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Review

Resistance to thyroid hormone mediated by defective thyroid hormone receptor alpha ☆

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ABSTRACT

Background: Thyroid hormone acts *via* receptor subtypes (TRα1, TRβ1, TRβ2) with differing tissue distributions, encoded by distinct genes (*THRA*, *THRB*). *THRB* mutations cause a disorder with central (hypothalamic–pituitary) resistance to thyroid hormone action with markedly elevated thyroid hormone and normal TSH levels.
Scope of review: This review describes the clinical features, genetic and molecular pathogenesis of a homologous human disorder mediated by defective *THRA*. Clinical features include growth retardation, skeletal dysplasia and constipation associated with low-normal T4 and high-normal T3 levels and a low T4/T3 ratio, together with subnormal reverse T3 levels. Heterozygous TRa1 mutations in affected individuals generate defective mutant receptors which inhibit wild-type receptor action in a dominant negative manner.
Major conclusions: Mutations in human TRα1 mediate RTH with features of hypothyroidism in particular tissues (*e.g.* skeleton, gastrointestinal tract), but are not associated with a markedly dysregulated pituitary–thyroid axis.
General significance: Human *THRA* mutations could be more common but may have eluded discovery due to the absence of overt thyroid dysfunction. Nevertheless, in the appropriate clinical context, a thyroid biochemical signature (low T4/T3 ratio, subnormal reverse T3 levels), may enable future identification of cases.
This article is part of a Special Issue entitled Thyroid hormone signalling.

1. Introduction

The cellular entry of thyroid hormones (thyroxine (T4) and triiodothyronine (T3)), particularly in the central nervous system is importantly mediated by monocarboxylate transporter 8 (MCT8), a membrane transporter. Intracellularly, deiodinase enzymes (DIOs) mediate hormone metabolism, with a high-affinity type 2 enzyme (DIO2) mediating T4 to T3 conversion in the central nervous system (CNS) including pituitary and hypothalamus, type I deiodinase (DIO1) in peripheral tissues generating T3, and type 3 deiodinase (DIO3) mediating catabolism of thyroid hormones to inactive metabolites. The effects of thyroid hormones on physiologic processes are mediated principally by a receptor protein, the thyroid hormone receptor (TR), belonging to the steroid/nuclear receptor superfamily of ligand-inducible transcription factors, which modulates target gene expression in different tissues. TR binds preferentially to regulatory DNA sequences (thyroid hormone response elements, TREs) in target gene promoters as a heterodimer with the retinoid X receptor (RXR), although the receptor can bind some TREs as a homodimer or monomer. In the absence of hormone, unliganded receptor homodimers/heterodimers recruit corepressors (*e.g.*, nuclear receptor corepressor [NCoR]; silencing mediator for retinoic acid and thyroid receptors [SMRT]) to repress or "silence" gene transcription. Hormone binding results in corepressor dissociation and relief of repression together with ligand-dependent transcriptional activation, mediated by a complex of coactivators (*e.g.*, steroid receptor coactivator 1 [SRC-1], CREB-binding protein [CBP], and CBP-associated factor [pCAF]) [1]. In humans, two highly homologous thyroid hormone receptors, TRα and TRβ are encoded by genes on chromosomes 17 and 3, respectively. Two different proteins are generated from the *THRA* locus by alternate splicing: TRα1 is an ubiquitously expressed receptor isoform, with particular abundance in the central nervous system, myocardium, gastrointestinal tract and skeletal muscle; TRα2, which exhibits a modified carboxy-terminal region such that it is unable to bind hormone, is expressed in a variety of tissues (*e.g.*, brain and testis) and its biological function is poorly understood. The REV-ERBα gene, located on the opposite strand of the *THRA* locus, is transcribed to generate a nuclear receptor which is involved in regulating circadian rhythm [2]. *THRB* generates two major receptor isoforms, TRβ1 and TRβ2, which differ in their amino-terminal regions; TRβ1, which is widely expressed, is the predominant isoform in liver and kidney, while TRβ2 expression is limited principally to the hypothalamus, pituitary, inner ear, and retina [3].

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Resistance to thyroid hormone (RTH), a dominantly-inherited disorder due to *THRB* mutations, is readily recognised due to a characteristic biochemical signature of elevated circulating T4 and T3 with non-suppressed pituitary TSH levels reflecting central (hypothalamic–pituitary) refractoriness to thyroid hormone action and is associated with variable refractoriness to hormone action in peripheral tissues [4]. Here, we describe a homologous human disorder mediated by defective *THRA*, manifesting with some features of hypothyroidism (*e.g.* growth and developmental retardation, skeletal dysplasia, constipation) but associated with near-normal thyroid hormone and TSH levels [5,6].

2. Case histories

Proband 1 (female child, age 6 years) came to attention at age 9 months with growth retardation, which persisted such that from age 3 years onwards her height was recorded at 1.5 SD–2.5 SD below the mean; the short stature was disproportionate with a normal sitting height but reduced subischial leg length >2 SD below the mean. Her weight was >1 SD above the mean, resulting in a borderline high BMI of 23.5. She was mildly dysmorphic with macrocephaly (head circumference +2 SD) and a flattened nasal bridge. Dentition was delayed; she had no teeth at the age of 1, only 8 teeth at the age of 26 months, and no secondary dentition at the age of 6 years, 4 months. Following weaning, constipation was a chronic problem, requiring regular laxatives and associated with severe abdominal distension.

Proband 2 (female child, 11 years) was initially referred to the department of endocrinology at the age of 2 years and 10 months for low serum FT4 (0.65 ng/dl [reference range 0.7–1.85 ng/dl]). Despite the low FT4, her serum T3 was raised (2.46 ng/ml [0.5–1.4 ng/ml]), in combination with a normal TSH (2.07 mU/L [0.4–4.3 mU/l]) [6].

Her medical history revealed a hospitalisation at 9 months of age, because of delayed motor development. At that age, she was not able to sit by herself and she did not have full control of head movement. In addition, she had delayed closure of skull sutures, macroglossia, delayed tooth eruption, and she suffered from congenital hip dislocation. X-ray examination showed absence of the hip ossification centres.

At six years of age, she was investigated for short stature, and bone age was clearly delayed (3 years instead of 6 years). Laboratory tests again revealed low circulating FT4, in combination with normal TSH and high-normal T3 levels. Clinically she had hypothyroidism with dry skin and hair, slow deep tendon reflexes, slow reactions and drowsiness.

Her father (47 years of age) is also short (height 3.7 SD below normal), and has similar thyroid function tests as his daughter. Constipation is a feature in both subjects.

3. Molecular genetics

Proband 1 is heterozygous for a nonsense mutation (E403X) in the thyroid hormone receptor alpha gene (*THRA*) which has arisen *de novo* in the patient, being absent in either unaffected parent; the mutation was present in cells derived from different embryonic lineages, making somatic mosaicism unlikely. Moreover, although this nonsense mutation prematurely truncates the receptor, wild-type and mutant receptor mRNAs are coexpressed equally in the patients' cells, excluding significant nonsense-mediated decay of the latter.

Both Proband 2 and her father are heterozygous for a single nucleotide insertion which results in a frame-shift from codon 397 of TRα1 and premature truncation of the protein five residues before its carboxyterminus (F397fs406X).

Notably, both mutations localise to a region within exon 9 of *THRA* which is unique to the TRα1 isoform, such that the coding regions of either TRα2 or Rev-Erbα are unaffected (Fig. 1).

4. Clinical phenotype

In addition to the clinical features recorded at presentation, each proband underwent detailed investigation of several systems and the key findings are summarised as follows:

4.1. Skeletal

Skull radiographs in Proband 1 from the age of 26 months recorded delayed fusion of cranial sutures with a patent anterior fontanelle; abnormal lacunae of intramembranous ossification, so called "wormian bones", resulted in an abnormally serpentine appearance of the lambdoid suture. She had bilateral femoral epiphyseal dysgenesis, such that the right epiphysis appeared fragmented age 6.2 years. Her carpal bone age was delayed by 13 months at age 2 years, rising to 36 months by age 6.2 years.

Skeletal dysplasia was also present in Proband 2, with hip dislocation congenitally and no hip ossification centres. Delayed tooth eruption and closure of skull sutures were noted; carpal bone age was delayed and recorded as 36 months at age 6 years.

4.2. Gastrointestinal

Soon after weaning at 8 months, constipation was a persistent problem in Proband 1; even with regular laxative use, she only had a bowel movement every 3–7 days at age 6 years. Severe abdominal distension necessitated wearing loose-waisted clothes. Abdominal radiography confirmed bowel dilatation, with abnormal retention of radiopaque pellets indicating delayed intestinal transit. Colonic manometry showed no contractile activity either at baseline or following stimulation with bisacodyl. Colonic biopsy showed no abnormal features to suggest Hirschsprung's disease.

Both Proband 2 and her father have constipation, with bowel movements every 2 to 4 days when not receiving levothyroxine and daily when receiving it [6].

4.3. Thyroid axis

Persistent growth retardation had prompted serial thyroid function tests (TFTs) in Proband 1 over a four year period, with a variable but similar pattern: her free T4 levels were at or slightly below the lower end of the normal range but with free T3 levels being at or above the upper end of normal, resulting in an abnormally low FT4/FT3 ratio; circulating TSH was normal. Circulating reverse T3 (rT3) levels were low. Proband 2 and her father showed a very similar pattern of TFTs, with low FT4, high FT3 and normal TSH levels.

4.4. Metabolic

Basal metabolic rate (BMR), measured by indirect calorimetry in Proband 1, was abnormally low compared to values predicted anthropometrically. Serum sex hormone binding globulin (SHBG) levels, a hepatic marker of thyroid hormone action, were raised in Proband 1 but normal in Proband 2 and her father. Circulating IGF-1 levels were low in both Probands 1 and 2 and low-normal in the father of Proband 2, with normal growth hormone levels in Proband 1. Total and LDL cholesterol levels were raised in Proband 2.

4.5. Cardiac

Both resting heart rate (1st centile) and blood pressure (systolic 0.4th centile; diastolic 25th centile) were low in Proband 1.