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MINI-REVIEW

Pituitary resistance to thyroid hormones: pathophysiology and therapeutic options

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Abstract Thyroid hormone secretion suppresses the expression of thyroid stimulating hormone (TSH), both of which are strictly controlled by a negative feedback loop between the hypothalamus-pituitary and thyroid. Pituitary resistance to thyroid hormone (PRTH) is defined as resistance to the action of thyroid hormone that is more severe in the pituitary than at the peripheral tissue level. Although the molecular basis of PRTH is not well understood, the clinical issue mainly involves imbalance between the hypothalamus-pituitary and peripheral thyroid hormone responsivity, which may induce peripheral thyrotoxic phenomena. Here, we review the pathogenesis and molecular aspects of PRTH, present a single case with inappropriate TSH secretion suffering from thyrotoxicosis treated with PTU, and discuss the possible choice of therapeutic options to correct the imbalance of thyroid hormone responsivity in both the hypothalamus–pituitary and peripheral tissues.

Keywords PRTH · GRH · SITSH · Deiodinase · Propylthiouracil

Definition of PRTH

Nuclear thyroid hormone receptor β (TRβ) abnormalities are associated with generalized resistance to thyroid hormone (RTH) [1]. RTH leads to a lack of negative feedback on T3 synthesis in the pituitary–thyroid axis with concomitant loss of T3 response in the periphery. The clinical manifestations of RTH mimic hypothyroidism despite the presence of elevated TSH and T3 levels, while pituitary resistance to thyroid hormone (PRTH) is defined as resistance to the action of thyroid hormone that is more severe in the pituitary than at the peripheral tissue level [2]. Patients suffer from tachycardia, thyroid enlargement, weight loss, and other signs or symptoms related to thyrotoxicosis due to inappropriate TSH secretion, i.e., peripheral thyrotoxicosis.

At present, the term "PRTH" is used based on TRβ abnormalities in terms of nuclear thyroid hormone action. Although the clinical appearance has been well characterized, genomic studies indicated that a diagnosis of PRTH is questionable because either PRTH or RTH was demonstrated in kindreds with the same mutations in the TRβ gene [3]. Multiple factors, including cofactors, transporters, deiodinases, and binding proteins as well as TRβ, which may affect the actions of thyroid hormone, have been investigated [4]. Moreover, acquired molecular mechanisms, including epigenetic factors, may affect the clinical manifestations. Thus, the pathogenesis of PRTH may consist of not only TRβ abnormalities, but also other abnormal molecular mechanisms or factors, although the TRβ abnormalities undoubtedly affect the PRTH phenotype.

Pathophysiological and genetic aspects

Thyroid hormone secretion suppresses TSH expression, both of which are strictly controlled by a negative feedback loop between the hypothalamus–pituitary and thyroid. Two etiological factors are considered in cases with high serum thyroid hormone concentration with inappropriate high serum TSH concentration: the first is spontaneous secretion

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of TSH, which stimulates the secretion of thyroid hormone, and the other is an abnormal negative feedback loop due to impairment of thyroid hormone function in the hypothalamus–pituitary–thyroid (HPT) axis. The former is observed in TSH-producing tumors, while the latter is associated with PRTH. Recent findings have suggested that some cases of TSH-producing tumor may be associated with somatic expression of splicing variant of TRβ, which interferes with T3-mediated transcriptional activity [5]. Thus, in some aspects of the pathogenesis, TSH-producing tumors may also have hormone-resistant features similar to PRTH.

Although the major locus of TSH and thyroid hormone regulation is the pituitary gland, we should note that the PRTH phenotype might be due to impairment in any of the different components of the HPT axis [6]. Recent observations have suggested that many other loci may be involved in dysregulation of the HPT axis, and these alterations may eventually be responsible for the occurrence of PRTH. It has been demonstrated that resistance at both the thyrotrophs and the hypothalamic TRH neurons is required to elevate thyroid hormone levels in patients with RTH [7]. Thus, PRTH may result from alterations in the three major sites involved in the physiological mechanism that regulates the HPT axis: the hypothalamic dorsomedial nucleus, which acts as a metabolic sensor for hypophysiotropic TRH neurons, the TRH-producing neurons, and the pituitary thyrotrophs [8].

Currently, three types of molecule, i.e., TRβ2, thyroid hormone transporters, and deiodinases, may be involved in the molecular pathogenesis of PRTH.

TRβ2 is preferentially expressed in the TRH neurons of the hypothalamic paraventricular nucleus and in the thyrotrophs of the pituitary gland as well as in the developing ear and retina. Recent molecular findings have indicated that TRβ2 binds to coactivators through multiple contact surfaces, while TRβ1 recruits these coactivators through a single contact surface [9]. The different contact mechanisms may result in differences in T3 responsivity in the hypothalamus–pituitary and peripheral tissues. The clinical phenotype of PRTH may be explained by the disruption of specific TRβ2 contact mechanisms rather than by classical mutant TRβ1-induced dominant negative activity. However, the abnormal contact does not satisfactorily explain the phenotypic abnormalities in RTH. It should be noted that possible alterations in thyroid hormone coregulators, either corepressors or coactivators, especially those that interact specifically with the TRβ2 isoform, may be involved in the pathogenesis of PRTH.

Possible mutations in the two thyroid hormone transporters, i.e., the organic anion transporting polypeptide (OATP) 14 and monocarboxylate transporter (MCT) 8, may be associated with PRTH. To date, there have been no reports regarding individuals with mutations in the OATP14 gene. Individuals with mutations in the MCT8 gene dominantly develop neurological abnormalities, such as central hypotonia, spastic quadriplegia, and global development delay, with elevated levels of T3 and TSH. However, apparent thyrotoxic manifestations are not clinically observed [10]. Although the expression of MCT8 is detected in not only neurons but also peripheral organs, including the liver, conventional studies in knockout mice demonstrated elevated hepatic expression of deiodinase 1 and α-glycerol-3-phosphate dehydrogenase, both of which are known as thyroid hormone responsive proteins, with high serum T3 and inappropriately high levels of serum TSH indicating that the clinical phenotype in the mice is similar to that seen in patients with PRTH [11].

The deiodinase type 2 (Dio2) is preferentially expressed in the placenta, brown adipose tissue, thyroid, pituitary, and brain, especially in the hypothalamus and in a unique glial cell type called tanycytes originating from the third ventricle [12]. The restricted expression of impaired Dio2 function may cause regional resistance to thyroid hormone, which may be similar to PRTH. Although polymorphisms may affect regulation of the HPT axis, no critical mutations in the Dio2 gene associated with apparent RTH have been reported to date [13]. However, experimental studies involving disruption of *Dio2* demonstrated high serum T4 level with elevated TSH level in mice, suggesting that impaired Dio2 function may be related to PRTH [14].

Although the molecular mechanisms of PRTH are not well understood, the main clinical issue is imbalance between hypothalamus–pituitary responsivity and peripheral responsivity to systemic thyroid hormone. This imbalance induces thyrotoxicosis with inappropriate TSH secretion. Although the main therapeutic approach should be to address the molecular targets, which may be responsible for development of PRTH, an optional approach is to somehow correct the imbalance of thyroid hormone responsivity. Here, we report a Japanese man showing inappropriate TSH secretion without evidence of either TSH-producing tumor or abnormal TRβ, who was treated successfully with propylthiouracil (PTU).

Clinical presentation

A 53-year-old man showed palpitations and tachycardia at the time of the initial outpatient visit. Diffuse large goiter, atrial fibrillation, and thyrotoxemia were detected on routine examination. His initial thyroid function was FT3 7.98 pg/ml, FT4 2.55 ng/dl, and TSH 1.33 μIU/ml. The patient's past history was unremarkable, and family history indicated no thyroid disorders in his parents. TRH provocation test showed a normal response. Pituitary magnetic

resonance imaging (MRI) with dynamic enhancement showed no pituitary tumors in the sella turcica. The physical manifestations strongly suggested thyrotoxicosis due to inappropriate TSH secretion. Normal responses to TRH are predominantly observed in cases of thyroid hormone resistance rather than those of TSH-producing tumors. These findings indicating the absence of TSH-producing tumor on MRI suggested a diagnosis of thyroid hormone resistance with peripheral thyrotoxic manifestations in this case.

Sequencing of the TRβ gene was performed with the approval of the Ethical Committee of Shinshu University, and the patient gave written informed consent. Sequence analysis indicated a cytosine-to-thymine transition at nucleotide 909 in the TRβ gene, which results in no substitution of the isoleucine residue at position 208, suggesting that the inappropriate secretion of TSH may not be associated with this silent mutation. However, it should be noted that there are no known single nucleotide polymorphisms at nucleotide 909 in Japanese or Caucasian populations [15, 16]. It remains possible that the nucleotide substitution may affect the protein structure, and this abnormal protein may result in resistance to thyroid hormone.

Administration of 15 mg of thiamazole per day was started based on an initial clinical diagnosis of thyrotoxicosis due to Graves' disease, although anti-TSH receptor antibody was always negative during the treatment period. After administration, serum TSH increased to > 100 μIU/ml (#2 in Fig. 1, Table 1). Although atrial fibrillation disappeared, the patient's thyromegaly deteriorated. Adding levothyroxine reduced the serum TSH concentration. Despite use of higher doses, TSH never decreased below 16 μIU/ml with gradual increases in FT3 and FT4 levels (#3–6 in Fig. 1, Table 1). The goiter remained. Liothyronine directly suppresses TSH production in thyrotrophic cells although this agent does not have a long duration of action. To suppress TSH and thyroid enlargement, liothyronine was introduced at an initial dose of 25 μg per day. TSH concentration showed a transient reduction to 2.2 μIU/ml, but increased gradually even though the loading doses were increased. Eventually, atrial fibrillation redeveloped at a dose of 75 μg (#7–8 in Fig. 1, Table 1). Liothyronine was carefully withdrawn and replaced with levothyroxine. Atrial fibrillation disappeared. Due to the expected suppressive effects of dopamine agonists on TSH production, 7.5 mg of bromocriptine per day was added. Serum TSH level decreased to 8.7 μIU/ml, although the discomfort due to thyromegaly persisted (#9–10 in Fig. 1, Table 1). The goiter remained with inappropriate TSH secretion. Considering the pathological mechanisms of inappropriate TSH secretion in the absence of peripheral thyroid hormone resistance, PTU was introduced instead of

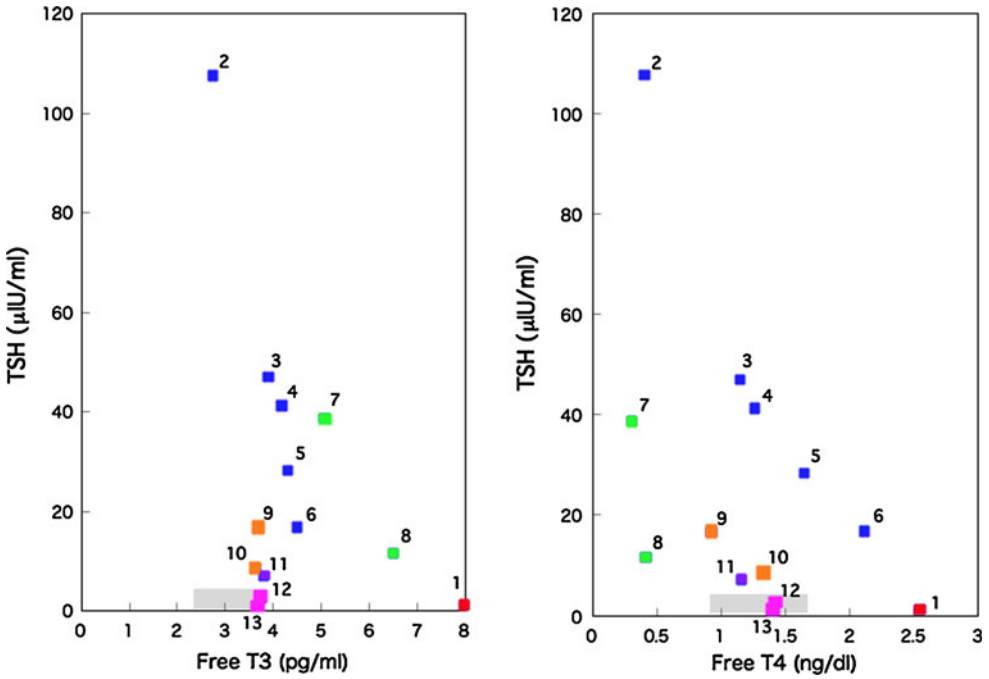

Fig. 1 Relationships between serum concentrations of free T3 and TSH (*left panel*), or free T4 and TSH (*right panel*). The *numbers* indicate the values obtained from the sample more than 2 weeks after the treatment described in Table 1. *Colored symbols* represent the values obtained during the period with no treatment (*red*), treatment with thiamazole alone or plus levothyroxine (*blue*), treatment with thiamazole plus liothyronine (*green*), treatment with levothyroxine and bromocriptine (*orange*), treatment with thiamazole, PTU, levothyroxine plus bromocriptine, and treatment with PTU and bromocriptine with or without levothyroxine (*magenta*). The *gray shaded areas* indicate the normal ranges of free T3 and TSH (*left panel*) or free T4 and TSH (*right panel*). *PTU* propylthiouracil

Table 1 Thyroid functions and treatment in the present case

#	FT3 (pg/ml)	FT4 (ng/dl)	TSH (μIU/ml)	Anti-thyroid drugs (mg/day)	Thyroid hormone (μg/day)	Bromocriptine (mg/day)
1	7.98	2.55	1.33			
2	2.76	0.41	107.7	Thiamazole 15		
3	3.91	1.15	47.13	Thiamazole 15	Levothyroxine 50	
4	4.19	1.27	41.4	Thiamazole 15	Levothyroxine 100	
5	4.32	1.65	28.46	Thiamazole 15	Levothyroxine 150	
6	4.5	2.12	16.94	Thiamazole 15	Levothyroxine 175	
7	5.08	0.31	38.79	Thiamazole 15	Liothyronine 50	
8	6.51	0.42	11.8	Thiamazole 15	Liothyronine 75	
9	3.71	0.93	16.79	Thiamazole15	Levothyroxine 100	7.5
10	3.64	1.34	8.7	Thiamazole 15	Levothyroxine 150	7.5
11	3.82	1.16	7.22	Thiamazole 10+ PTU 100	Levothyroxine 125	7.5
12	3.75	1.42	2.66	PTU 200	Levothyroxine 50	7.5
13	3.71	1.41	1.23	PTU 150		7.5

Thyroid function was evaluated after more than 2 weeks of the indicated treatment. The numbers correspond to those in Fig. 1

PTU propylthiouracil

thiamazole. A dose of 150 mg of PTU improved thyroid enlargement, and thyroid function was normalized with additional administration of 7.5 mg of bromocriptine (#11–13 in Fig. 1 and Table 1).

Therapeutic approach and options

Some patients with PRTH suffer from thyrotoxic phenomena, such as weight loss, tachycardia, and atrial fibrillation with thyromegaly due to measurable levels of TSH [17]. The therapeutic approach to TSH-producing tumors essentially involves removal of the tumors. In contrast, as noted in the above case, adequate treatment strategies have not been established for cases with inappropriate TSH secretion without visible TSH-producing tumors. Some thyroid hormone analogs have been reported as therapeutic drugs for generalized RTH.

Clinically, 3,5,3′-triiodothyroacetic acid (TRIAC) was reported to be available for the management of thyrotoxicosis due to PRTH [18–20]. The molecular aspects revealed that TRIAC has a higher affinity for TRβ1 than T3, whereas the two compounds show equivalent affinities for TRα1 [21, 22]. The different binding features may be useful for the treatment of TRβ1 abnormalities in cases of RTH [22]. Recent studies indicated the beneficial effects of TRIAC in children with thyroid hormone resistance [23, 24].

As bromocriptine, a dopamine agonist, blocks TSH secretion as well as prolactin secretion, this agent either alone or in combination with TRIAC was also reported to suppress inappropriate TSH secretion in RTH [25–27]. As stereospecific transport of thyroid hormone was demonstrated in vitro, several studies demonstrated that the D-stereoisomer of thyroxine, dextrothyroxine, is available as a TSH suppressor in PRTH patients [28–31]. Long-term studies of the effects of TRIAC or dextrothyroxine have been reported [32, 33].

As the action of thyroid hormone is mediated by several factors, including nuclear receptors, T3 transporters, deiodinases, etc., genetic abnormalities in these factors affect the clinical phenotype, i.e., thyroid hormone resistance syndrome [34, 35]. From the viewpoint of the therapeutic approach, these molecular factors related to thyroid hormone action may become targets for treatment or to improve thyroid hormone resistance syndrome, including thyrotoxic phenomena with inappropriate TSH secretion.

Propylthiouracil shows a unique feature that is not shared with thiamazole. As PTU inhibits type 1 deiodinase activity, but not that of type 2, which is preferentially expressed in the hypothalamus and thyrotrophic cells, PTU is expected to reduce the intracellular content of T3 in peripheral tissues, but not in pituitary thyrotrophic cells [36]. PTU may correct the imbalance between peripheral and pituitary resistance to thyroid hormone in patients with inappropriate secretion of TSH, including PRTH.

Conclusions

Here, we reviewed the mechanisms of PRTH development and discussed the optional choices of treatment in terms of imbalance between thyroid hormone responsivity in the pituitary and peripheral tissues. We presented a case of inappropriate TSH secretion in which thyrotoxicosis was

controlled by PTU. In addition to therapeutic agents, such as TRIAC, D-thyroxine, and bromocriptine for RTH, we recommend PTU rather than thiamazole as an optional agent in cases with inappropriate TSH secretion showing apparent peripheral thyrotoxicity.

Conflict of interest The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

Disclosure The authors have nothing to disclose.

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