Journal of Genetic and Environment Conservation (JOGEC)
www.jogec.com
Print ISSN: 3007-4509 Online ISSN: 3007-4517

Effect of mutation on thyroid hormone receptor Beta

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Received: June 13th 2024
Accepted: July 5th 2024
Published: August 9th 2024

ABSTRACT

Thyroid hormone is essential for normal development, growth, neural differentiation, and metabolic regulation in mammals. Thyroid stimulating hormone (TSH), secreted by the anterior pituitary in response to feedback from circulating thyroid hormone, acts directly on the TSH receptor (TSH-R) expressed on the thyroid follicular cell basolateral membrane. These actions are most apparent in conditions of thyroid hormone deficiency during development, such as maternal iodine deficiency or untreated congenital hypothyroidism, manifesting as profound neurologic deficits and growth retardation. Moresubtle and reversible defects are present when ligand deficiency occurs in the adult. There are two TR genes, TRα and TRβ, with different patterns of expression in development and in adult tissues. mutations in *THRB* gene producing RTHβ, having as a signature elevated serum free iodothyronines levels but non-suppressed thyrotropin (TSH) in the absence of other conditions that may produce some of the characteristic test abnormalities such as congenital hypothyroidism (CH), thyroid dysgenesis and Autoimmune Thyroid Disease.

Keywords: Thyroid hormone, TSH receptor, Receptor beta (THRB), Receptor alpha (THRB), Thyroid Dysgenesis.

Introduction

There are two TR genes, TRα and TRβ, with different patterns of expression in development and in adult tissues (Tata, 2012; Furlow and Neff, 2006). TRα has one T3-binding splice product, TRα1, predominantly expressed in brain, heart, and skeletal muscle, and two non–T3-binding splice products, TRα2 and TRα3, with several additional truncated forms. TRβ has three major T3-binding splice products: TRβ1 is expressed widely; TRβ2 is expressed primarily in the brain, retina, and inner ear; and TRβ3 is expressed in kidney, liver, and lung (Cheng *et al*., 2010). Human genetics, animal models, and the use of selective pharmacologic agonists have been informative about the role and specificity of the two major isoforms (Brent, 2000; Webb, 2010). The selective actions of thyroid hormone receptors are influenced by local ligand availability (Bianco *et al*., 2002; Visser *et al*., 2011); by transport of thyroid hormone into the cell by monocarboxylate transporter 8 (MCT8) or other related transporters (Oetting and Yen, 2007); by the relative expression and distribution of the TR isoforms and nuclear receptor corepressors and coactivators (Astapova *et al*., 2008); and, finally, by the sequence and location of the thyroid hormone response element. In addition, nongenomic actions of thyroid hormone, those actions not involving direct regulation of transcription by TR, have been increasingly recognized (Davis *et al*., 2010). Membrane receptors, consisting of specific integrin αv/β3 receptors, have been identified (Bergh *et al*., 2005) and found to mediate actions at multiple sites, including blood vessels and the heart (Davis *et al*., 2011). Several studies have identified direct actions of TR on signal transduction systems'(Cheng *et al*., 2010; Cao *et al*., 2005), which may be especially significant in relation to actions in cell proliferation and cancer.

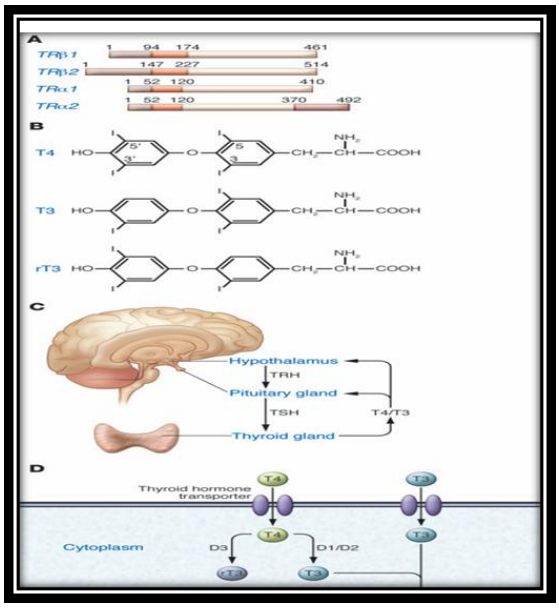

Figure (1) Nuclear action of thyroid hormone

Figure (1) Shown are the key components required for thyroid hormone action, as demonstrated by a range of clinical observations. (A). The TR gene has 2 major isoforms, TRβ and TRα; the structures of TRα1 and TRα2 (non–T3-binding)
and TRβ1 and TRβ2 are shown. (B) The major thyroid hormone forms, T4, T3, and rT3. (C) Circulating T4 is converted locally in some tissues by membrane-bound D2 to the active form, T3. D3 converts T3 to the inactive rT3. (D) In specific tissues, such as brain, transporters such as MCT8 transport T4 and T3 into the cell. Unliganded TR heterodimerizes with RXR and binds to a TRE and then to a corepressor, such as NCoR or SMRT, repressing gene expression. T3 binding to the ligand-binding domain results in movement of the carboxyterminal helix 12, disruption of corepressor binding, and promotion of coactivator binding, which then leads to recruitment of polymerase III and initiation of gene transcription**.**

Resistance to Thyroid Hormone Beta: The term resistance to thyroid hormones (RTH) refers to the clinical syndrome of reduced sensitivity to thyroid hormones (TH) first described in 1967 (Refetoff *et al*., 1967**)** and until recently it was synonymous with mutations in the *thyroid hormone receptor beta (THRB)* gene. In the past decade, mutations in the *THRA* gene, as well as genetic defects involving TH cell transport and metabolism were added to those of defects of TH action, broadening our understanding of impaired TH sensitivity (Refetoff *et al*., 2014; Vela *et al*., 2019). This mini-review is dedicated to RTH due to mutations in *THRB* gene producing RTHβ, having as a signature elevated serum free iodothyronines levels but non-suppressed thyrotropin (TSH) in the absence of other conditions that may produce some of the characteristic test abnormalities. It focuses on emerging concepts, unusual associations and controversies involving diagnosis and management, while providing a succinct overview of RTHβ covered in most medicine and specialty textbooks (Dumitrescu *et al*., 2021; Gurnell *et al*., 2016).

Overview of RTHβ: As most neonatal screening programs are based on TSH measured in dry blood spots, the precise incidence of RTHβ is unknown. Surveys of 80,884 and 74,992 newborns using TSH and T4 measurements identified 2 and 4 infants with THRB gene mutations indicating a prevalence of 1 in 40,000 and 1 in 19,000 live births respectively (Lafranchi *et al*., 2003; Vela *et al*., 2019). Frequency among sexes is equal, whereas prevalence may vary somewhat among ethnic groups. The inheritance of RTHβ is typically autosomal dominant. This is explained by the formation of dimers between the mutant and normal (wild-type; WT) TH receptor (TR) interfering with the function of the WT TRβ. Since the first description of a THRB gene missense mutation causing RTHβ (Sakurai *et al*., 1989), 236 different mutations in 805 families have been identified. They are located in the functional areas of the ligand (T3)-binding domain and adjacent hinge region (Mamanasiri *et al*., 2006). In 14% of individuals manifesting the RTHβ phenotype no THRB mutations were identified. Rarely familial, they may be caused by mosaicism, whereas it has been postulated that mutations in enhancers, repressors or cofactors may be responsible for this subgroup of RTHβ (Reutrakul *et al*., 2000). He distinctive biochemical feature of RTHβ is high serum free iodothyronine levels (principally free T4) with normal or high TSH concentration. This discrepant correlation has brought the term “inappropriate TSH secretion”. Its wide use is deplorable as in fact the degree of TSH secretion is appropriate for the reduced sensitivity of the hypothalamic-pituitary axis to TH. Individuals with RTHβ maintain a nearly euthyroid state compensated by the high TH level in concert with the tissue expression level of the mutant receptor. Thus, features of TH deficiency and excess may co-exist, producing sinus tachycardia in the heart expressing mainly the WT TRα and goiter by TSH stimulation, as the pituitary expresses mainly TRβ including the mutant form. Visual disorders may also be present due to retinal photoreceptor dysfunction (Campi *et al*., 2017). Serum TSH

determination remains the most sensitive test to determine reduced sensitivity to TH. In contrast, serum markers of TH action on peripheral tissues, such as cholesterol, creatine kinase, alkaline phosphatase, osteocalcin and sex hormone-binding globulin are less reliable, unless they are measured before and after administration of T3(Refetoff *et al*., 1993). After excluding assay interference as a cause of discrepant thyroid function tests (Campi *et al*., 2020), the principal other condition to be considered in the differential diagnosis of RTHβ is TSH secreting pituitary adenoma (TSH-oma), particularly in the absence of family history. Thus, testing of first-degree relatives is helpful and cost effective. Characteristics of a TSH-oma include failure to suppress TSH after the administration of supra-physiologic doses of T3, failure to normally stimulate TSH with TSH releasing hormone (TRH) (although exceptions of TSH-omas with TSH response to TRH have been reported), elevated sex hormone binding globulin levels and increased ratio of pituitary α glycoprotein relative to TSH (Macchia *et al*., 2014).

Combined RTHβ and Thyroid Dysgenesis: The diagnosis of RTHβ is challenging and its management complicated when it co-exists with other disorders, such as congenital hypothyroidism (CH) and thyroid dysgenesis. Children with RTHβ commonly have short stature, goiter and learning difficulties (Refetoff *et al*., 1993) and in association with CH will present high serum TSH and may exhibit hypothyroid symptoms when treated with standard levothyroxine doses. Five reports of RTHβ with CH due to ectopic thyroid tissue have been reported (Grasberger *et al*., 2005; Zhou *et al*., 2018). Of note, the case reported by Guo et al., had a lingual thyroid with a typical RTHβ phenotype but no detectable mutations in the *THRB* gene (Guo *et al*., 2016). Persistent serum TSH elevation is frequently encountered during the early treatment of CH despite reaching serum T_4 level in the upper limit of normal. This has been attributed to a delayed maturation of the T_4 mediated feedback control of TSH (Fisher *et al*., 2000). Defining the cause of persistent TSH elevation and addressing it appropriately is of paramount importance, as under treatment may adversely impact growth and mental development. When non-compliance and suboptimal treatment are excluded by measurement of serum T_4 and T_3, suspicion for co-existence of RTHβ should be raised and, when confirmed, treatment with supraphysiologic doses of levothyroxine aims to bring the serum TSH to near normal while following growth, bone maturation and cognitive development. When RTHβ and ectopic thyroid tissue co-exist, another reason to aim at TSH suppression is to prevent thyroid tissue expansion in anatomic locations, such as the base of the tongue, that may cause dysphonia and hemoptysis.

Autoimmune Thyroid Disease and RTHβ: Autoimmune thyroid disease (AITD) is a common thyroid condition affecting the general population and its coexistence with RTHβ has been considered incidental (Larsen *et al*., 2013; Shiwa *et al*., 2011). However, in a study of 330 individuals with RTHβ and 92 unaffected first-degree relatives, subjects with RTHβ had an over 2-fold higher frequency of positive thyroid auto-antibodies (Barkoff *et al*., 2010), suggesting that this association is not coincidental. A proposed pathophysiologic mechanism by the group of Gavin et al. invoked chronic stimulation of intrathyroidal lymphocytes by elevated TSH in RTHβ leading to pro-inflammatory cytokine production and thyrocyte destruction (Gavin *et al.,* 2008). Yet, in the study of Barkoff et al., the prevalence of AITD by age group was not influenced by the TRβ genotype which argues against high TSH being the cause of AITD (Barkoff *et al*., 2010). Previous studies have shown that TH activates the immune system by acting on thymic epithelial cells and by direct effect on neutrophils, natural killer cells, macrophages and dendritic cells (Fabris *et al*., 1986; Villa-Verde *et al*., 1992). TH augments dendritic cell maturation and induces pro-inflammatory and cytotoxic responses. Given that dendritic cells are involved in the pathogenesis of AITD (Ganesh *et al*., 2009; Montesinos *et al*., 2019), this might be a pathway mediating the association between RTHβ and AITD.

Variability in RTHβ Manifestation: RTHβ manifestations can be variable in tissue expression and in severity. The terms “generalized”, “isolated pituitary” and “peripheral tissue” resistance have been used to describe different clinical manifestations of RTHβ suggesting tissue variability in the resistance to TH. The term generalized resistance to TH (GRTH) was applied to most patients with RTHβ that appear to maintain a euthyroid state whereas pituitary resistance to TH (PRTH) referred to patients with RTHβ that have symptoms of thyroid excess in peripheral tissues or demonstrate changes in peripheral tissue markers compatible to TH action without significant suppression of TSH (Safer *et al*., 1999). A single patient with presumed isolated peripheral RTH (PRTH) was reported, in whom administration of high dose of liothyronine (L-T3) suppressed serum

TSH but elicited no clinical signs of TH excess (Kaplan *et al*.,1981). Subsequently shown not to have a THRB gene mutation, this case likely represents acquired reduced sensitivity to TH through deiodinase-3 induced hormone inactivation. The clinical spectrum in RTHβ is quite broad and overlapping, even among carriers of the same THRB mutation and within the same family, suggesting that the classifications of generalized and pituitary RTHβ are rather semantics to describe a varying range of clinical signs and symptoms resulting from altered sensitivity to TH (Pohlenz *et al*., 1995; Toumba *et al*., 2015). In some instances, the variability in the severity of the resistance to TH is readily explained on the basis of the character and position of the genetic defect. Homozygous THRB mutations are clinically more severe as they lack a WT TRβ and they interfere with the function of the WT TRα through heterodimerization (Ferrara *et al*., 2012; Yen *et al*., 1992). Frame-shift mutations, producing a nonsense extension of the TRβ carboxyl terminus, interfere not only with ligand binding but also with interaction of the cofactors (Wu *et al*., 2006). Similarly, mutations with near normal ligand-biding can interfere with function through impaired binding to DNA (R243Q/W) (Yagi *et al*., 1997; Safer *et al*., 1998) and others (L454V and R383H) have altered binding to coactivators or corepressors leading as in the case of R429Q (Machado *et al*., 2009) to more prominent suppression of TSH through predominant effect on genes negatively regulated by TH (Alberobello *et al*., 2011) , showed that when a single nucleotide polymorphism located in an intronic enhancer was associated with R338W, it produced pituitary specific over-expression of the mutant TRβ2 receptor illustrating the role of regulatory regions in tissue specific manifestation of RTHβ.

Conclusion

There are two Thyroid receptor gene (TR), TRα and TRβ, with different patterns of expression in development and in adult tissues. mutations in *THRB* gene producing RTHβ , having as a signature elevated serum free iodothyronines levels but non-suppressed thyrotropin (TSH) in the absence of other conditions that may produce some of the characteristic test abnormalities such as congenital hypothyroidism (CH), thyroid dysgenesis and Autoimmune Thyroid Disease.

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