Published in final edited form as:
Curr Opin Endocrinol Diabetes Obes. 2013 October ; 20(5): 434–440. doi:10.1097/01.med.0000432531.03233.ad.

Inherited defects of thyroid hormone-cell-membrane transport: review of recent findings

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Abstract

Purpose of review—This review summarizes the most significant findings over the last year regarding human and animal models deficient in thyroid hormone cell-membrane transporters (THCMTs). Although several THCMTs have been modelled in genetically engineered mice, the only THCMT defect known in humans is that caused by mutations in the monocarboxylate transporter 8 (*MCT8*) gene.

Recent findings—The importance of several amino acid residues has been assessed *in vitro* to further our understanding on the structure–function of the MCT8. The administration of the thyromimetic compound, diiodothyropropionic acid, has been tested in patients with *MCT8* gene mutations, following studies of its use in mice. Another thyroid hormone analogue, 3,3′,5,5′-tetraiodothyroacetic acid, was tested in Mct8-deficient mice. The phenotypes of L-type aminoacid transporter 2 and organic anion transporting polypeptide 1C1 deficiencies have been studied in mouse models. *Mct8/organic anion transporting polypeptide 1C1* double knockout mice have been shown to manifest neurodevelopmental deficits. Zebrafish is emerging as another vertebrate model that may be useful to study the role of Mct8 in brain development.

Summary—Studies on the pathogenesis and therapy of MCT8 deficiency are in progress, and new vertebrate models that are suitable to study the neurological consequences of the syndrome are being explored.

Keywords

Allan-Herndon-Dudley syndrome; diiodothyropropionic acid; Lat2; monocarboxylate transporter 8; organic anion transporting polypeptide 1C1

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Conflicts of interest

There are no conflicts of interest

INTRODUCTION

In the last two decades, the identification of several thyroid hormone cell-membrane transporters (THCMTs) has advanced our understanding of thyroid hormone physiology. The monocarboxylate transporter (MCT) 8 is an active and specific THCMT expressed in multiple tissues, and in particular the brain [1]. Mutations of the *MCT8* gene were found to be responsible for the Allan–Herndon–Dudley syndrome, an X chromosome linked mental retardation syndrome initially described in 1944 that is now synonymous with the MCT8 defect [2–4]. Patients with this syndrome display severe neuro-developmental deficits, including truncal hypotonia, cognitive retardation and spastic quadriplegia; the inability to walk or speak; and have characteristic thyroid abnormalities of high serum T_3, low rT_3, low normal to reduced T_4 and normal or slightly elevated thyrotropin (TSH) concentrations.

The pathophysiology of MCT8 deficiency has been studied *in vitro* using human cell lines [5,6] and *in vivo* using Mct8 knockout (*Mct8KO*) mice, which replicate the thyroid hormone abnormalities found in humans [7,8]. Coexistence of thyroid hormone excess and deprivation in different tissues is a distinct characteristic of this syndrome. Tissues expressing THCMTs other than MCT8, such as liver and kidney, respond to the high circulating T_3 levels resulting in a local hyperthyroid state, whereas tissues depending on MCT8 for thyroid hormone entry into cells, such as the brain, are hypothyroid [9]. This feature, however, complicates the management of the disease. Recently, two therapeutic options, propylthiouracil (PTU) combined with L-T_4 [10▪,11] and a thyromimetic compound, diiodothyropropionic acid (DITPA), which is not dependent on MCT8 for cellular entry [12▪▪], have been used to treat several patients harbouring *MCT8* gene mutations.

The absence of gross neurological symptoms in *Mct8KO* mice limits their use for the study of the pathogenesis of the psychomotor manifestations in humans. The sufficient compensation of alternative transporters, such as the heterodimeric L-type amino acid transporters (LAT) 2 and the Na^+-independent organic anion transporting polypeptide (OATP) 1C1 in murine brain, may contribute to this discrepancy [13,14]. However, deficiencies of THCMTs other than MCT8 have not been identified in humans, and the characteristics of Lat2 and Oatp1C1 deficiencies have been studied instead in genetically engineered knockout mice [15,16▪]. Of interest, *Mct8/Oatp1C1* double-knockout mice were recently generated and found to have severe neurodevelopmental impairments. Zebrafish is emerging as another animal model that may be suitable to study the role of MCT8 in brain development [17▪▪].

In this review, we provide a summary of the most significant findings over the last year regarding patient and animal models deficient in the THCMTs.

MONOCARBOXYLATE TRANSPORTER 8 DEFICIENCY IN HUMANS

Several new cases of MCT8 deficiency have been published in the past year [10▪,18▪,19]. More than 200 individuals belonging to some 100 families of all races and diverse ethnic origins harbouring more than 70 different mutations have been identified. Correlation between genotype and phenotype of patients with *MCT8* gene mutations has been observed.

Most mutations result in the virtually complete loss of THCMT function, primarily that of T_3. However, several mutants, S194F, L434W, L492P, L598P and F501del, showed sufficient residual transport capacity, and are associated with less severe psychomotor defects, including the ability to walk with ataxic gait and/or dysarthric speech [5,10▪,20]. The transport activity of MCT8 mutations can be affected by unsuccessful plasma membrane translocation, even when they are functional THCMTs [21]. The effects on the subcellular distribution and transport activity have been studied in three different cell lines for seven reported MCT8 mutants: G221R, insV236, G282C, P321L, D453 V, P537L, G558D [22▪]. Impairment of thyroid hormone cell-uptake and metabolism was observed with all these mutants. Three of the mutants, insV236, G282C and G558D, were retained in the endoplasmic reticulum, with only small amounts reaching the plasma membrane, indicating abnormal protein expression and trafficking. Cell-specific residual thyroid hormone uptake by G282C, P537L and G558D mutants has been observed, suggesting that MCT8 mutant proteins may have tissue-specific effects on transport of thyroid hormone, depending on yet unidentified MCT8-interacting proteins [21].

Several studies have evaluated the structure– function of the MCT8 by using amino acid specific chemical modification and site-directed mutagenesis [23–25], in order to identify critical amino acids along the transport channel cavity responsible for thyroid hormone recognition and transport. The study of the 10 Cys residues, located within the MCT8 molecule, identified Cys497 and Cys481 as being equally accessible to both the substrate and inhibitor, thus indicating that they are located in the substrate-recognition site [24]. One study [23] of several His residues identified His192 to be located at or near the site within the MCT8 protein that is involved in recognition of thyroid hormone. A ‘His-Arg clamp’, similar to that reported in the crystal structure of the T3-receptor/T3 complex, identified His415 and Arg301 as a possible substrate channel for T_3 [25].

The regulation of human *MCT8* gene at the transcriptional level remains unclear. The expression of the mouse *Mct8* gene has been shown to be cell-type-specific and induced by retinoic acid, although a homologous sequence for the retinoic acid response element has not been found in the *MCT8* locus [26]. Until recently, putative proteins that interact with MCT8 were not known. The pituitary tumour transforming gene-binding factor, a proto-oncogene implicated in endocrine cancer, including thyroid cancer, was shown to interact with MCT8 [27▪▪]. Through binding with MCT8, the pituitary tumour transforming gene-binding factor altered the subcellular localization of MCT8 *in vitro* and resulted in a reduction in thyroid hormone secretion and an accumulation of thyroid hormone within the thyroid gland *in vivo*.

Therapeutic options for patients with MCT8 deficiency remain limited. The administration of PTU, which blocks thyroid hormone production and inhibits T_4 to T_3 conversion, combined with L-T_4 in some patients has shown some clinical benefits [10▪,11] that are primarily metabolic. After 10–24 weeks of PTU treatment (200–400 mg/day), FT_3 normalized, FT_4 decreased and TSH increased. When high doses of L-T_4 (100mg/day) were added, abnormalities of thyroid hormone nearly completely normalized without thyrotoxic side-effects (Table 1). However, this treatment did not improve the psychomotor deficits. In

addition, the side-effects associated with PTU, including granulocytopenia and hepatic toxicity, are potential risks [12▪▪,28].

The analogue of thyroid hormone DITPA is able to be transported into the brain and corrects the thyroid hormone abnormities without causing thyrotoxic effects on peripheral tissues in *Mct8KO* mice [29]. On the basis of these data, DITPA was given to four affected children for 26–40 months [12▪▪,30]. Treatment was initiated at ages 9–25 months, beginning with small doses 1.8–2 mg/day and gradually increasing to 2.1–2.4 mg/kg/day. DITPA doses above 1 mg/kg/day normalized or nearly normalized the thyroid tests by reducing the serum T_3 and TSH to normal range and increasing serum T_4 and rT_3 to low normal or slightly below normal levels, without any associated adverse effects (Table 1). Other benefits of DITPA on peripheral tissues were the decline in sex hormone binding globulin levels (in all subjects), heart rate (in three of four) and ferritin (in one of four), as well as the increase in cholesterol levels (in two of four). Significant weight gain and slight psychomotor progression were observed in a pair of twins. These improvements, however, may be attributed to their specific nutritional supply and supportive measurements that include intensive physical, mental and occupational therapies. Unfortunately, no significant neurodevelopment improvement was observed, which is likely due to the irreversible neurological damage incurred during the foetal and neonate periods. It is possible that thyromimetic compounds will have to be initiated early, perinatally or *in utero*, in order to rescue this phenotype. Studies concerning earlier initiation and long-term therapy of these compounds are yet to be performed.

MONOCARBOXYLATE TRANSPORTER 8 DEFICIENT MICE

To elucidate the pathophysiology of MCT8 deficiency, two *Mct8KO* mouse models have been extensively studied [7,8,13,31–33]. These models fully replicate the thyroid abnormalities, but do not manifest obvious neurological symptoms (Table 2). The activation of type 1 (D1) and type 2 (D2) iodothyronine deiodinases stimulated by opposite states of intracellular thyroid hormone availability lead to an additive consumptive effect on T_4 levels, resulting in excess T_3 generation. D1 is responsible for maintaining the high serum T_3 level in those with an MCT8 defect, whereas D2 is mainly responsible for maintaining T_3-mediated intracellular actions, thus compensating for local hypothyroidism [34]. Low serum T_4 in MCT8 deficiency is not only attributed to consumption through deiodination but also to reduced secretion from the thyroid gland and increased loss from the kidney [32,33]. The modestly increased serum TSH in the MCT8 defect is related to central resistance to T_3, particularly at the hypothalamic level [32]. More information regarding this is found in two reviews published recently [9,35▪].

Despite the lack of neurological symptoms, *Mct8KO* mice have been successfully used to test the in-vivo therapeutic potential of DITPA [29]. Another therapeutic candidate, 3,3’, 5,5’-tetraiodothyroacetic acid (TETRAC), a T_4 metabolite, was evaluated recently in Mct8-deficent mice [36]. Although it is not transported by MCT8 and OATP1C1, TETRAC can be activated by D2 intracellularly to 3,3’,5-triiodothyroacetic acid (TRIAC), which further interacts with thyroid hormone receptors, thus replacing T_3. As it has a relatively longer half-life than TRIAC, TETRAC has been given to newborn *Mct8KO*, *Pax8KO* and *Mct8/*

Pax8 double knockout mice. Progression of thyroid hormone dependent neuronal differentiation in cerebellum, cerebral cortex, and striatum was observed during the first 3 postnatal weeks. However, an ineffective suppression of hypothalamic TRH expression, despite the strong suppressive effect on thyrotrophs, was observed in all mutant mice. Accordingly, its efficacy may vary among distinct neuronal populations or different genes that are controlled by thyroid hormone in a positive or negative manner. However, in contrast to DITPA, treatment with TETRAC fails to ameliorate the thyrotoxic state in peripheral tissues.

MICE DEFICIENT IN OTHER THYROID HORMONE TRANSPORTERS

In the exploration of additional thyroid hormone transporters that compensate for the absence of Mct8 in murine brain, Lat2 and Oatp1C1 are emerging as promising candidates. Lat2, an energy-independent exchanger of neutral amino acid, has been shown to transport thyroid hormone in a Na^+-independent manner [37]. It is enriched in the kidney and the brain of mice. It has been demonstrated that the expression pattern of *Lat2* overlapped that of *Mct8* in the neurons of the developing and the adult mouse brain, whereas its expression is absent in the neurons of the developing human brain [13,38]. Consequently, in a setting of MCT8 deficiency, the nervous system of humans may be more vulnerable than that of mice. To further investigate the role of Lat2 in thyroid hormone physiology, *Lat2KO* mice were recently generated [15] (Table 2). However, the cerebral and cerebellar development of these mice appeared normal, except for slightly impaired movement coordination on rotarod testing due to abnormal amino acid levels. The thyroid hormone levels and the T_3-dependent gene expression, including *Dio1*, *Dio2* and *TSH*β, are unchanged. These patterns in *Lat2KO* mice may potentially be explained by compensation through Mct8. Further study of the combined inactivation of both genes could address this hypothesis.

OATP1C1, which preferentially transports T_4, is highly enriched in the choroid plexus and endothelial cells of the blood–brain barrier, wherein it may mediate the entry of T_4 into the astrocytes [14,39,40]. Within the astrocytes, T_4 is deiodinated to active T_3, which is then released and taken up by neurons or oligodendrocytes, wherein it exerts its transcriptional regulatory function [41]. The finding of central nervous system specific hypothyroidism in *Oatp1C1KO* mice provides further evidence to its unique role in T_4 transport in murine brain [16▪] (Table 2). *Oatp1C1KO* mice, though without any obvious neurological abnormalities, showed decreased thyroid hormone content and D3 activity and increased D2 activity in the brain, similar to those observed in *Mct8KO* mice. Also, the expression levels of genes positively regulated by T_3 were decreased. In contrast to *Mct8KO* mice, however, the thyroid state of peripheral tissues in *Oatp1C1KO* mice was normal. One study regarding the species-specific expression of OATP1C1 showed a high microvessel expression in rodent compared with human brain [14], which may contribute to providing higher levels of T_4 across the blood–brain barrier in mice than in humans. Thus, the milder neurological symptoms in *Oatp1C1KO* and *Mct8KO* mice might be attributed to the reciprocal compensation of both transporters and/or other THCMT proteins. Mice deficient in both Mct8 and Oatp1C1 have been generated [42▪▪]. In contrast to the single respective knockouts, the *Mct8/Oatp1C1* double-knockout mice exhibit a more severe hypothyroid state in the brain with associated coordination and locomotor deficits (Table 2). However, it

is uncertain whether these mice can serve as a model for human MCT8 deficiency, considering that they have an additional defect that could confound the interpretations.

Outside the brain, these transporters also seem to mediate THCMT in components of the auditory system, according to the expression pattern of Lat1, Mct8, Mct10 and Oatp1C1 in mouse cochlear development [38]. Oatp1C1 primarily localizes to fibrocytes wherein *Dio2* is expressed. Lat1 is strongly expressed in cochlear blood vessels. Mct8 localizes to the greater epithelial ridge and is also present in the spiral ganglion neurons in which it overlaps with Thrb, and in the tympanic border cells, in which it overlaps with Oatp1C1. Mct10 is restricted in some specialized cells of the outer sulcus. It is difficult to test patients with MCT8 deficiency for auditory function, due to the lack of cooperation; when tested, auditory evoked potentials have been normal [18▪].

NEW ANIMAL MODELS OF MONOCARBOXYLATE TRANSPORTER 8 DEFICIENCY

Zebrafish is a useful model for studies of vertebrate development and gene function due to its rapidly developing transparent embryo. Similar to mammals, Mct8 in zebrafish serves as a THCMT important for local T_3 availability [43]. The Mct8 protein sequence of zebrafish shares approximately 60% identity with its human homologue, and the hypothalamic pituitary thyroid axis is largely conserved [17▪▪,43,44▪]. The expression patterns of THCMTs in zebrafish show that Mct8 is abundantly expressed in nervous and vascular systems. Oatp1c1 is restricted to vascular structures within the brain and Mct10 is exclusively expressed in liver and the trigeminal ganglia, suggesting a relatively small possibility of full compensation for Mct8 in zebrafish, thus allowing for the propagation of Mct8-deficient zebrafish [17▪▪]. To establish the model, *Mct8* was knocked down by injecting two different morpholino-modified antisense oligonucleotides into one-cell stage embryos. Knocking down *Mct8* results in severe alternations of neural development in brain and spinal cord, which can be rescued by the injection of Mct8 mRNA. Moreover, muscular and vascular development remains intact, indicating an essential role of Mct8 in the development of the central nervous system. Further studies of the role of thyroid hormone transporters on thyroid hormone physiology in different tissues of zebrafish are needed.

CONCLUSION

The recent findings discussed in this review provide some important clinical data for the use of DITPA and PTU combined with L-T_4 in patients with *MCT8* gene mutations. Studies of THCMTs in mice have advanced our understanding of thyroid hormone physiology in different tissues, including the auditory system, and indicate the presence of alternative THCMTs that compensate for the absence of MCT8. New models that mimic the patho-physiological condition of MCT8 deficiency in humans are being explored.

Acknowledgments

J.F. is supported by an award from the China Scholarship Council. S.R. is a recipient of grant DK015070 from the National Institutes of Health and is currently receiving research funds from the Sherman Family and consultation fees from Quest Diagnostics. A.M.D. was supported by grant DK091016 from the National Institutes of Health.

The China Scholarship Council provided funding to J.F. The National Institutes of Health grant DK 15070 and the Sherman Family provided funding to S.R. The National Institutes of Health grant DK91016 was awarded to A.M.D.

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KEY POINTS

- The hypermetabolic state of MCT8 deficiency can be improved with PTU combined with high L-T_4 treatment, and with administration of the thyromimetic compound DITPA.
- Alternative transporters may sufficiently compensate for the absence of Mct8 in mouse brain.
- *Mct8/Oatp1C1* double knockout mice exhibit a more severe hypothyroid state in the brain and manifest coordination and locomotor deficits.
- Zebrafish is emerging as another vertebrate suitable to study the role of MCT8 in brain development.

Table 1

Comparison of the therapeutic options for monocarboxylate transporter 8 deficient patients

	PTU +L-T_4 (*n* = 5)	**DITPA (*n* =4)**
Doses	200–400 mg/day PTU + 100 μg/day L-T_4	1~2 mg/kg/d
Effects on weight	↑ (2/2)	↑ (2/4) or remain unchanged (2/4)
Effects on TFTs	nl T_3, rT_3, T_4, TSH	nl T_3 and TSH, ↑ rT_3 and T_4 to low normal or slightly below normal range, nl T_3 to T_4 ratio
Effects on HPT	Suppressed	Not suppressed
Effects on liver	↓ SHBG (2/2)	↓ SHBG (4/4), ↑ serum cholesterol (2/4)
Effects on other peripheral tissues	↓ heart rate (1/2)	↓ heart rate (3/4), ↓ ferritin (1/4), transient ↑ CKs (4/4)
Effects on psychomotor function	No significant change	No significant change
Adverse effects	Hypogranulocytosis (1/5)	Not observed

CK, cytokines; DITPA, diiodothyropropionic acid; HPT, hypothalamic–pituitary–thyroid axis; PTU, propylthiouracil; SHBG, sex hormone binding globulin; TFTs, thyroid function tests.

↑, increase; ↓, decrease; nl, normalize.

Table 2

Characteristics of patients and mice deficient in thyroid hormone cell-membrane transporters

	TFTs									
	FT_3	**FT_4**	**rT_3**	**TSH**	**HPT**	**CNS**	**Liver**	**Kidney**	**Neurological manifestations**	**Ref.**
MCT8-deficient patients	↑↑	↓	↓↓	nl, sl↑	Resistance	Delayed myelination, mild cerebellar atrophy	–	–	Severe psychomotor impairment (no speech, no walk, poor head control)	[2–4,9]
Mct8 KO mice	↑↑	↓	↓↓	nl, sl↑	Resistance	↓ T_4, ↓ T_3, ↑ D2, ↓ D3; ↓*RC3* (Striatalneurons)	↑ D1; ↑*Gsta2*, ↑*Gpd2*	↑ T_4, ↑ T_3, ↑ D1	nl	[7,8,31]
Lat2 KO mice	nl	nl	–	nl	nl	nl	nl D1	nl D1, ↑ Loss of small neutral amino acid	Slight impairment of motor coordination on rotarod (caused by aminoacid abnormalities)	[15]
Oatp1C1 KO mice	nl	nl	–	–	nl	↓ T_4, ↓ T_3, ↑ D2, ↓ D3	nl D1	nl D1	nl	[16▪]
Mct8/Oatp1C1 DKO mice	–	–	–	–	–	↓↓ T_4, ↓↓ T_3, ↑↑ D2; Impaired myelination and neuronal differentiation	–	–	Coordination and locomotor deficit	[42▪▪]

↓, decreased; ↑, increased; CNS, central nervous system; D1, Type 1 deiodinase; D2, Type 2 deiodinase; D3, Type 3 deiodinase; DKO, double knockout; Gpd2, a-glycerol-3-phosphate dehydrogenase; Gsta2, glutathione S transferasea; HPT, hypothalamic–pituitary–thyroid axis; KO, knockout; nl, normal; sl, slight; TFTs, thyroid function tests.