Resistance to Thyroid Hormone (RTH) and Resistance to TSH (RTSH)

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Key Points

- Resistance to TH (RTH) refers to a group of disorders manifesting as impaired sensitivity to thyroid hormone.
- The classical form of RTH is caused in the majority of cases by mutations in the TH receptor beta (*THRB*) gene and is classified as RTH-beta. 15% of patients with this phenotype do not have a detectable mutation in the *THRB* gene, and this entity is known as non-TR-RTH.
- Mutations in the *THRA* gene have been recently reported to cause RTH-alpha. Patients with this defect are phenotypically different from the RTH patients with *THRB* gene mutations in terms of thyroid function tests and clinical features.
- Other disease entities reported are the TH cell membrane transport defect caused by *MCT8* gene mutations and TH metabolism defect caused by *SBP2* gene mutations. These disorders can be distinguished by their characteristic abnormalities of thyroid function.
- Resistance to TSH (RTSH) manifests with high serum TSH of normal biological activity in the absence of goiter. Several genetic defects have been reported to present the phenotype of RTSH, including inactivating mutations in the TSH receptor *TSHR* gene, mutations in the *PAX 8* gene, and a dominantly inherited form without TSHR and PAX8 mutations that is linked to a region on chromosome 15.

20.1 Resistance to Thyroid Hormone (RTH)

20.1.1 Introduction and Background Information

Resistance to thyroid hormone (RTH) refers to impaired sensitivity to thyroid hormone (TH).

The classical syndrome, now known as RTH-beta, is characterized by reduced intracellular action of the active TH, triiodothyronine (T3), in target tissues. This syndrome was first reported in 1967 [1] and was subsequently associated with mutations in the gene encoding the beta isoform of the TR [2], *THRB*. Biochemically, the syndrome is characterized by high serum concentrations of free T4 and usually free T3 as well, accompanied by normal or slightly high serum TSH levels. The reduced sensitivity to TH in the hypothalamus and pituitary leads to mildly elevated TSH levels, which stimulate the thyroid gland to increase production of TH. The severity of TH resistance varies among tissues in an affected individual, due to differences in the relative expression of TR-beta and TR-alpha in different tissues [3] (Fig. 20.1). Thus, patients with RTH-beta may have variable symptoms or signs of hypothyroidism and/or hyperthyroidism. Clinical features of hypothyroidism may include growth retardation, delayed bone maturation, learning disabilities, mental retardation, sensorineural deafness, and nystagmus. Clinical features of hyperthyroidism may include tachycardia, hyperactivity, and increased basal metabolic rate. The majority of patients with the RTH-beta phenotype have autosomal dominant mutations of the *THRB* gene. Patients have been identified from a wide range of races and ethnic groups; the exact geographic distribution of the disorder

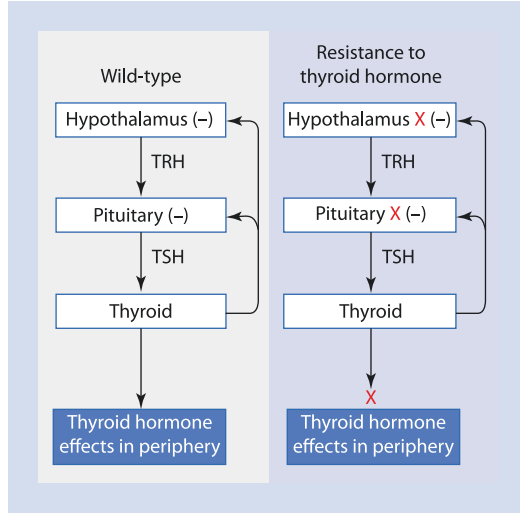

Fig. 20.1 The hypothalamic-pituitary-thyroid axis in RTH-beta patients. TRβ mutations or other (as yet undefined) defects in patients with RTH lead to reduced thyroid hormone responsiveness in the hypothalamus and pituitary, resulting in increased production of thyroid hormone. Impaired thyroid action elsewhere in the body results in the clinical phenotype seen in patients with RTH-beta. However, increased thyroid hormone action on TRα receptors leads to selective tissue hyperthyroidism (e.g., in the heart conduction system)

is unknown, but it has been estimated that RTH occurs in about 1 case per 50,000 live births [4]. Individuals without an identifiable *THRB* mutation but with thyroid function tests consistent with RTH-beta may have non-TR-RTH, and dynamic testing is required to confirm or exclude the diagnosis. Therapeutic strategies for RTH-beta are not well-defined and treatment (if any) must be individualized. Most studies of patients with RTH-beta have been performed in adults, and approaches for the pediatric population may need to be deduced in the absence of firm data. In the past several years, additional syndromes of reduced sensitivity to thyroid hormone, distinct from the classic RTH-beta, have been described, and these will be discussed below.

Until recently, mutations in the *THRA* have remained elusive. In fact, because *THRA* mutations were not previously identified, they were believed to be extremely rare, potentially lethal, or subclinically expressed [5]. Mouse models of TRα defects (knockouts [6, 7] and knock-ins [8]) were investigated in an attempt to infer the phenotype of human *THRA* mutations. The first patients with *THRA* mutations were reported in 2012 [9, 10], and their phenotype is now classified as RTH-alpha. Because TRα is not involved in the feedback regulation of the hypothalamic-pituitary-thyroid axis, their TFTs are distinct from RTH-beta, namely, they have low serum T4, borderline high T3, and very low rT3, with normal to elevated TSH levels. The clinical manifestations in this syndrome are variable but consistent with the manifestations of untreated congenital hypothyroidism in peripheral tissues expressing predominantly TRα such as bone, GI, and CNS tissues [5].

20.1.2 Etiology

The thyroid hormone receptor (TR) is a member of the nuclear hormone receptor (NHR) family of transcription factors. These proteins directly bind DNA to modulate gene transcription [11, 12]. NHRs contain a number of important domains: an N-terminal transactivation or AF-1 domain (A/B domain); a central DNA-binding domain (DBD); and a C-terminal ligand-binding domain (LBD) with ligand-dependent activation (AF-2) function. In addition to binding ligand, the LBD is involved in the recruitment of key nuclear cofactors such as corepressors and coactivators.

TRs and other NHRs bind sequences within regulatory regions of genes; for the TR, these regions are termed thyroid hormone response elements (TREs) [13, 14]. When TRs bind to "positive" TREs (pTREs) in the presence of TH, gene transcription is increased; in contrast, "negative" TREs (nTREs) are involved in thyroid hormone-mediated repression of transcription. Negative TREs have been identified in the promoters of TRH and TSH subunit genes [15–17], but their regulation is less clear. When recruited to pTREs, TRs bind nuclear proteins termed corepressors, including the nuclear corepressor protein (NCoR) and the silencing mediator of retinoid and thyroid hormone receptors (SMRT) [18–23] (Fig. 20.2). These cofactors, in turn, recruit a protein complex with histone deacetylase function [24–26], leading to gene silencing. The binding of T3 leads to a conformational change in the TR, loss of corepressor binding, and subsequent recruitment of coactivators [27]. Coactivators stimulate gene expression by increasing the degree of histone acetylation, modulating interactions with general transcription factors, and other mechanisms [28–36]. More recently, rapid non-genomic actions of thyroid hormone have been identified (independent of transcription) [11], although it is currently unclear how these effects relate to syndromes of RTH.

There are two major isoforms of the TR, termed TRα and TRβ, which are encoded by genes on different chromosomes: *THRA* on chromosome 17 and *THRB* on chromosome 3 [37, 38]. Additional isoforms of TRα and TRβ are generated by alternative splicing or differential promoter usage. Although TRα1 is a true thyroid hormone receptor, TRα2 is an alternatively spliced isoform that does not bind thyroid hormone [39]. In contrast, TRβ1, TRβ2, and the more recently described TRβ3 isoform [40] all bind thyroid hormone and differ only in their N terminus. The function of TRβ3 in vivo remains unknown.

Mutations in the *THRB* gene have been identified in many patients with RTH, and are now classified as RTH-beta. In the vast majority of cases, this syndrome is inherited in an autosomal dominant fashion. A subset of classical RTH patients, however, does not exhibit *THRB* mutations [41], and this entity is known as non-TR-RTH. These patients may have defects in other

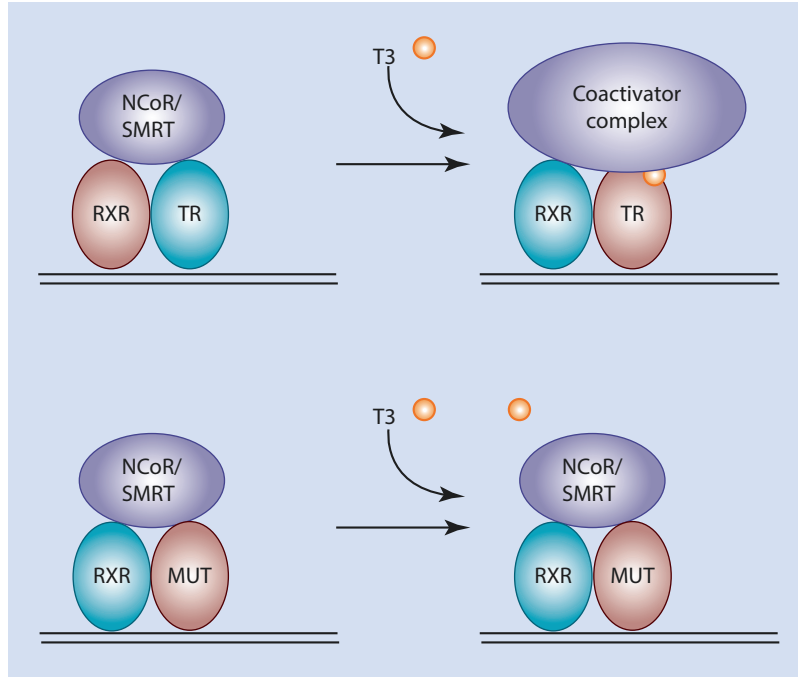

Fig. 20.2 Role of abnormal TR-corepressor interactions in the pathogenesis of RTH. The thyroid hormone receptor (TR) binds DNA as a TR-retinoid X receptor (RXR) heterodimer (or potentially as a TR-TR homodimer). The presence of ligand (T3) results in a conformational change in the TR, leading to dissociation of corepressors (CoR) and subsequent recruitment of coactivators. Mutations of the TR that abolish T3 binding result in constitutive CoR recruitment and loss of T3-mediated stimulation of gene transcription

proteins involved in thyroid hormone action [42], but such mutations have not yet been identified [43]. This is an ongoing area of research, and novel mutations are being sought. A recent search for mutations in the retinoid X receptor gamma (*RXRγ*) gene was not successful [44]. It has been hypothesized that some non-TR-RTH patients may exhibit mosaicism for de novo *THRB* mutations [45].

Mutations of *THRB* that cause RTH-beta generally cluster in three "hot spot" regions of the gene [46, 47]. Most of these mutations interfere with the binding of T3 to the receptor. In these cases, the mutant receptor strongly binds corepressors such as NCoR or SMRT even in the presence of T3 (Fig. 20.2). In a few patients though, the defect does not affect ligand binding, but results in altered corepressor and/or coactivator recruitment [48, 49]. Interestingly, it has been shown that mutant TRs interfere with wild-type TR function, an effect that has been termed "dominant-negative inhibition" [50, 51]. Recently, mouse models have clarified the role of the mutant TRs in the pathogenesis of RTH. Although complete knockout of TRβ produces mice with thyroid function tests consistent with RTH-beta [52], modeling "knock-in" of *Thrb* mutations found in patients with RTH-beta yields mice with more severe resistance [53, 54].

RTH-beta can be subdivided into (i) generalized resistance to thyroid hormone (GRTH) and (ii) pituitary resistance to thyroid hormone (PRTH). In GRTH, the elevated thyroid hormone levels generated by resistance at the level of the hypothalamus and pituitary have diminished activity in the periphery; thus, there is a variable degree of generalized resistance. In contrast, in PRTH (also called central resistance to thyroid hormone, or CRTH), there is resistance solely (or at least primarily) at the level of the hypothalamus and pituitary. This resistance leads to elevated levels of thyroid hormone, but in contrast to GRTH, sensitivity to thyroid hormone is maintained in peripheral tissues, causing thyrotoxicosis. Patients with GRTH frequently exhibit tachycardia due to the high levels of thyroid hormone stimulating intact TRα1 receptors in the heart; thus, tachycardia should not be used to differentiate GRTH and PRTH. Some investigators do not recognize the existence of PRTH as a distinct clinical entity [55], arguing that the same mutations have been reported to cause both GRTH and PRTH [56]. However, a careful evaluation of clinical and biochemical indices in a patient with RTH suggested that PRTH may very well exist [57]. In addition, experiments have revealed that mutant TRs of patients with PRTH behave differently than TRs of patients with GRTH, particularly with respect

to the TRβ2 isoform [58, 59]. A mouse model of the R429Q mutation (which has been reported to cause PRTH) showed that the mutant TR selectively interferes with negative regulation by thyroid hormone [60]. Another study identified differential recruitment of nuclear cofactors by a different TRβ defect associated with PRTH [61].

In contrast, knockout of *Thra* in mice causes a syndrome of hypothyroidism with growth arrest [6, 7]. Mice with heterozygous knock-in *Thra1* mutations are viable and have a heterogeneous phenotype, depending on the severity and the location of the mutation [8]. Most adult *Thra1* mutant mice have a mildly elevated TSH. Various knock-in mouse models manifest other features, such as delayed endochondral ossification resulting in dwarfism, disturbed behavior, memory impairment, locomotor dysfunction, mild bradycardia, and insulin resistance [8]. Thus, a patient with a dominant-negative *THRA* mutation was expected to have a different phenotype from the classical RTH-beta phenotype. In fact, because *THRA* mutations were not identified until recently, they were considered to be extremely rare, lethal, or subclinically expressed [5].

In 2012 the first patients with *THRA* mutations were reported [9, 10], and their phenotype was classified as RTH-alpha. Since these initial reports, additional patients have been reported [62–65], bringing the number of patients known to date to 14, belonging to 9 families. There are eight known mutations affecting the *THRA* gene in patients with RTH-alpha, and they are located in the ligand-binding domain. Four mutations are frame shifts with early termination resulting in a truncated receptor, and the other four are point mutations in the ligand-binding domain and in the C-terminal helix. Six of the eight mutations are located in the part of the gene specific only to the TRa1 isoform, while the other two are located in the part of the protein common between the TRa1 and TRa2 isoforms. As in the case of *THRB* mutations, this results in three different mechanisms causing functional impairment: (i) reduced affinity for T3, (ii) interference of the normal TR-alpha allele by the mutant TR alpha, resulting in a dominant negative effect; and (iii) defective coactivator recruitment to the ligand bound receptor. Interestingly, some of the mutations identified in the *THRA* gene in cases of RTH-alpha were also identified in the *THRB* gene in cases of RTH-beta. Comparison of the alpha and beta forms of RTH for equivalent mutations enables the study of the distinctive roles of the different receptors [5].

20.1.3 Clinical Presentation

20.1.3.1 RTH-Beta Phenotype

The clinical presentation of RTH-beta is variable (► Box 20.1). The initial family described by Refetoff et al. [1] included an 8 1/2-year-old girl and a 12 1/2-year-old boy, both of whom were overall clinically euthyroid but exhibited goiter, deaf-mutism, stippled epiphyses on radiological skeletal survey, and elevated protein-bound iodine (PBI) levels. In contrast to most cases of RTH-beta, this family was shown to have an autosomal recessive pattern of inheritance, and affected family members were later found to have a complete deletion of the *THRB* gene [66]. The heterozygous parents were phenotypically normal, suggesting that a single wild-type TR (in the absence of a mutant TR) may be sufficient for thyroid hormone action. In contrast, most cases of RTH-beta are inherited in an autosomal dominant fashion because mutant TRs exhibit dominant-negative inhibition over wild-type alleles.

Box 20.1 Clinical Characteristics of RTH-Beta in Children

1. Physical exam
    1. Goiter
    2. Tachycardia
    3. Short stature
    4. Low body weight
2. Associated symptoms
    1. Neurological
        1. Developmental delay
        2. Attention deficit hyperactivity disorder (ADHD)
        3. Low IQ
    2. ENT
        1. Deafness
        2. Speech impediment
        3. Recurrent ear, nose, and throat infections
3. Radiological findings
    1. Delayed bone age
    2. Increased thyroid ^{123}I uptake

Derived from data in Refs. [2, 68]

Clinical findings found in patients with resistance to thyroid hormone

Patients with RTH-beta come to medical attention of a variety of reasons. Goiter is the presenting sign in about 38% of cases; less common reasons include learning disabilities, developmental delay, tachycardia, suspected thyrotoxicosis, and elevated thyroxine levels at birth [4]. Thyroid function tests reveal elevated thyroid hormone levels in the setting of a non-suppressed TSH (see "Diagnostic Guidelines" below). Infants with RTH-beta may have congenital deafness, congenital nystagmus, neonatal jaundice, and hypotonia [2]. Patients with RTH-beta may have an increased risk of developing autoimmune thyroid disease [67]. Individuals with RTH-beta who inappropriately undergo thyroidectomy or radioactive iodine treatment will exhibit signs and symptoms of hypothyroidism despite thyroid hormone levels in the normal range following replacement therapy.

A National Institutes of Health study [68] evaluated prospectively a cohort of 42 kindreds manifesting the RTH-beta phenotype. There was autosomal dominant transmission in 22 kindreds, sporadic transmission in 14, and an unknown transmission in 6. This last group was characterized as non-TR-RTH, as they manifested the classical RTH-beta like phenotype without a detectable *THRB* mutation. A palpable goiter was identified in 74% of females and 53% of males. Attention-deficit hyperactivity disorder (ADHD) was present in 72% of the males and 43% of females. IQ was about 13 points lower in patients with the RTH-beta phenotype compared to controls, and one-third of patients had an IQ <85. In contrast, only a few patients had actual mental retardation. Patients with the RTH-beta phenotype had a higher incidence of speech delay (24%), stuttering (18%), and hearing loss than controls. Although resting pulse was higher in patients with RTH-beta, in this particular study, the correlation did not persist after adjustment for age (though it has been noted by other groups). Children with the RTH-beta phenotype exhibited delayed bone maturation. Bone age was delayed in 29% of patients, and 18% had short stature, though another study suggested that the RTH-beta phenotype is not associated with decreased final adult height [69].

As noted above, certain tissues demonstrate increased thyroid hormone-mediated effects in patients with RTH-beta. This is presumably caused by thyroid hormone stimulation of TRα1 in these (TRα1-predominant) tissues. The classic example of this phenomenon is tachycardia, which has been reported in many patients with GRTH. More recently, Mitchell et al. reported that patients with RTH also exhibit increased energy expenditure, muscle mitochondrial uncoupling, and hyperphagia [70].

Findings of abnormal IQ and ADHD in patients with RTH suggest the importance of thyroid hormone in CNS development and function. Matochik et al. used positron emission tomography (PET) scans to study CNS activity in patients with RTH [71]. This study showed that RTH patients have higher cerebral metabolism in certain key areas of the central nervous system (CNS) during a continuous auditory discrimination task, including the anterior cingulate gyrus and the parietal lobe. While PET scanning techniques remain a research tool for RTH-beta, these results suggest an important role for thyroid hormone in these CNS regions. A study of children with ADHD with and without coexisting RTH-beta examined the role of thyroid hormone therapy (in this case, L-T3) in ADHD [72]. The majority of patients with RTH-beta and ADHD improved when placed on T3 therapy, whereas patients with ADHD (in the absence of RTH) deteriorated or remained stable. Thus, ADHD in patients with RTH-beta appears to be distinct from ADHD in patients without RTH [73].

While a number of unusual coexisting conditions in patients with RTH have been reported, some of these may have occurred by chance. These include a birdlike appearance of the face, various vertebral and other skeletal anomalies, short fourth metacarpals, patent ductus arteriosus, and non-communicating hydrocephalus [2].

20.1.3.2 RTH-Alpha Phenotype

The first patient identified with RTH-alpha presented with delayed linear growth, delayed tooth eruption and severe constipation, decreased muscle tone and impaired gross and fine motor skills [9]. Additional defects in the cardiovascular system, including decreased heart rate and blood pressure, were also reported [9]. Currently, 14 patients belonging to 9 families and harboring

8 different *THRA* mutations have been reported in the literature [5]. Clinical data for only 13 of them are available, as the genetic identification of the remaining patient was through whole genome sequencing in subjects with familial forms of autism [64]. The only information about this case was that the female patient was autistic and had a brother who was also autistic but did not harbor the *THRA* mutation identified in his sister [64]. Overall 9 women and 5 men have been reported, but it is too early to define a sex ratio. The cases included de novo and familial mutations. The age at molecular diagnosis varied (7 children or adolescents, and 7 adults), which contributes to certain variations in the clinical descriptions. Further, in the adult patients reported, there is some uncertainty regarding the description of the phenotype in childhood. The clinical presentation of RTH-alpha includes to varying degrees the combination of a dysmorphic syndrome and psychomotor development disorders [5]. The absence of goiter, which is among the typical manifestations of RTH-beta, is particularly notable.

20.1.4 Diagnostic Considerations

20.1.4.1 RTH-Beta

The initial testing of a patient suspected to have RTH-beta phenotype should include routine thyroid function tests. Patients with RTH-beta phenotype have elevated free thyroid hormone levels in the setting of non-suppressed (normal or elevated) TSH levels. Other causes of "euthyroid hyperthyroxinemia" should be excluded (▶ Box 20.2), including methodological laboratory artifacts due to the presence of heterophile antibodies [74]. Such patients may actually be hyperthyroid, with elevated thyroid hormone levels and (appropriately) suppressed TSH levels when measured accurately. This problem has been decreased, but not eliminated, with improvements in the TSH assay. Reevaluation of TSH levels after serial dilutions may be useful. Similarly, patients with autoimmune hypothyroidism occasionally exhibit falsely elevated thyroid hormone levels due to the presence of antibodies interfering with the measurement of T4 and/or T3.

Box 20.2 Causes of Euthyroid Hyperthyroxinemia

1. Methodological artifacts
   1. Antibodies to thyrotropin (TSH)
   2. Antibodies to thyroid hormones (T4, T3)
2. Binding protein abnormalities
   1. Acquired forms of increased TBG
      Estrogen use/pregnancy
      Liver disease
      Acute intermittent porphyria
      Other drugs (methadone, perphenazine, 5-FU)
   2. Inherited
      TBG excess
      Familial dysalbuminemic hyperthyroxinemia (FDH)
      Mutant transthyretin variants
3. T4 to T3 conversion defects
   1. Acquired
      Amiodarone
      Propranolol (high doses)
      Oral cholecystographic contrast agents
   2. Inherited (SBP2 mutations, possibly deidonase defects)
4. Miscellaneous causes
   1. Acute psychiatric illness
   2. High altitude
   3. Amphetamine use
   4. Thyroxine therapy
   5. Non-steady-state conditions of thyroid hormone testing
5. Resistance to thyroid hormone (RTH)

Causes of euthyroid hyperthyroxinemia in the differential diagnosis of resistance to thyroid hormone. Thyrotropin-secreting pituitary adenomas are not included, as they are generally associated with hyperthyroidism

Patients with defects in thyroid hormone-binding proteins, such as TBG, transthyretin, and albumin, can also exhibit abnormal levels of total T4 and T3. Euthyroid patients with TBG excess, which can be congenital or acquired (e.g., in pregnancy [75] and liver disease [76]), have elevated total T4 levels in the setting of a non-suppressed TSH. These patients have normal free T4 levels, when measured directly or estimated based on T3 resin uptake, T3RU. Familial dysalbuminemic hyperthyroxinemia (FDH) is a syndrome caused by the production of albumin variants with Arg-His or Arg-Pro mutations at codon 218 [77, 78]. These albumin variants have increased affinity for

T4. Therefore, measurement of total serum T4 is elevated; correction of T4 based on T3RU may also yield abnormally high results. Free T4 levels are falsely elevated when measured by certain analog measurements, but a free T4 level measured by dialysis will be normal. Serum T3 levels are normal in FDH and exclude the diagnosis of RTH.

Certain medications such as amiodarone [79] and propranolol (at high doses) inhibit T4 to T3 conversion. Euthyroid patients with T4 to T3 conversion defects may have elevated T4 levels and inappropriately normal TSH levels; however, these patients have low-normal or low T3 levels, excluding the diagnosis of RTH. Finally, a few other conditions such as acute psychiatric illness [80] can also cause abnormal thyroid function tests that can occasionally be confused with RTH (► Box 20.2).

Once these various conditions are excluded, the diagnosis is generally one of RTH-beta vs. thyrotroph adenoma [81]. Differentiation between these two disorders can be difficult. In general, TSH adenomas are associated with hyperthyroidism, whereas patients with RTH-beta have variable degrees of compensated thyroid hormone hyporesponsiveness. In addition, patients with thyrotroph adenomas generally have higher serum levels of the glycoprotein alpha subunit than patients with RTH-beta [81], though there is significant overlap.

In terms of radiology studies, patients with TSH adenomas generally have pituitary findings on MRI scans, but it should be noted that patients with RTH-beta may develop incidental pituitary adenomas, mimicking a thyrotroph adenoma [82]. A study used Doppler ultrasonography to determine whether thyroid blood flow distinguishes between RTH-beta and thyrotroph adenomas [83]. These investigators showed that parameters of thyroid blood flow normalized in T3-treated RTH-beta patients, but not in those with TSH-secreting adenomas, but this evaluation is not common practice.

An effective method to confirm a diagnosis of RTH-beta (at least GRTH) is to administer graded doses of T3 and measure a battery of thyroid hormone-responsive tests. Although patients with thyrotroph adenomas have impaired TSH responses to T3, they retain intact peripheral responses to T3. In contrast, patients with GRTH have impaired TSH and peripheral responses to exogenous T3. Patients are generally admitted to a clinical research center for the duration of the protocol. A few different protocols have been described, during which time exogenous T3 is given in an escalating regimen, and various thyroid hormone-responsive measurements are taken [2, 57, 84].

Most cases of RTH-beta are associated with mutations in the TRβ gene. Ultimately, the most secure way to make a diagnosis of RTH-beta is to demonstrate (a) elevated thyroid hormone levels in the setting of a non-suppressed TSH, (b) thyroid hormone hyporesponsiveness, and (c) a *THRB* gene mutation.

20.1.4.2 Neonatal Considerations

If a child is born to a parent with RTH with a known *THRB* mutation, the most straightforward way to confirm or exclude the diagnosis in the infant is to sequence the known mutation. There are two other ways infants with RTH frequently come to medical attention: (a) symptoms consistent with RTH and (b) abnormal thyroid screening tests. Infants with RTH may have congenital deafness, congenital nystagmus, neonatal jaundice, and hypotonia. In addition, screening programs that are in place to identify infants with congenital hypothyroidism occasionally identify RTH instead. A fetus with suspected RTH can be tested for TR mutations by chorionic villus sampling or amniocentesis and DNA analysis [85], though the benefits of making the diagnosis at this stage of development have not been clearly established.

20.1.4.3 RTH-Alpha

As RTH-alpha patients present primarily with dysmorphic features and GI symptoms in the context of only mild thyroid test abnormalities, they might not present early to the attention of the endocrinologist. There is no standard testing recommended for these patients at this point. Astute clinicians who identify the syndromic features of this defect and review the literature will be able to consider *THRA* mutations as a possible diagnosis. The typical pattern of TFTs includes low or normal T4, high normal T3, and normal or slightly elevated TSH. Identification of more patients will allow further insight into this novel defect.

20.1.5 Outcomes and Possible Complications

20.1.5.1 RTH-Beta

There is no reason to treat patients with RTH-beta who have elevated levels of TH that are appropriate for the degree of both thyrotroph and peripheral tissue resistance. In fact, the mainstay of the management of asymptomatic RTH-beta patients is to recognize the correct diagnosis and avoid antithyroid treatment. Attempts aimed to decrease the circulating TH levels, either with antithyroid drugs, or with ablative treatment by surgery or radioiodide, will result in objective findings of TH deprivation and administration of supraphysiological doses of TH is required. The dose of TH needs to be uptitrated in order to normalize the serum TSH levels and high doses of L-T4 be necessary, sometimes as high as 500–1000 μg/d.

20.1.5.2 RTH-Alpha

Mutations in THRA gene have been only recently recognized, and limited data is currently available to accurately assess long-term outcomes and possible complications. Based on the few patients known to date, it seems that L-T4 treatment during childhood has some benefits; however, there is the risk of making the TR-beta predominant tissues hyperthyroid. Lack of intervention has an overall poor outcome in patients with severe *THRA* mutations.

20.1.6 Treatment

20.1.6.1 RTH-Beta

No specific therapy is available to correct the underlying defect in RTH. Frequently, patients with RTH are in a clinical state of compensated thyroid hormone hyporesponsiveness. In these patients, no specific therapy is indicated. In those few patients who have greater peripheral hyporesponsiveness and thus clinical hypothyroidism, treatment with thyroid hormone (e.g., levothyroxine) may be considered. If used, the specific dosage must be individualized based on markers of thyroid hormone action (such as SHBG, cholesterol, ferritin, BMR, and bone density) [56]. The use of TRIAC (3,5,3′-triiodothyroacetic acid), a thyroid hormone analog with relative specificity toward the TRβ receptor [86, 87], has been advocated for use in patients with RTH, but its specific role has not been clearly defined. D-Thyroxine has also been used [88], though one study suggested it was less effective than TRIAC [89]. Novel TR analogs hopefully will be developed that activate mutant receptors [90]. Overall, therapy (or lack thereof) must be individualized for each patient. Of course, for patients who have had their thyroid glands inappropriately ablated for misdiagnosed hyperthyroidism, treatment with thyroid hormone will be necessary.

In patients with PRTH, beta blockers have been used to control symptoms; the use of antithyroid drugs in this situation is controversial, and these medications are not indicated in patients with GRTH. Agents that have been used to decrease TSH levels include somatostatin analogs and bromocriptine, but these have had only limited success.

The care of RTH patients during pregnancy needs to be individualized as well and depends on the genotype of both the fetus and mother [91]. High miscarriage rates of wild-type fetuses of pregnant RTH mothers has been suggested to be due to high circulating levels of thyroid hormone [92]. A prenatal diagnosis of RTH was made [85] in the fetus of a 29-year-old pregnant woman at 17 weeks' gestation. The fetus and mother were both found to harbor the *THRB* mutation (T337A), and the pregnant woman was treated with TRIAC with beneficial effects on maternal symptoms and fetal goiter size. Cordocentesis was performed to evaluate effects of the medication on fetal thyroid function tests. However, an accompanying editorial to the report [56] points out some potential dangers of this approach, since cordocentesis led to the need for emergency C-section.

In children with RTH, special care should be directed toward issues of growth and mental development. Patients with delayed bone age may be candidates for therapy. One approach is to consider treatment in children with the following signs and symptoms: (a) elevated serum TSH levels, (b) unexplained failure to thrive, (c) unexplained seizures, (d) developmental delay, and (e) history of growth or mental retardation in other affected members of the family [56]. As noted above, patients with RTH and coexisting ADHD may improve when treated with thyroid hormone [72]. In any case, patients who require treatment

should be followed closely, with careful evaluation of growth, bone age, and thyroid-responsive biochemical indices.

20.1.6.2 RTH-Alpha

L-T4 therapy has been shown to have beneficial effects on certain components of the phenotype, however, cognitive and fine motor skill defects do not improve [5]. During L-T4 treatment, serum T4 and rT3 normalized while serum T3 remained elevated, and this resulted in suppressed TSH. However, some peripheral markers of TH action have been reported to respond to L-T4 therapy, and markers of bone turnover rose progressively upon L-T4 treatment, with certain markers, including procollagen type 1 N-propeptide, and C-telopeptide cross-linked collagen type I, becoming frankly elevated. Some of the patients reported being more energetic and showed greater alertness after the initiation of L-T4 therapy, and L-T4 therapy induced an initial catch-up growth in one patient. Of note, in all patients, L-T4 treatment had a beneficial effect on constipation. However, L-T4 therapy may be of limited benefit in RTH-alpha, as the resulting hyperthyroidism in TRβ-expressing tissues may preclude the use of higher doses of L-T4. L-T3 treatment was tried in only one case and led to a reduction in TSH and consequently T4 levels, with an increase in heart rate; thus, L-T3 treatment might be difficult to implement [5]. It is possible that different treatment regimens could be used in children vs. adults, considering the important role of TH in growth and development. Thus judicious supplementation may be necessary in young patients, while the L-T4 doses used in adults could be lower. As only a few patients with RTH-alpha are known, there is limited information about treatment of this condition. Alternative therapeutic strategies could involve development of TRα1 subtype-specific hormone analogues.

Case Study

A 1-year-old baby presents for genetic evaluation of his thyroid condition. He is the first child born to unrelated parents. He was premature due to the mother developing preeclampsia and C-section was performed at 32 weeks. Apgar score was 9/9, BW 1320 g, BL 46 cm, he was diagnosed as being small for gestational age, and heart rate was 130/min. Due to initial hypoglycemia, GH, insulin, cortisol, TSH, and fT4 were tested. TSH and fT4 were found to be elevated at 7.1 mIU/L and 51 pmol/L, respectively. Thyroid ultrasound showed a mildly enlarged gland (right lobe of 0.76 × 1.05 cm and left lobe of 0.84 × 0.71 cm), with normal structure. He had no signs of hypo- or hyperthyroidism, and heart rate was 134/min even when asleep. He was initially treated with PTU and propranolol; however a pediatric endocrine consult recommended stopping this regimen. He was seen later in Pediatric Endocrine Division at 4.5 months, and at that time his weight was 5.380 kg, length 59.7 cm, head circumference 41 cm, and HR 160/min, ranging from 130/min to 160/min, even during sleep. Thyroid gland was easily palpable and TSH was 5.53 mIU/L (0.62–8.05) and fT4 60.10 pmol/L. A complete panel of thyroid function tests showed markedly elevated TH levels TT4 18.8 mcg/dL (5–11.6), TT3 418 ng/dL (90–195), while TSH 2.9 mU/L (0.4–3.6). This phenotype was indicative of RTH-beta, and sequencing of the *THRB* identified a de novo mutation in the patient, predicted to be a pathogenic variant. This case illustrates a case of early diagnosis of RTH-beta prompted by abnormal blood tests in perinatal period. It also illustrates an initial incorrect approach attempting to decrease TH levels although TSH was not suppressed. Symptomatic evaluation of these patients over time will dictate what intervention is needed if at all.

20.1.6.3 Summary

RTH is an inherited syndrome characterized by reduced responsiveness of target tissues to thyroid hormone caused by mutations in the TH receptor genes.

Mutations in the *THRB* cause the classical form of RTH known as RTH-beta and patients present with elevated TH levels with unsuppressed TSH. The reduced sensitivity to TH at the level of the hypothalamus and pituitary leads to elevated TSH levels, which stimulate the thyroid gland to increase production of TH. Both hyperthyroid and hypothyroid signs or symptoms may be present depending on the relative expression of TR-β and TR-α in different tissues.

Identification of *THRA* mutations has led to the characterization of RTH-alpha. These patients are phenotypically different from the RTH-beta patients in both TFTs and clinical features. Typical TFTs include low serum T4, borderline high T3, and very low rT3, with normal to elevated TSH. The resistance to TH is limited to tissues in which TH action is predominately mediated by TR-α such as bone, the GI tract, and the CNS.

20.2 Additional Thyroid Hormone Insensitivity Syndromes

In recent years, additional genetic syndromes have been identified that are associated with decreased thyroid hormone sensitivity in one form or another (but distinct from RTH). Such syndromes generally involve defects in thyroid hormone metabolism or transport.

For many years, it was thought that thyroid hormone diffused passively through cell membranes. We now know that thyroid hormone is transported into cells by a variety of transporter proteins [93]. One of these transporters is MCT8 and its gene is located on the X chromosome. Multiple patients with *MCT8* mutations have now been identified that exhibit X-linked mental retardation, dysarthria, athetoid movements, muscle hypoplasia, spastic paraplegia and hypotonia presenting in infancy or childhood [94, 95], also called the Allan-Herndon-Dudley syndrome. In these patients, serum T3 levels are elevated (from increased Type 1 deiodinase deficiency), free T4 levels are low, and TSH is normal or mildly increased. The severe CNS symptoms are due at least in part to impaired transport of thyroid hormone in the brain. Although brain T3 levels have been documented to be low, liver T3 levels are high [96], so that patients have a complex mix of hypothyroid and hyperthyroid symptoms. While current therapeutic options are limited to supportive measures, a recent study identified a thyroid hormone analog (3,5-diiodothyropropionic acid (DITPA)) that did not require MCT8 for transport and may represent a novel modality for patients suffering from this syndrome [97].

While mutations in deiodinase genes have not been identified, a recently described syndrome identified mutations in *selenocysteine insertion sequence-binding protein 2 (SECISBP2 or SBP2)*. SBP2 is involved in the incorporation of the rare amino acid selenocysteine to generate selenoproteins. Since deiodinase enzymes are selenoproteins, these recessive mutations result in abnormalities in thyroid hormone metabolism. Affected patients exhibit low T3 levels, high T4 levels, and normal or slightly elevated TSH levels [98, 99]. Recently, other kindreds with *SBP2* mutations were found to have coexisting azoospermia, axial muscular dystrophy, photosensitivity, abnormal immune function, and insulin sensitivity [100], suggesting that SBP2 deficiency produces a complex, systemic selenoprotein deficiency syndrome.

20.3 TSH Receptor Mutations

20.3.1 Introduction and Background Information

Thyrotropin (TSH) is a member of the glycoprotein family of hormone secreted by the anterior pituitary, along with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [101]. These hormones along with chorionic gonadotropin consist of noncovalently linked α and β subunits, with linked carbohydrate chains. While the β subunit of each hormone is unique, all share a common α subunit. TSH stimulates the growth and function of thyroid follicular cells, leading to the production of thyroid hormone. Thus, resistance to TSH (RTSH) ranges from a compensated state of euthyroid hyperthyrotropinemia to frank hypothyroidism. The first report of a patient with resistance to the biological properties of TSH was in 1968 [102], but it was not until 1995 that the first patient with a *TSH receptor (TSHR)* mutation was firmly documented [103].

20.3.2 Etiology

In 1995, Sunthornthepvarakul et al. documented the first case of a *TSHR* mutation leading to TSH resistance [103]. The index case was an infant born to unrelated parents found to have an elevated TSH level on routine neonatal screening. Two siblings were also found to have high TSH levels and normal thyroid hormone levels. All were clinically euthyroid and found to be compound heterozygotes for mutations in exon 6 of the *TSHR* corresponding to a region in the TSH extracellular domain [103]. In vitro data confirmed the mutant

receptors exhibited decreased biological activity. Since that time, a number of other patients have been identified with *TSHR* mutations and TSH resistance, though additional patients have been identified without identifiable mutations. Most patients with *TSHR* mutations are either homozygotes or compound heterozygotes.

The TSHR is a transmembrane G-coupled receptor (Fig. 20.3). It contains a large extracellular domain with three regions—the middle of these regions (approximately amino acids 58–288) contains the most significant homology to FSH and LH receptors [104]. The extracellular domain may inhibit constitutive activity of the receptor [105]. The carboxy-terminal portion of the TSH receptor includes the transmembrane domain, which spans the plasma membrane seven times, and an 82 amino acid cytoplasmic tail [105]. The gene encoding the TSH receptor has been localized to chromosome 14q31 [106, 107].

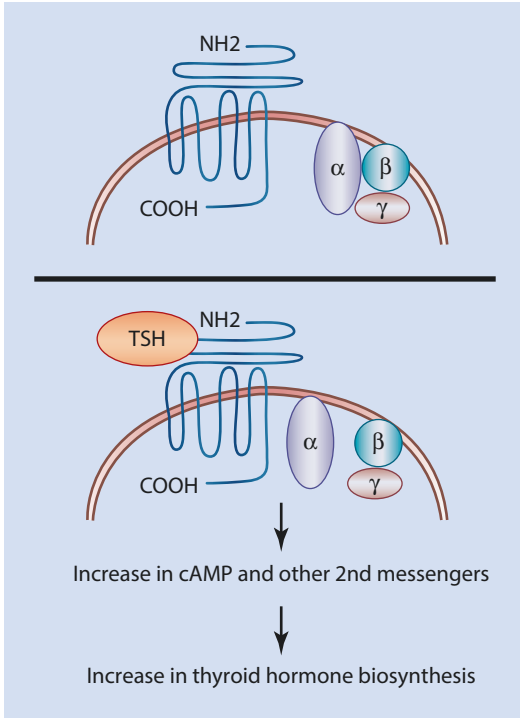

Fig. 20.3 Schematic diagram of the TSHR. The TSH receptor is composed of an N-terminal extracellular domain, a transmembrane region (which spans the plasma membrane seven times), and a cytoplasmic tail. Stimulation of the TSH receptor leads to G-protein dissociation and activation

20.3.3 Clinical Presentation

There are two general modes of presentation for patients with loss-of-function germline *TSHR* mutations. The first is similar to the family identified by Sunthornthepvarakul et al. [103]. In these patients, high TSH levels are necessary to overcome partial TSH resistance, and patients remain euthyroid (compensated euthyroid hyperthyrotropinemia). Four additional families with these clinical characteristics were identified by de Roux et al. [108]. One patient had a homozygous mutation in codon 162 of the *TSHR*; the other three were compound heterozygotes. Interestingly, one of the mutations (C390W) caused loss of TSH binding, whereas another (D410N) resulted in normal TSH binding but an inability to activate the second messenger adenylate cyclase. Mutations affecting signal transduction were also found in extracellular (D410N) and intracellular (F525 L) domains [108]. Additional mutations have been identified from patients with euthyroid hyperthyrotropinemia [109, 110].

In contrast, other *TSHR* mutations cause more extreme hormone resistance. Patients with these mutations present with hypothyroidism and may be identified by neonatal screening. Abramowicz et al. reported two such patients, a brother and sister, who were diagnosed with congenital hypothyroidism [111]. Ultrasound evaluation revealed hypoplastic thyroid glands. A homozygous mutation of the *TSHR* in the fourth transmembrane domain (A553T) was identified; the parents and unaffected siblings were heterozygous for the same mutation. In vitro analysis suggested that there was decreased expression of the mutant receptor at the cell surface [111]. Severely affected patients have been identified by other groups as well [112–114].

Not all patients with resistance to TSH have mutations in the *TSHR* [115]. Patients with pseudohypoparathyroidism caused by mutations in *GNAS* may exhibit resistance to a variety of hormones including TSH [116]. Mutations in transcription factors involved in thyroid gland development such as Pax8 [117] and TITF1 (Nkx2.1) [118] have been reported to cause resistance to TSH. Finally, Grasberger et al. identified multiple kindreds with resistance to TSH inherited in an autosomal dominant fashion without identifiable mutations [119]. However, the

phenotype in these patients was linked to a locus on chromosome 15 [120].

Recently, *DUOX2* genetic defects have been recognized to manifest a phenotype of TSH resistance. *DUOX2* mutations have been shown to cause elevated TSH at neonatal screening in Korean and Chinese patients that were found to be either euthyroid or have subclinical hypothyroidism, transient, or permanent congenital hypothyroidism [121, 122]. In this population, pathogenic variants in other genes known to manifest as TSH resistance were also identified, namely, *TSHR* and *PAX8*. The coexistence of multiple pathogenic variants seemed correlated to the severity of the hypothyroid condition.

20.3.4 Diagnostic Considerations

Mild TSH resistance (euthyroid hyperthyrotropinemia) is easily confused with subclinical hypothyroidism, since both present with elevated TSH levels in the setting of normal free thyroid hormone levels. Most cases of subclinical hypothyroidism are due to underlying autoimmune thyroid disease, which is generally absent in resistance to TSH. Patients with more severe TSH resistance present with thyroid function tests consistent with primary hypothyroidism. Patients with resistance to TSH, however, do not have a goiter, and the disorder is usually (but not always) inherited in an autosomal recessive pattern.

TSH resistance may be detected by neonatal screening programs. Since congenital hypothyroidism is not generally inherited, a significant family history of congenital hypothyroidism is suggestive for TSH resistance. A recent study in Japan of congenital hypothyroid infants found that 4.3% had biallelic TSH receptor mutations; the authors estimated that the frequency of *TSHR* heterozygous carriers to be 1 in 172 in that population [123]. Thus, the prevalence of TSH resistance may be higher than previously appreciated.

20.3.5 Outcome and Possible Complications

Outcome is generally good for these patients as they compensate for the TSH resistance with increased TSH levels. Only in rare instances of severe TSH resistance that go undetected at neonatal screening does one see the natural history of congenital hypothyroidism. However this occurrence is rare as detection at the neonatal screen prompts treatment with L-T4.

The opposite situation can occur when a patient with mildly elevated TSH and normal TH levels gets treated with L-T4 in an attempt to normalize TSH. In this case the identification of the genetic defect in the *TSHR* can prevent further unnecessary treatment.

20.3.6 Treatment

Patients with mild TSH resistance and mild hyperthyrotropinemia are clinically euthyroid and do not require treatment, although they should receive genetic counseling. Patients with more severe TSH resistance and frank hypothyroidism are treated with levothyroxine.

Case Study

A 7-year-old boy presents for genetic evaluation of his thyroid condition. He had elevated TSH at newborn screening, and without initial thyroid imaging he was started on L-T4. Reportedly his TSH was increased at every trial made to discontinue L-T4, while TT4 and freeT4 were normal. At 2 years of age, thyroid uptake and scan I-123 showed activity bilaterally, with mildly asymmetric increased activity on the right, no nodules, and uptake of 12.2% at 2 h (5–10%) and 6.8% at 24 h (6–33%). Thyroid ultrasound showed normal size and echogenicity with the right lobe measuring 1.6 × 0.8 × 0.6 cm, left lobe 0.6 × 1.3 × 0.4 cm, and isthmus 1 mm. A complete panel of thyroid function tests performed in the patient and his family showed mild elevation of TSH in the patient, his sister and father ranging from 5.3 mU/L to 11.6 mU/L (normal values 0.4–3.6). T4, T3, and rT3 levels were in the normal range and anti-TG and anti-TPO antibodies were negative. Sequencing of the *TSHR* gene identified a missense mutation in exon 10 inherited from the father and present in the heterozygous state in all three individuals. This case illustrates that occasionally even heterozygous *TSHR* mutation can manifest a typical phenotype of resistance to TSH, mostly depending on the consequence of the mutation on the function of the TSHR protein.

20.3.7 Summary

Resistance to TSH is characterized by high serum TSH and normal or low serum T4 and T3 in the setting of normal or hypoplastic thyroid glands.

The phenotype of RTSH can be caused by inactivating autosomal recessive or rarely autosomal dominant mutations in the *TSH receptor* gene and autosomal dominant mutations in the *PAX 8* gene. Most recently also *DUOX2* gene mutations have been recognized as a possible genetic defect resulting in this phenotype. Other cases have been linked to a locus on the chromosome 15.

RTSH should be suspected in patients who have high serum TSH concentrations, normal or low serum free T4 and T3 concentrations, and a normally located thyroid gland.

For RTSH patients in whom the impaired response to TSH is fully compensated by the increased TSH and who are euthyroid, no TH treatment is needed

If the elevated serum TSH cannot fully compensate for the defect, the patient should be treated with thyroid hormone, similar to treatment of hypothyroid patients.

Review Questions

1. A 10-year-old boy presents for evaluation of goiter and growth delay. Previously he was diagnosed with ADHD. His thyroid function tests were checked, and free T4 was found elevated at 4.6 mcg/dL (0.9–1.7), and TSH was 5 mU/L (0.4–3.6). Thyroid antibodies and TSI were negative. Thyroid ultrasound showed an enlarged gland. What is the most likely diagnosis?
   A. TSH secreting pituitary adenoma
   B. Activating *TSHR* mutation
   C. RTH caused by mutations in the *THRB* gene
   D. RTH caused by mutations in the *THRA* gene
2. A baby boy born to non-consanguineous parents living in the USA presents with an elevated TSH of 30 mU/dL at neonatal screening. On day 7, T4 and T3 levels are in the normal range, thyroid gland is normal on ultrasound, and he does not have hypothyroid symptoms. What is the diagnosis?
   A. Iodine deficiency
   B. TSH secreting pituitary adenoma
   C. *TSH receptor* mutations
   D. Resistance to thyroid hormone

Answers

1. C
2. C

20.4 Conclusions

Hormone resistance leading to thyroid dysfunction can occur at multiple levels of the hypothalamic-pituitary-thyroid axis. Care of patients with RTH must be individualized, and the endocrine status of the patient must be determined. In children, special attention must be paid to growth, bone development, and mental development. Further studies in children should be performed so that medical care can be optimized in these patients. RTH is usually caused by autosomal dominant mutations of the *THRB* gene. In contrast, resistance to TSH is usually caused by autosomal recessive mutations in the *TSH receptor* gene. However, patients with both disorders have been identified without identifiable mutations. These patients probably harbor mutations in other important endocrine genes. Further evaluation of these patients will be important not only to optimize their medical care but also to gain fundamental insights into the mechanisms of action of thyroid hormone, TSH, and other hormones.

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