ABSTRACT. Resistance to TSH is a syndrome of reduced sensitivity to a biologically active TSH molecule. Subjects have elevated TSH levels but no goiter. However, thyroid hormone concentration may vary from normal to very high, depending on the severity of the resistance. Individuals with very high TSH, low T4 and hypoplastic thyroid glands can be mistakenly diagnosed as having primary hypothyroidism due to a defective development of the thyroid gland. Those with normal or slightly decreased T4 can be misdiagnosed as having central hypothyroidism especially if their serum TSH concentration is only slightly elevated. Mutations in the TSH receptor (TSHr) gene have been reported in 16 families with homozygous or compound heterozygous inheritance. The mutant TSHrs show reduced or no function due to either altered ligand binding or defect in membrane targeting. Some individuals, heretozygous for a TSHr gene mutation can present mild resistance to TSH manifesting as euthyroidism with slight hyperthyrotropinemia. A larger proportion of families express the phenotype of resistance to TSH in the absence of a TSHr defect. In many the inheritance is dominant and the genetic cause has not been yet determined.

©2003, Editrice Kurtis

THYROID HORMONE SUPPLY
The constant supply of thyroid hormone is ensured by two mechanisms: 1) secretion of hormone controlled by a feedback system involving the hypothalamo-pituitary-thyroid axis, and 2) hormone activation within the cells regulated by tissue iodothyronine deiodinases. TSH, originating from thyrotrrophs in the pituitary gland, promotes the synthesis and secretion of thyroid hormone, principally 3,5,3',5'-tetraiodothyronine or T4. TSH synthesis and secretion is, in turn, stimulated by TRH, a tripeptide derived from the median eminence of the hypothalamus (1). The synthesis and secretion of TSH, as well as action of TRH, are inhibited by T3, the active thyroid hormone generated by 5'-monodeiodination of T4 (2, 3). Thus, homeostatic supply of thyroid hormone is insured by the negative feedback on its precursor, T4, and the production of T3 by intracellular, tissue specific T4 deiodinases.

MEDIATION OF TSH ACTION
TSH is a heterodimeric glycoprotein molecule of pituitary origin, which exerts its biological effect by binding to the extracellular domain (ectodomain) of the TSH receptor (TSHr) molecule located in the basal membrane of thyroid follicular cells. By doing so, TSH relieves the transmembrane (serpentine) portion of the TSHr from the inhibitory effect of the ectodomain and converts this receptor into a full agonist (4, 5). The process is translated in the activation of the guanine nucleotide-binding (G) protein to which the TSHr is coupled. Activation involves the dissociation of the α5 subunit of the G protein (G5α) that in turn increases the activity of adenyl cyclase, leading to the generation of cAMP. In some species, including man, TSHr also activates the phospholipase C through Gq, resulting in the production of diacylglycerol and inositol phosphate (IP). cAMP is, however, the principal second messenger that mediates virtually all the biological effects of TSH (6, 7).
**TSHR STRUCTURE AND GENE ORGANIZATION**

TSHr, a member of the large family of G protein-coupled receptors (8), is a single chain glycoprotein of 744 amino acids and approximately 100 kDa (Fig. 1). It has seven transmembrane segments connected by three extracellular and three intracellular loops. As other glycoprotein hormone receptors [LH/chorionic gonadotropin receptor (LH/CGr) and FSH], TSHr has a long aminoterminal ectodomain of 398 amino acids that is rich in oligosaccharide chains (6 potential sites of N-linked glycosylation). This domain of the TSHr is composed of eight leucine-rich repeat motifs (not to be confused with leucine zippers) forming a horseshoe-shaped sector (9). The inner concave surface of this structure is composed of curved parallel β-sheets that interact with the protein ligand. The specificity of ligand interaction, in this case TSH as well as some abnormal thyroid stimulators, is likely dependent on the composition of non-conserved residues. The intracellular, carboxyterminal domain is short (76 amino acids) and devoid of carbohydrate residues. TSHr is encoded by a single gene copy located on chromosome 14 (10). It spans more than 60 kbp and is composed of 10 coding exons (11) (Fig. 1). Exons 1 through 9 are small and encode the ectodomain of the TSHr. The large terminal exon 10 is more than 1490 bp long and encodes 1/3 of the ectodomain as well as the entire transmembrane and intracellular domains. The major mRNA species of TSHr is 4.6 kb long, owing to a long 3’ untranslated segment. It contains an open reading frame of 2292 nucleotides (12).

**DEFINITION AND PHENOTYPE OF RESISTANCE TO TSH**

Resistance to TSH (RTSH) is a syndrome of variable hyposensitivity to a biologically active TSH molecule. The defect is characterized by: 1) elevated levels of serum TSH; 2) absence of goiter (normal or hypoplastic thyroid gland); and 3) normal to very low serum levels of thyroid hormone, depending on the degree of TSH insensitivity. Thus, metabolically, subjects can present with euthyroid hyperthyrotropinemia, at the one extreme of the spectrum, or severe hypothyroidism, at the other.

---

**Fig. 1 - Structure and gene organization of the TSH receptor (TSHr).** The diagram depicts the extracellular, transmembrane and intracellular domains of the molecule. Exons encoding each segment of the molecule are indicated by alternating colored boxes corresponding to the similarly colored circles, each representing an amino acid. Note the large size of the principal mRNA species, owing to its extended 3’-untranslated region. For details see text.