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Resistance to thyroid hormone due to defective thyroid receptor alpha

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Thyroid hormones act via nuclear receptors (TRα1, TRβ1, TRβ2) with differing tissue distribution; the role of α2 protein, derived from the same gene locus as TRα1, is unclear.

Resistance to thyroid hormone alpha (RTHα) is characterised by tissue-specific hypothyroidism associated with near-normal thyroid function tests. Clinical features include dysmorphic facies, skeletal dysplasia (macrocephaly, epiphyseal dysgenesis), growth retardation, constipation, dyspraxia and intellectual deficit. Biochemical abnormalities include low/low-normal T4 and high/high-normal T3 concentrations, a subnormal T4/T3 ratio, variably reduced reverse T3, raised muscle creatine kinase and mild anaemia.

The disorder is mediated by heterozygous, loss-of-function, mutations involving either TRα1 alone or both TRα1 and α2, with no discernible phenotype attributable to defective α2. Whole exome sequencing and diagnostic biomarkers may enable greater ascertainment of RTHα, which is important as thyroxine therapy reverses some metabolic abnormalities and improves growth, constipation, dyspraxia and wellbeing.

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The genetic and phenotypic heterogeneity of RTHα and its optimal management remain to be elucidated.

Introduction

The diverse physiological actions of thyroid hormones (TH: thyroxine, T4; triiodothyronine, T3) include regulation of growth, control of metabolic rate, positive chronotropic and inotropic cardiac effects and development of the central nervous system (Table 1). TH synthesis is controlled by hypothalamic thyrotropin-releasing hormone (TRH) and pituitary thyroid stimulating hormone (TSH) and, in turn, T4 and T3 regulate TRH and TSH synthesis as part of a negative feedback loop. These physiological effects are mediated by thyroid hormone-dependent changes in expression of specific target genes in different tissues (Table 1). The cellular entry of thyroid hormones , particularly in the central nervous system, is mediated by a membrane transporter [monocarboxylate transporter 8 (MCT8)] [1]. 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) generating T3 in peripheral tissues, and type 3 deiodinase (DIO3) mediating catabolism of thyroid hormones to inactive metabolites [2]. Thyroid hormones alter target gene expression via a receptor protein (TR), belonging to the steroid/nuclear receptor superfamily of ligand-inducible transcription factors. 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 a protein complex containing corepressors (e.g. nuclear receptor corepressor [NCoR]; silencing mediator for retinoic acid and thyroid receptors [SMRT]) and histone deacetylase (HDAC) to repress basal gene transcription. Receptor occupancy by hormone (T3) results in dissociation of the corepressor complex and relief of repression together with recruitment of coactivator proteins which mediate transcriptional activation [3].

In humans, two highly homologous thyroid hormone receptors, TRα and TRβ are encoded by genes (*THRA*, *THRB*) 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; α2 protein, which exhibits a divergent carboxy-terminal region such that it is unable to bind thyroid hormones (Fig. 1), is expressed in a variety of tissues (e.g. brain and testis) and its biological function is poorly understood [4]. 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 [5]. *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

Table 1
Summary of some major physiological actions of thyroid hormone in tissues and associated target genes.

Actions of thyroid hormone		
Tissue	Action	Target genes
Brain	Cortical & cerebellar development; myelination	Krüppel-like factor 9; Hairless; Myelin basic protein
Liver	Lower cholesterol	LDL receptor
	Raises SHBG	SHBG
Myocardium	Positive inotropic and chronotropic effect	α- myosin heavy chain
		Sarcoplasmic Ca^{2+}-ATPase
Hypothalamus	Inhibits TRH secretion	Pro-thyrotrophin releasing hormone
Pituitary	Inhibits TSH secretion	TSH α and β subunits
Multiple	Increases basal metabolic rate	Multiple