparu évident que le récepteur de la TSH est aussi exprimé largement dans une variété de tissus extrathyroïdiens incluant l'antéhypophyse, l'hypothalamus, l'ovaire, le testicule, la peau, le rein, le système immun, la moelle osseuse et les cellules sanguines circulantes, le tissu adipeux blanc et brun, les fibroblastes orbitaires préadipocytaires, et l'os. Un grand nombre de preuves émergent démontrant le rôle fonctionnel du récepteur de TSH à ces différents sites, même si en plusieurs circonstances leur importance physiologique constitue un sujet de controverses et d'intérêt. La compréhension actuelle des actions du récepteur de TSH dans le tissu extrathyroïdien et de leurs possibles implications physiologiques est ici discutée.

Mots clés : TSH ; Récepteur de TSH ; Thyrostimuline ; Extrathyroïdien

Abstract

The TSH receptor expressed on the cell surface of thyroid follicular cells plays a pivotal role in the regulation of thyroid status and growth of the thyroid gland. In recent years it has become evident that the TSH receptor is also expressed widely in a variety of extrathyroidal tissues including: anterior pituitary; hypothalamus; ovary; testis; skin; kidney; immune system; bone marrow and peripheral blood cells; white and brown adipose tissue; orbital preadipocyte fibroblasts and bone. A large body of evidence is emerging to describe the functional roles of the TSH receptor at these various sites but their physiological importance in many cases remains a subject of controversy and much interest. Current understanding of the actions of the TSH receptor in extrathyroidal tissues and their possible physiological implications is discussed.

Keywords: Thyroid stimulating hormone; TSH; TSH receptor; Thyrostimulin; Extra-thyroidal

1. Introduction

The thyroid stimulating hormone (TSH) receptor (TSHR) is a 7-transmembrane domain G protein-coupled receptor expressed at high levels in thyroid follicular cells. Binding of TSH to the TSHR principally activates cAMP signaling and results in increased iodide uptake, thyroid hormone synthesis and secretion, and proliferation and growth of thyroid follicular cells [1,2]. These responses mediate an important role for the TSHR in maintenance of thyroid status by the hypothalamic-pituitary-thyroid (HPT) axis, which maintains thyroid hormones and TSH in a reciprocal relationship. Despite these well-established physiological actions that control thyroid follicular cell growth and thyroid hormone production, it is now recognized that the TSHR is also expressed widely in extrathyroidal tissues.

2. Anterior pituitary Gland

In the anterior pituitary gland, TSHR expression has been identified in folliculo-stellate cells and postulated to mediate short paracrine feedback inhibition of TSH secretion from anterior pituitary thyrotrophs [3,4]. This activity of the TSHR in folliculo-stellate cells may further contribute to control of thyroid status by the HPT axis. Intriguingly, a novel high affinity ligand for the TSHR was also identified recently. Thyrostim-

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ulin is a glycoprotein hormone, comprised of α and β-subunits encoded by *GPA2* and *GPB5*, which stimulates cAMP production after binding the TSHR [5]. It is expressed in the anterior pituitary and hypothalamus and, although its physiological role is unclear, thyrostimulin may also be involved in paracrine regulation of TSH signaling via local actions mediated by TSHR expressed in the pituitary [5–7].

3. Hypothalamus

The TSHR also has unexpected but important actions in the regulation of seasonal reproduction. The changing seasons are critical for animals living in temperate zones and for migratory birds, in which reproduction must be controlled according to seasonal variations in the day-night photoperiod. Sensing of the photoperiod and subsequent control of gonadal growth by light-induced leutinizing hormone (LH) secretion is localized in the mediobasal hypothalamus. Detailed studies in the Japanese quail (*Coturnix japonica*) have shown the photoperiod response is triggered by light-induced expression of TSH in the pars tuberalis [8]. TSH from the pars tuberalis activates a TSHR-cAMP mediated pathway in ependymal cells of the mediobasal hypothalamus that involves the type 2 iodothyronine deiodinase enzyme and results in LH secretion and gonadal growth [9]. In mammals the photoperiod response is initiated by melatonin but is otherwise conserved and also involves TSH, TSHR and the type 2 iodothyronine deiodinase. Thus, seasonal reproduction in mammals and birds is controlled by conserved mechanisms that involve activation of the TSHR in the mediobasal hypothalamus [10,11].

4. Gonads

Further studies in the European sea bass (*Dicentrarchus labrax*) indicate that seasonal effects of TSH on gonadal growth may also be mediated directly by the TSHR expressed in ovary and testis [12]. Seasonal alterations in TSHR mRNA expression were identified associated with seasonal changes in gametogenesis and gonadal maturation, indicating a possible direct role for TSHR in the ovary and testis. Intriguingly, recent studies in the rat also identified TSHR expression in the ovary. In these studies TSHR mRNA was regulated positively by gonadotrophins and negatively by oestrogen in granulosa cells [13]. Expression of the thyrostimulin subunits *Gpa2* and *Gpb5* was also identified in developing oocytes, and studies with a TSHR-expressing human ovarian cell line treated with recombinant thyrostimulin demonstrated increased cAMP activity in the presence of follicle stimulating hormone. These findings were interpreted to suggest the presence of a local paracrine signaling pathway in the ovary that is regulated by FSH and oestrogen and which involves thyrostimulin secreted from the developing oocyte acting at the TSHR expressed on granulosa cells [13].

5. Epidermis and hair follicles

Additional studies outside the central nervous and reproductive systems suggest further diverse roles for the TSHR and HPT axis. Components of the axis including thyrotrophin releasing hormone (TRH), TRH receptor, TSH, thyrostimulin and the TSHR are expressed in cells of the skin epidermis and in hair follicles [14–17]. Treatment of organ cultures with TSH resulted in altered hair follicle gene expression and stimulation of epidermal cell differentiation, whilst treatment with TRH stimulated hair growth [16,17]. Furthermore, skin was found to synthesize a local supply of TSH that was regulated by TRH and thyroid hormones in a way that is analogous to feedback control of the classical HPT axis [15]. The physiological importance of these findings, however, will require further study as detection of HPT axis components in the skin and hair follicle requires highly sensitive RT-PCR and immunodetection techniques. Nevertheless, the intriguing possibility of a functional local HPT axis in the skin is an emerging avenue of research.

6. Kidney

Demonstration of TSH expression by ribonuclease protection and immunohistochemistry has also been demonstrated in normal human kidney and adrenal tissue [18]. Additional studies confirmed TSHR expression in the kidney by RT-PCR. Furthermore, treatment of primary human kidney cells with TSH resulted in increased cAMP production, suggesting the TSHR may be functional in renal cells [19], although more extensive studies will be necessary to investigate the implications of this work.

7. Immune system and circulating blood

A body of evidence is now accumulating in support of a role for TSHR expression and signaling in bone marrow, thymus, peripheral blood and immune cells, tissue T lymphocytes and dendritic cells [18,20–26]. In the bone marrow, immature CD45-positive leukocyte precursors synthesize and secrete TSH whilst cluster of differentiation molecule 11b (CD11b) negative lymphocyte precursor cells secrete tumour necrosis factor-α (TNF-α) in response to TSH, suggesting a local paracrine TSH-TSHR signaling pathway that regulates haematopoietic responses to TNF-α [20]. More recent studies indicate that TSH also inhibits cytokine-induced TNF-α production from CD11b-positive bone marrow cells via a pathway involving activation of the activator protein-1 (AP-1) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB) transcription factors [21]. Thus, the role of TSHR signaling in bone marrow is complex with opposing effects on TNF-α secretion observed in different stromal cell subsets. In addition to the suggested effects of TSH-stimulated TNF-α production on haematopoiesis, the effect of TSH to inhibit TNF-α production from CD11b-positive cells has been proposed to inhibit osteoclast formation and bone resorption [21].

In peripheral blood the TSHR is expressed on erythrocytes where it may influence activity of the Na(+)/K(+)-ATPase [22], and on lymphocytes where its effects are less clear [23,24]. In the intestinal epithelium the TSHR receptor is expressed on intraepithelial lymphocytes and local production of TSH by intestinal epithelial cells regulates recruitment, development and