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Therapeutic applications of thyroid hormone analogues

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ABSTRACT

Cellular thyroid hormone homeostasis requires adequate function of: (1) thyroid hormone transporter proteins at the plasma membrane, (2) deiodinating enzymes and (3) nuclear thyroid hormone receptors (TRs). Defects in any of these processes give rise to distinct disease entities, collectively called thyroid hormone signaling disorders. Thyroid hormone analogues hold therapeutic potential in thyroid hormone signaling disorders by bypassing defective transporters or binding to mutant TRs. This review will focus on the application of analogues in thyroid hormone signaling disorders, particularly monocarboxylate transporter (MCT)8 deficiency, and resistance to thyroid hormone due to mutations in TRβ (RTHβ)

1. Introduction

Thyroid hormone is crucial for normal development and metabolism of all tissues. Cellular thyroid hormone homeostasis requires adequate function of [1] thyroid hormone transporter proteins at the plasma membrane, [2] deiodinating enzymes and [3] nuclear thyroid hormone receptors (TRs). Defects in any of these processes give rise to distinct disease entities, collectively called thyroid hormone signaling disorders. Thyroid hormone analogues hold therapeutic potential in thyroid hormone signaling disorders by bypassing defective transporters or binding to mutant TRs. The use of thyroid hormone analogues has also been explored for other diseases. In the past, its role in TSH suppression as substitute or adjunct to levothyroxine therapy in thyroid cancer has been investigated [1]. In recent years, thyroid hormone analogues have been applied in more common diseases such as non-alcoholic steatohepatitis [2] or as lipid-lowering treatment [3]. This short review will focus on the application of analogues in thyroid hormone signaling disorders, particularly monocarboxylate transporter (MCT8) deficiency.

2. MCT8 deficiency

MCT8 is a specific thyroid hormone transporter that is crucial for transport of tri-iodothyronine (T3) and thyroxine (T4) in several tissues, including the brain [4–7]. Mutations in the gene encoding MCT8 (SLC16A2 on chromosome Xq13.2) cause MCT8 deficiency, also known as the Allan-Herndon-Dudley syndrome (AHDS), a debilitating disorder with an estimated prevalence of 1 in 70,000 male individuals [8]. MCT8 deficiency is characterized by profound intellectual and motor disability due to a hypothyroid state in the brain. Endocrine abnormalities associate marked elevation of serum T3 concentrations with low to low-normal (F)T4 concentrations and normal TSH concentrations. The increased T3 concentrations result in a thyrotoxic state in many organs, contributing to a deterioration of body weight for age over time, muscle wasting and tachycardia [8]. The low T4 concentrations measured in patients with MCT8 deficiency in the neonatal screening indicates the potential to diagnose MCT8 deficiency in newborns, perhaps with a modification of the current neonatal screening strategy.

The phenotype is due to defective thyroid hormone transport by mutant MCT8. MCT8-dependent tissues (e.g. brain) are in a hypothyroid state, while MCT8-independent tissues (e.g. liver, muscle, heart) normally sense the elevated serum T3 concentrations. The clinical features are the net result of hypothyroid and hyperthyroid tissues.

Apart from empirical symptomatic treatment, a number of therapeutic options have been explored. Thyroxine replacement therapy is not effective in normalizing FT4 levels and rather further worsens the increased serum T3 concentrations, probably due to immediate conversion of T4 to T3 [9]. A combination of the antithyroid drug PTU and thyroxine has been shown to normalize serum T3 and T4 concentrations and, consequently, alleviating some clinical features due to the thyrotoxicity. Those approaches are unlikely to improve neurodevelopment, as thyroxine is not expected to enter the brain given its MCT8-dependent uptake. Also, as PTU has an unfavorable safety profile, the risk-benefit ratio should be taken into account when counseling parents.

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Effective therapy should both normalize toxic thyroid hormone effects in peripheral tissues and improve the hypothyroid state in brain. Therefore, analogues that mimic T3 action but rely on other transporters than MCT8 for cellular entry are suited to reverse or prevent the neurological phenotype in such patients. Also, T3 analogues expectedly negatively regulate TSH concentrations, thereby reducing endogenous thyroid hormone concentrations.

Diiodothyropropionic acid (DITPA) and triiodothyroacetic acid (Triac) are two different thyroid hormone analogues that have been investigated in MCT8 deficiency. After beneficial effects in Mct8 KO mice were noted, DITPA has reportedly been applied in 4 patients [10,11]. Serum T3 and sex-hormone binding globulin (SHBG) concentrations improved in all patients, although no consistent effect on body weight was observed. The absence of beneficial effects on the neurological phenotype can be explained by different possibilities including the irreversibility of brain damage, age beyond therapeutic window or insufficient access to the brain with the used doses.

Triac was able to normalize the abnormal brain development in Mct8/Oatp1c1 double KO mice, the mouse model most accurately reflecting human MCT8 deficiency [12]. Abnormal Purkinje cell development in Mct8/Oatp1c1 double KO was improved with a low dose of Triac and fully restored with a high dose of Triac. Also, Triac was shown to enter fibroblasts of MCT8 deficient patients to a similar extent as cells from unaffected individuals [13].

Based on these preclinical studies, an international trial was started to investigate the effects of Triac in patients with MCT8 deficiency, the results of which have been reported recently [8]. In total, 46 patients (median age 7.1 years [range 0.8–66.8]) received Triac for 12 months and a subset of the patients were included in a long-term treatment-extension period. After 12 months of Triac treatment, serum T3 concentrations (primary end point) were largely reduced in all patients.

In patients who completed the 12-month treatment period, there was a significant mean increase in weight for age. In addition, systolic blood pressure and resting heart rate decreased and also the high number of premature atrial contractions was largely reduced. Different markers for thyroid hormone action in tissues (e.g. creatine kinase, creatine, SHBG) improved. Triac was well tolerated with only mild and transient symptoms of perspiration and irritability. Together, Triac was safe and effectively normalized the serum T3 concentrations in paediatric and adult patients with MCT8 deficiency with sustainable improvements in clinically relevant outcomes including body weight, heart rate and blood pressure. Being severely underweight and cardiovascular dysfunction are important clinical sequelae of chronic peripheral thyrotoxicosis, causing significant morbidity and mortality in MCT8 deficiency, amelioration of the thyrotoxicosis under Triac treatment benefits patients with MCT8 deficiency irrespective of their age.

Another phase 2 clinical trial will investigate the effects of Triac on neurodevelopment, with treatment being started at a very young age (NCT02396459). The future will reveal if Triac has the potential to modulate the neurodevelopment in MCT8 deficiency.

3. Resistance to thyroid hormone due to mutations in TRβ (RTHβ)

The main effects of thyroid hormone are exerted through binding of T3 to its nuclear receptor (thyroid hormone receptor, TR), which functions as a ligand-dependent transcription factor. The main T3 binding receptor isoforms are TRα1 and TRβ1 and 2, which differ in their tissue distribution [14].

Heterozygous mutations of TRβ are the most common genetic cause of RTHβ and have a prevalence of – 1:50,000 [15]. The endocrine hallmark of RTHβ are elevated serum (free) T4 and T3 concentrations accompanied by non-suppressed or elevated serum TSH concentrations. The clinical features of RTHβ comprise a combination of hypothyroid and thyrotoxic symptoms, resulting from the tissue-specific distribution of the TR isoforms. T3 action is reduced in TRβ-expressing tissues (e.g. pituitary and liver) [16,17]. In contrast, TRα-expressing tissues (e.g. heart and brain) normally sense the high serum thyroid hormone concentrations and may result in tachycardia, hyperactivity, anxiety and learning disabilities [16,17]. There is a wide clinical spectrum in RTHβ, ranging from asymptomatic individuals with abnormal thyroid functions tests to patients with a severe motor and intellectual disability. Therefore, the need for treatment is assessed on an individual basis [15]. In the majority of patients who suffer from tachycardia and palpitations, symptomatic treatment with beta-blockers is sufficient to alleviate those symptoms.

In patients that do not respond to those treatment possibilities, an ideal treatment should selectively increase T3 action in TRβ-expressing tissues while maintaining euthyroidism in TRα-expressing tissues. Triac preferentially acts through the TRβ isoform [19–21]. Importantly, Triac exhibits a higher affinity than T3 for several TRβ mutants [19–21].

These in vitro observations are in line with case reports and case series in patients with RTHβ (for an overview, see [22]). Dependent on the mutation, Triac has the potential to inhibit TSH production and secretion, resulting in a reduction in serum (F)T4 and (F)T3 concentrations. As a consequence, a (partial) alleviation of the thyrotoxic symptoms including tachycardia, excessive perspiration and behavioral problems can be expected. The putative negative effects of the relatively high doses Triac in the TRα-expressing tissues, including the bone, are difficult to evaluate based on the available literature.

Clinical trials and long-term follow-up studies are required to describe the positive and adverse effects of Triac at the tissue level in RTHβ in more detail. It would be of clinical relevance to document the effects of Triac in RTHβ patients using established treatment protocols and well-defined outcome measures.

4. Perspectives

Ever since the report of Triac in 1953 [23], the field has actively developed and tested other thyroid hormone analogues. The potential application of such analogues varies from selected rare thyroid hormone signaling disorders (e.g. RTHβ and MCT8 deficiency) to more common diseases (e.g. multiple sclerosis, hypercholesterolemia and NASH) [2,8,24–27]. Rational design of thyroid hormone analogues with appropriate preclinical studies should pave the way for clinical trials in populations with rare and common disorders.

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Disclosure of interest

The Erasmus Medical Centre (Rotterdam, Netherlands), which employs WEV, might receive royalties from Rare Thyroid Therapeutics (the manufacturer of Triac) in the future, dependent on any future commercialisation. The author declares he has no competing interest.

References

[1] Mechelany C, Schlumberger M, Challeton C, Comoy E, Parmentier C. Triac (3,5,3'-triiodothyroacetic acid) has parallel effects at the pituitary and peripheral tissue levels in thyroid cancer patients treated with L-thyroxine. Clin Endocrinol 1991;35(2):123–8.

[2] Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2019;394(10213):2012–24.

[3] Ladenson PW, Kristensen JD, Ridgway EC, Olsson AG, Carlsson B, Klein I, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. N Engl J Med 2010;362(10):906–16.

[4] Friesema EC, Ganguly S, Abdalla A, Manning Fox JE, Halestrap AP, Visser TJ. Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. J Biol Chem 2003;278(41):40128–35.

[5] Heuer H, Maier MK, Iden S, Mittag J, Friesema EC, Visser TJ, et al. The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations. Endocrinology 2005;146(4):1701–6.

[6] Ceballos A, Belinchon MM, Sanchez-Mendoza E, Grijota-Martinez C, Dumitrescu AM, Refetoff S, et al. Importance of monocarboxylate transporter 8 for the blood-brain barrier-dependent availability of 3,5,3'-triiodo-L-thyronine. Endocrinology 2009;150(5):2491–6.

[7] Vatine GD, Al-Ahmad A, Barriga BK, Svendsen S, Salim A, Garcia L, et al. Modeling psychomotor retardation using ipscs from mct8-deficient patients indicates a prominent role for the blood-brain barrier. Cell Stem Cell 2017;20(6):831–43 [e5].

[8] Groeneweg S, Peeters RP, Moran C, Stoupa A, Auriol F, Tonduti D, et al. Effectiveness and safety of the tri-iodothyronine analogue Triac in children and adults with MCT8 deficiency: an international, single-arm, open-label, phase 2 trial. Lancet Diabetes Endocrinol 2019;7(9):695–706.

[9] Visser WE, Vrijmoeth P, Visser FE, Arts WF, van Toor H, Visser TJ. Identification, functional analysis, prevalence and treatment of monocarboxylate transporter 8 (MCT8) mutations in a cohort of adult patients with mental retardation. Clin Endocrinol 2013;78(2):310–5.

[10] Verge CF, Konrad D, Cohen M, et al. Diiodothyropropionic acid (DITPA) in the treatment of MCT8 deficiency. J Clin Endocrinol Metab 2012;97:4515–23.

[11] Di Cosmo C, Liao XH, Dumitrescu AM, et al. A thyroid hormone analog with reduced dependence on the monocarboxylate transporter 8 for tissue transport. Endocrinology 2009;150:4450–8.

[12] Mayerl S, Müller J, Bauer R, et al. Transporters MCT8 and OATP1C1 maintain murine brain homeostasis. J Clin Invest 2014;124:1987–99.

[13] Kersseboom S, Horn S, Visser WE, et al. In vitro and mouse studies supporting therapeutic utility of triiodothyroacetic acid in MCT8 deficiency. Mol Endocrinol 2014;28:1961–70.

[14] Cheng SY, Leonard JL, Davis PJ. Molecular aspects of thyroid hormones actions. Endocr Rev 2010;31:139–70.

[15] Dumitrescu AM, Refetoff S. The syndromes of reduced sensitivity to thyroid hormone. Biochim Biophys Acta 2013;1830:3987–4003.

[16] Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev 1993;14:348–99.

[17] Forrest D, Hanebuth E, Smeyne RJ, Everds N, Stewart CL, Wehner JM, et al. Recessive resistance to thyroid hormone in mice lacking thyroid hormone receptor beta: evidence for tissue-specific modulation of receptor function. EMBO J 1996;15:3006–15.

[19] Takeda T, Suzuki S, Liu RT, DeGroot LJ. Triiodothyroacetic acid has unique potential for therapy of resistance to thyroid hormone. J Clin Endocrinol Metab 1995;80:2033–40.

[20] Messier N, Laflamme L, Hamann G, Langlois MF. In vitro effect of Triac on resistance to thyroid hormone receptor mutants: potential basis for therapy. Mol Cell Endocrinol 2001;174:59–69.

[21] Martínez L, Nascimento AS, Nunes FM, Phillips K, Aparicio R, Dias SM, et al. Gaining ligand selectivity in thyroid hormone receptors via entropy. Proc Natl Acad Sci USA 2009;106(49):20717–22.

[22] Groeneweg S, Peeters RP, Visser TJ, Visser WE. Therapeutic applications of thyroid hormone analogues in resistance to thyroid hormone (RTH) syndromes. Mol Cell Endocrinol 2017;458:82–90.

[23] Pitt-Rivers R. Physiological activity of the acetic-acid analogues of some iodinated thyronines. Lancet 1953;265(6779):234–5.

[24] Malm J, Grover GJ, Färnegårdh M. Recent advances in the development of agonists selective for β1 type thyroid hormone receptor. Mini Rev Med Chem 2007;7:79–86.

[25] Chiellini G, Apriletti JW, Yosihhara HA, Baxter JD, Ribeiro RC, Scanlan TS. A high affinity subtype selective agonist ligand for the thyroid hormone receptor. Chem Biol 1998;5:299–306.

[26] Grover GJ, Mellstrom K, Malm J. Development of the thyroid hormone receptor beta-subtype agonist KB-141: a strategy for body weight reduction and lipid lowering with minimal cardiac side effects. Cardiovasc Drug Rev 2005;23:133–48.

[27] Hartley MD, Banerji T, Tagge IJ, Kirkemo LL, Chaudhary P, Calkins E, et al. Myelin repair stimulated by CNS-selective thyroid hormone action. JCI Insight 2019;4(8), pii: 126329 (PMID:30996143).