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doi:10.6072/H0.MP.A002333.01
Volume 2, Issue 1, 2013

Review Article Open Access

Tsh receptor

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The TSH receptor is a member of the G protein-coupled receptor(GPCR)family. It is one of the glycoprotein hormone receptors, which also includes the FSH and LH/CG receptors. The TSH receptor mediates the action of the pituitary-derived glycoprotein, TSH (thyroid stimulating hormone, thyrotropin or thyrotrophin). TSH binds to the TSH receptor which is located on thyroid follicular cells (but is also expressed in extrathyroidal sites). Glycosylation of the TSH receptor occurs, as does cleavage of the receptor from an intact to an extracellular form (α subunit), which may be shed after deletion of a short region (aa 316-366) near the C terminal of the extracellular domain, thus leaving a transmembrane form (β subunit). The α subunit is responsible for ligand/autoantibody binding, facilitated by glycosylation and possibly by the extracellular loops of the 7 transmembrane segments. The intracellular loops of the β subunit interact with G proteins when the receptor is activated. The receptor may also exist in multimeric forms, although it is not clear whether these forms play a role in TSH receptor function. TSH action involves cAMP and IP/DAG responses. The TSH receptor controls positively both the function (production of thyroid hormones T3 and T4) and growth of the thyroid.

KEYWORDS
Thyroid stimulating hormone receptor; Thyrotrophin receptor; Thyrotropin receptor; Tsh receptor; TSH-R; Tshr

IDENTIFIERS
Molecule Page ID:A002333, Species:Mouse, NCBI Gene ID: 22095, Protein Accession:NP_035778.3, Gene Symbol:Tshr

PROTEIN FUNCTION
The TSH (thyroid simulating hormone, thyrotropin or thyrotrophin) receptor is a seven transmembrane domain receptor which mediates the action of the pituitary derived glycoprotein TSH. TSH binds to the TSH receptor located on the baso-lateral surface of thyroid follicular cells and facilitates production of the thyroid hormones T4 and T3. The TSH receptor is a member of the G protein-coupled receptor superfamily. It is proposed that the basal state of the receptor is due to inhibition of function resulting from interaction between the extracellular and transmembrane domains; thus the extracellular domain itself functions as a tethered inverse agonist (Vlaeminck-Guillem *et al*. 2002). Binding of TSH to the extracellular domain is proposed to lead to full activation of the receptor. In addition to stimulation of thyroid hormone production, TSH stimulates iodine uptake, thyroid growth and also protects thyroid cells from apoptosis (Szkudlinksi *et al*. 2002). The TSH receptor is activated by TSH, thyroid auto-antibodies and activating mutations (Rodien *et al*. 2003, Kleinau *et al*. 2007). Outside the autoimmune field, abnormal function of the TSH receptor is associated with congenital hypothyroidism, hereditary nonautoimmune hyperthyroidism and toxic adenomas(Schoneberg *et al*. 2004, Szkudlinksi *et al*. 2002, Corvilain *et al*. 2001, Gruters *et al*. 2004, Smit *et al*. 2007, Vassart and Costagliola. 2011).

REGULATION OF ACTIVITY
Binding of TSH occurs to specific residues in the concave portion of the extracellular leucine-rich repeat domain (LRRD) of the TSH receptor (Nagayama *et al*. 1990, Smits *et al*. 2003). After bovine TSH binding to the human TSH receptor, interaction with the so-called “hinge” region, common to other glycoprotein hormone receptors, occurs within the N-terminal extracellular region. Thereafter, conformational changes in the receptor and signal transduction through the transmembrane region occur (Mueller *et al*. 2008, Vassart *et al*. 2009). Glycosylation of the TSH receptor occurs, as does cleavage of the receptor from an intact form to an extracellular form (α subunit)(which may be shed) and a transmembrane form (β subunit), which is membrane bound (Rapoport *et al*. 1998). The intracellular loops of the β subunit interact with G-proteins (G_s and G_q: Allgeier *et al*. 1994) when the receptor is activated. The receptor may also exist in multimeric forms although the role in TSH receptor function is not clear. TSH activation leads to c-AMP and inositolphosphate responses (Van Sande *et al*. 1995).

INTERACTIONS
The extracellular region of the TSH receptor interacts with its ligand TSH (reviewed in Rapoport *et al*. 1998 and Szkudlinski *et al*. 2002). G protein recognition occurs upon the intracellular loops of the receptor (Claus *et al*. 2006). Although a high degree of sequence homology exists with other glycoprotein hormone receptors, this is not usually of any clinical consequence. Exceptions are rare conditions such as hydatidiform mole, choriocarcinoma, metastatic embryonal carcinoma of the testis and mutations of the hormone binding domain of the receptor, in which HCG cross-reacts with the TSH receptor and induces hyperthyroidism (Pekonen *et al*. 1988, Hershman *et al*. 1988, Yoshikawa *et al*. 1989, Rodien *et al*. 1998).

Two glycoprotein hormone subunits (glycoprotein hormone α2-subunit or GPA2 and glycoprotein hormone β5-subunit or GPB5), localised in pituitary, eye or testis in the rat, and known as thyrostimulin, form heterodimers in vitro and show affinity for the TSH receptor, similar to that seen with TSH (Nagasaki *et al*. 2006).

In addition to the endogenous ligand TSH, TSH receptor stimulating autoantibodies (associated with Graves’ disease) bind to the TSH receptor, typically to epitopes of the extracellular component of the receptor which are distinct (allosteric) from binding sites for TSH (ie., orthosteric binding sites) (Sanders *et al*. 2007, Costagliola *et al*. 2004). A number of TSH receptor monoclonal antibodies that bind to various allosteric sites of the receptor and may also act as agonists,

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Published online: 21 Dec 2012 | doi:10.6072/H0.MP.A002333.01

antagonists or inverse agonists have been described (Sanders *et al*. 2004, Chen *et al*. 2008, Chen *et al*. 2009, Sanders *et al*. 2010). Small molecule ligands of the TSH receptor, which have agonistic or antagonistic activity to TSH and TSH stimulating antibodies have also been developed (Neumann *et al*. 2008, Neumann *et al*. 2009, Neumann *et al*. 2011), as have modified forms of TSH, which may possess properties of superagonism (Szkudlinski *et al*. 1996, Grossmann *et al*. 1998, Leitolf *et al*. 2000) or antagonism (Morris *et al*. 1990, Fares *et al*. 2001).

PHENOTYPES

TSH receptor knockout mice present with developmental and growth delays and are profoundly hypothyroid, dying within one week of non-replacement with thyroid hormone (Marians *et al*. 2002) although heterozygotes are unaffected. Affected animals produce uniodinated thyroglobulin and lack sodium-iodide symporter expression. An immune response to the TSH receptor is inducible in TSH receptor knockout mice (Nakahara *et al*. 2010).

Selective knockout of the TSH receptor in adipocytes using the Cre-loxP system results in reduced TSH-induced lipolysis (Elgadi *et al*. 2010).

GPB5 knockout mice show hypothyroxinemia, especially in juvenile mice (van Zeijl *et al*. 2010).

Selective knockout of the α subunit of G_q/G_{11} in the thyroid in mice results in reduced iodine organification and thyroid hormone secretion in response to TSH, hypothyroidism and a lack of thyroid proliferative response to TSH or a goitrogenic diet (Kero *et al*. 2007).

A range of gain of function and loss of function TSH receptor mutations have now been described in human hyperthyroidism (including toxic adenomas) and hypothroidism (e.g. Tonacchera *et al*. 2004, Jordan *et al*. 2003, Sykiotis *et al*. 2003, Lee *et al*. 2002, Nagashima *et al*. 2001, Kosugi *et al*. 2000, Tonacchera *et al*. 1998, Krohn *et al*. 1998, Fuhrer *et al*. 1997, Parma *et al*. 1997, Duprez *et al*. 1997, deRoux *et al*. 1996).

Glycoprotein hormone receptor databases are available for mutation information (Van Durme *et al*. 2006: available at http://gris.ulb.ac.be and Kreuchwig et al. 2011: available at http://www.ssfa-gphr.de).

MAJOR SITES OF EXPRESSION

The major site of TSH receptor expression is the thyroid follicular cell, but extrathryoidal expression also occurs. The TSH receptor protein has been detected in fibroblasts and adipose tissue in normal subjects and in patients with Graves' ophthalmopathy and pretibial myxoedema and is involved in adipogenesis (Daumiere *et al*. 2002). In addition, the TSH receptor has been detected in extraocular, but not non-ocular or cardiac muscle of normal subjects (Kloprogge *et al*. 2005, Kloprogge *et al*. 2006, Busuttil *et al*. 2001). It is also present in the brain in ependymal cells of the mediobasal hypothalamus, where it participates in the photoperiodic regulation of endocrine functions (Ono *et al*. 2008, Yasuo *et al*. 2011). TSH receptor transcripts are also found in other extrathyroidal sites (in the mouse): these include the olfactory bulb, pituitary gland, retina, adrenal gland, aorta, vena cava, trachea, kidney, bone marrow, ovary, testis, uterus and skin (Regard *et al*. 2008; data are available at http://pdsp.med.unc.edu/ShaunCell/home.php). The functional significance of these extrathyroidal TSH receptor transcripts is unknown. The TSH receptor is also present in osteoclasts and may have an anti-resorptive role in bone function (Abe *et al*. 2003, Abe *et al*. 2007, Sun *et al*. 2008). However, others have found that thyroid hormone, rather than TSH, may play a role in regulating bone function (Bassett *et al*. 2008).

SPLICE VARIANTS

The major transcript encoding the human TSH receptor has 10 exons and a transcript length of 4410 bp (found at http://www.ncbi.nlm.nih.gov/nuccore/NM_000369.2). Two alternatively spliced variants, "transcript variant 2" and "transcript variant 3", are described (found at http://www.ncbi.nlm.nih.gov/nuccore/NM_001018036.2 and /NM_001142626.2, respectively). There are a number of other splice variants described (found at http://ncbi.nlm.nih.gov/IEB/Research/Acembly/av.cgi?c=geneid&org=9606&l=7253). There is no evidence for any functional relevance of these splice variants.

The TSH receptor is also subject to post-translational cleavage. Thus, a short polypeptide region (aa 316-366) near the C terminal of the extracellular domain may be deleted (Loosfelt *et al*. 1992, Chazenbalk *et al*. 1997), leading to α subunit loss (Couet *et al*. 1996). The functional relevance of this α subunit shedding is unclear, but it may play a role in receptor signalling, trafficking and internalization (Latif *et al*. 2009).

REGULATION OF CONCENTRATION

The gene encoding the TSH receptor is localised on chromosome 14q31 and consists of 10 exons, over 60kb (Libert *et al*. 1990, Rousseau-Merck *et al*. 1990, Gross *et al*. 1991). Downregulation of the TSH receptor protein occurs in the presence of its natural ligand TSH (Nagayama *et al*. 1994). In addition, phosphodiesterase induction downregulates cAMP accumulation when the receptor is stimulated (Persani *et al*. 2000). Subsequent recycling to the cell surface occurs (Baratti-Elbaz et al. 1999) and involves an hScrib-betaPIX-GIT1-ARF6 pathway (Lahuna *et al*. 2005).

ANTIBODIES

Anti-TSH receptor antibodies are commercially available.

Abnova

Mouse monoclonal antibody clone 4C1/E1/G8 against extracellular region of recombinant human TSH receptor (catalog number MAB3576).

Mouse monoclonal antibody clone 3A6 against full length recombinant human TSH receptor (catalog number MAB6678).

Rabbit polyclonal antibody against synthetic peptide of extracellular region of human TSH receptor (catalog number PAB15551).

ThermoScientific

Mouse monoclonal antibody clone 28 against extracellular region of recombinant human TSH receptor (catalog number MA3-217).

Mouse monoclonal antibody clone 49 against extracellular region of recombinant human TSH receptor (catalog number MA3-218).

Rabbit polyclonal antibody against synthetic peptides of human

TSH receptor conjugated to KLH (catalog number PA1-23530).

RSR Limited for Autoimmune Diagnostics

Monoclonal antibody against human TSH receptor (blocking type)(catalog number K170/FD/0.01).

Monoclonal antibody against human TSH receptor (stimulating type)(catalog number M22/FD/0.004 and M22/FD/0.04).

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
Tshr	plasma membrane	
receptor-ligand interactions	plasma membrane	
covalent/postranslational modifications	plasma membrane	
Small molecule agonists/antagonists	extracellular region	Neumann S *et al.* 2009; Neumann S *et al.* 2011
TSHR activates Gs protein	plasma membrane	Allgeier A *et al.* 1994
TSHR activates Gq protein	plasma membrane	Allgeier A *et al.* 1994
covalent/postranslational modifications	extracellular region	Costagliola S *et al.* 2002
Receptor-ligand	plasma membrane	Nagasaki H *et al.* 2006; Rapoport B *et al.* 1998

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