Review

Thyroid hormone transport in and out of cells

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Thyroid hormone (TH) is essential for the proper development of numerous tissues, notably the brain. TH acts mostly intracellularly, which requires transport by TH transporters across the plasma membrane. Although several transporter families have been identified, only monocarboxylate transporter (MCT)8, MCT10 and organic anion-transporting polypeptide (OATP)1C1 demonstrate a high degree of specificity towards TH. Recently, the biological importance of MCT8 has been elucidated. Mutations in *MCT8* are associated with elevated serum T_3 levels and severe psychomotor retardation, indicating a pivotal role for MCT8 in brain development. *MCT8* knockout mice lack neurological damage, but mimic TH abnormalities of MCT8 patients. The exact pathophysiological mechanisms in MCT8 patients remain to be elucidated fully. Future research will probably identify novel TH transporters and disorders based on TH transporter defects.

Introduction

Thyroid hormone (TH) exerts its actions on virtually all tissues of mammals. The major biologically active TH is 3,3′,5-triiodothyronine (T_3), which is generated from the prohormone thyroxine (3,3′,5,5′-tetraiodothyronine, T_4) by the deiodinating enzymes D1 and D2 [1]. The deiodinase D3 inactivates T_4 to 3,3′,5′-triiodothyronine (rT_3) and T_3 to 3,3′-diiodothyronine (T_2) [1]. The genomic actions of T_3 are mediated by nuclear T_3 receptors (TRs) [2]. Because the active sites of the deiodinases and the TRs are located intracellularly, TH metabolism and action require transport of the hormone from extracellular compartments (e.g. the bloodstream) across the plasma membrane. Based on their lipophilic nature, it was assumed previously that translocation of iodothyronines across the lipid bilayer of cell membranes occurred by diffusion. However, experimental evidence over the last three decades and clinical studies in recent years show clearly that TH traverses the cell membrane mainly through transporters [3–6]. This review will focus on the molecular characterization of TH transporters. Particular attention will be paid to monocarboxylate transporter 8 (MCT8) and its role in disease.

Molecular characterization of TH transporters

Several observations have indicated that TH uptake has different characteristics across cell types, with regard to ligand specificity, energy (ATP) dependence, Na^+ dependence and interactions with a variety of compounds [3]. This suggested that TH uptake might be facilitated by different types of transporters. In recent years, this hypothesis was confirmed by the molecular identification of TH-transporting proteins [5]. These include the Na^+/taurocholate cotransporting polypeptide [7], fatty acid translocase [8], multidrug resistance-associated proteins [9], amino acid transporters (reviewed in [10]) and members of the organic anion-transporting polypeptide (OATP) family (reviewed in [11]) and monocarboxylate transporter (MCT) family (reviewed in [12]).

Most studies report on cellular TH uptake, whereas far less is known about TH export from cells. This is surprising, because it is conceivable that not only influx but also efflux processes are required for optimal regulation of cellular TH availability. The majority of the TH transporters known currently accepts a wide variety of compounds and demonstrates a relatively low apparent affinity towards TH. To date, only OATP1C1 [13–15], MCT8 [16] and MCT10 [17] are reported to have high affinities for iodothyronines. The relative contribution of low-affinity versus high-affinity TH transporters to the transport of TH *in vivo* is unknown currently.

High-affinity transporters OATP1C1 and MCT10

The human *SLCO1C1* gene encodes the OATP1C1 protein, which comprises 712 amino acids and 12 putative transmembrane domains (TMDs). It is highly expressed in brain capillaries of rats and mice [14,15,18]. Although the particular cell types are unknown, OATP1C1 is distributed widely in the human brain [13]. OATP1C1-expressing cells show preferential transport of T_4 and rT_3 [13–15]. These studies suggest an important role for OATP1C1 in T_4 transport across the blood–brain barrier. However, no patients with *OATP1C1* mutations or knockout (KO) animal models have been reported so far. Thus, the precise *in vivo* function of OATP1C1 remains to be elucidated.

Because iodothyronines are basically composed of two tyrosine residues, it is feasible that a T-type amino acid transporter (TAT), which mediates transport of aromatic amino acids, is also involved in TH transport. Specific interactions between transport of T_3 and tryptophan have been described, supporting this view [19,20]. Recently, one such transporter (TAT1) was cloned and reported to transport aromatic amino acids, although not T_3 or T_4 [21,22]. Its amino acid sequence indicates that it belongs to the MCT family; it is also named MCT10 [or solute-carrier family 16 member 10 (SLC16A10)].

We retested the possible involvement of MCT10 in TH transport and demonstrated substantial uptake of T_3 and T_4 by cells transfected with human MCT10 [17]. The

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1043-2760/$ – see front matter doi:10.1016/j.tem.2007.11.003

negative findings with respect to TH transport by MCT10 in previous reports might be explained by the high ligand concentration used and the subsequent supersaturation of the transporter in these studies. MCT10 is distributed widely, including the entire intestine, kidney, liver and placenta [21–23]. Recently, it was reported that a common polymorphism in the 3′-UTR region of *MCT10* is not associated with altered serum TH levels [24]. No other studies investigating associations of aromatic amino acid or TH levels with polymorphisms or mutations in *MCT10* have been published as yet. Investigations of *MCT10* null mice would probably provide valuable insights into the precise physiological role of MCT10 in the transport of aromatic amino acids and TH.

Identification and function of MCT8

The human (h) *MCT8* (*SLC16A2*) gene is located on the X-chromosome (at Xq13.2) and contains six exons. Its homology to the MCT family justifies its classification, although only MCT1–4 and MCT6 are known to transport monocarboxylates [12]. *hMCT8* encodes two hMCT8 proteins of 613 and 539 amino acids, depending on which of the two putative translation-start sites (TLSs) is used. It is unknown currently whether there are two human MCT8 proteins expressed *in vivo* and, if so, whether they are subject to differential expression and regulation. Non-primate *MCT8* genes lack the first TLS but are homologous with *hMCT8* downstream from the second TLS [5]. MCT8 has 12 putative transmembrane domains and a N-terminus that is enriched in proline (P), glutamic acid (E), serine (S) and threonine (T) residues (abbreviated as PEST domain), which is why MCT8 was named XPCT (X-linked PEST-containing transporter) previously. Proteins containing PEST sequences often undergo rapid degradation [25]. It is unclear if this is relevant for MCT8.

More than a decade after characterization of the *hMCT8* gene, rat MCT8 was identified as a specific and active TH transporter [16]. Oocytes injected with rat MCT8 cRNA showed a rapid uptake of the iodothyronines T_4, T_3, rT_3 and T_2 but not of sulfated iodothyronines, aromatic amino acids or monocarboxylates. Recently, the functional characterization of *hMCT8* was described [26]. Cells transfected with *hMCT8* cDNA displayed a marked T_3 and T_4 uptake but there was little effect on rT_3 or T_2 uptake. Cells cotransfected with *hMCT8* and one of the deiodinases exhibited a significant increase in TH metabolism compared with cells transfected with deiodinase only. This phenomenon is illustrated for T_3 metabolism by cells (co)transfected with *hMCT8* and/or *D3* in Figure 1. These findings show clearly that MCT8 increases the availability of TH for intracellular metabolism by the different deiodinases.

The initially high TH uptake rate by MCT8 reaches a plateau phase quickly, indicating a rapid balance between TH uptake and export. Indeed, direct measurement of T_4 and T_3 efflux showed rapid cellular release of the hormones in hMCT8-expressing cells [17]. To investigate this in more detail, cells were cotransfected with *MCT8* and μ-crystallin (*CRYM*), an intracellular binding protein with a high affinity for iodothyronines, to increase intracellular TH-binding capacity. T_4 and T_3 efflux from cells co-expressing

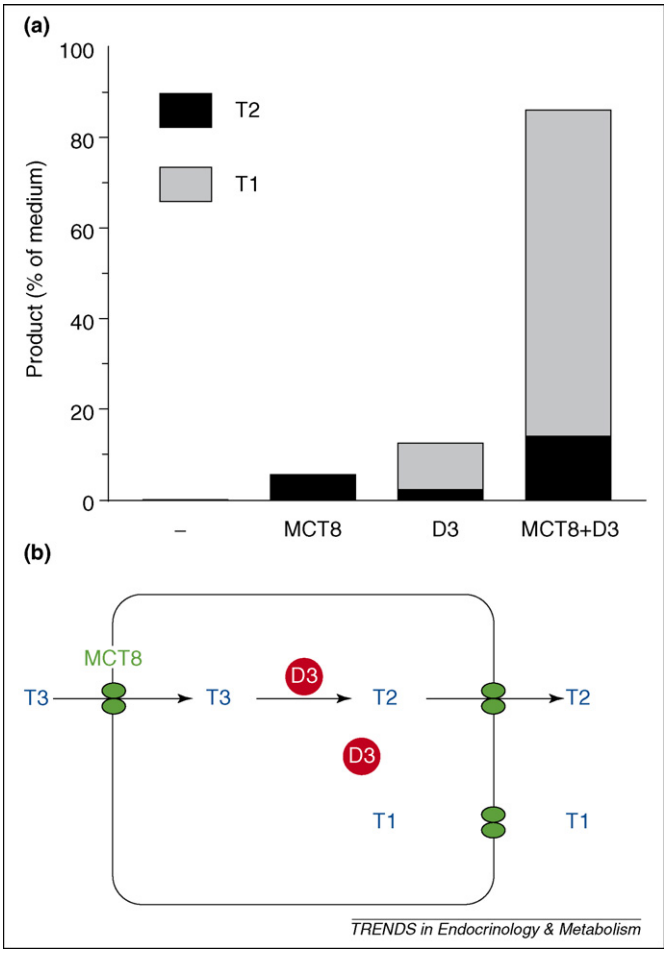

Figure 1. (**a**) Metabolism of T_3 in COS1 cells transfected with empty vector, hMCT8, hD3 and a combination of hMCT8 and hD3. Cells were incubated for 4 h at 37 °C with 1 nM T_3. Bars represent the amount of metabolites [T_2 (black), T_1 (gray)] that result from T_3 metabolism. Cells cotransfected with hMCT8 and hD3 exhibited a significant increase in TH metabolism compared with cells transfected with hMCT8 or hD3 alone. (**b**) Experimental model of T_3 metabolism. MCT8, which is expressed at the plasma membrane, facilitates T_3 uptake. D3, which is expressed intracellularly, catalyzes the conversion of T_3 to T_2 and T_2 to T_1. The metabolites T_2 and T_1 are exported into the incubation medium by as yet unidentified transporter proteins. The amount of T_2 and T_1 serves as a measure of intracellular T_3 metabolism.

hMCT8 and *hCRYM* was diminished significantly. These findings substantiate the concept that MCT8 is not only important for uptake but also for export of TH.

MCT8 expression

MCT8 shows a broad tissue distribution in all species studied. *In situ* hybridization studies revealed that MCT8 mRNA is expressed significantly in mouse liver, kidney, thyroid and brain [6,27]. In mouse brain, MCT8 mRNA is expressed predominantly in the choroid plexus of the ventricles and in the neo- and allo-cortical regions [28]. In rats, the MCT8 protein has been detected in heart and brain [16,29].

In humans, MCT8 is found in many tissues, in particular in liver and heart [30]. Expression of MCT8 mRNA and MCT8 protein in human placenta shows an increase during gestation [31]. MCT8 mRNA is upregulated in placentae associated with intrauterine growth retardation during the early third trimester of pregnancy, suggesting a compensatory mechanism to increase TH transport. MCT8

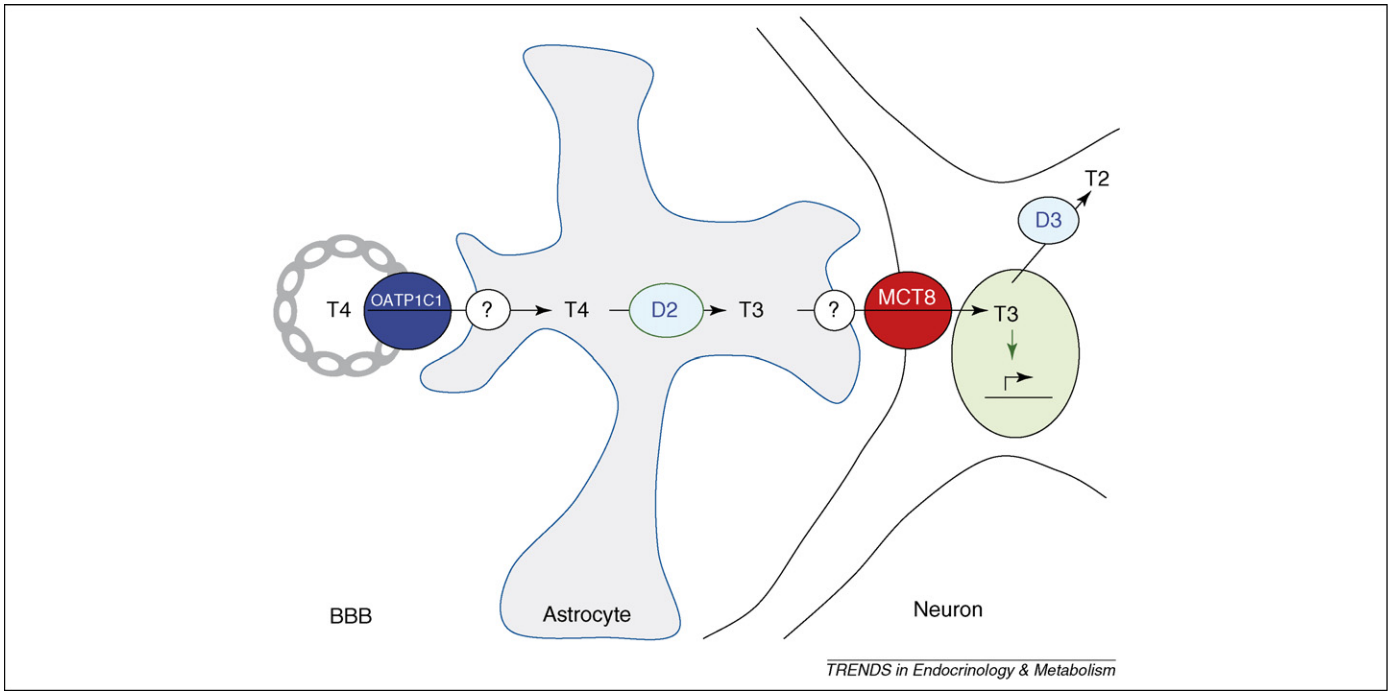

Figure 2. Model for the local control of T_3 availability in the brain. T_4 is transported through the blood–brain barrier (BBB) by OATP1C1 (dark blue). Subsequently, T_4 is taken up by astrocytes through an unknown transporter (?) and activated by D2. After T_3 export from the astrocyte through an unidentified transporter (?), MCT8 (red) facilitates T_3 uptake into the neuron. Neuronal T_3 interacts with its nuclear receptor, thyroid hormone receptor α (not shown), and results in the transcription of various genes and the consequent generation of proteins. Neurons also express D3 for conversion of T_3 to T_2, thereby terminating T_3 activity. Reproduced from [28], with publisher's permission.

is also localized clearly in neurons of the paraventricular, supraoptic and infundibular nuclei of the hypothalamus and in glial cells of the ependymal lining of the third ventricle and median eminence [32]. In the human pituitary, the folliculostellate cells, rather than the thyroid-stimulating hormone (TSH)-producing cells, show MCT8 expression [33]. It is assumed that these sites are involved in the negative-feedback control of TSH-releasing hormone (TRH) in the hypothalamus and TSH in the pituitary, respectively, by TH.

Role of MCT8

The biological importance of MCT8 for brain development became apparent when mutations therein were associated with X-linked psychomotor retardation and elevated T_3 levels (see below) [34,35]. The tight spatiotemporal regulation of TH during brain development is supposed to be controlled locally by functional units of astrocytes and neurons. Mainly based on immunohistochemical studies, this process is thought to involve at least the following steps (Figure 2). First, T_4 (and a smaller amount of T_3) is transported across the blood–brain barrier through OATP1C1. Second, T_4 is taken up into astrocytes by an as-yet-unknown transporter. Third, in astrocytes, T_4 is converted to T_3 by D2. Fourth, the biologically active T_3 is released from the astrocytes by another unidentified transporter. Fifth, neuronal uptake of T_3 is facilitated by MCT8. Sixth, T_3 exerts its genomic action by binding to its nuclear receptor. Finally, T_3 is degraded by D3 to T_2 and both T_3 and T_2 might also leave the cells through MCT8. Too low or too high local TH concentrations might lead to abnormal TH signaling and might eventually result in abnormal brain development.

In addition to its role in brain development, MCT8 has been implicated in the differentiation of embryonic stem cells into neural cells [36]. So far, only iodothyronines have been shown to be ligands for MCT8. However, this does not preclude a role of MCT8 in the transport of other crucial ligands for brain development.

Patients with *MCT8* mutations

It has been recognized that clinical features of patients with *MCT8* mutations resembled those of Allan–Herndon–Dudley syndrome (AHDS) patients. Indeed, *MCT8* mutations were found in all AHDS families tested, thereby providing a molecular basis for a syndrome already described in 1944 [37]. Affected males show a homogeneous neurological phenotype (Table 1 and reviewed in detail in [38]). There is a generalized low muscle tone with an inability to hold the head up, which usually progresses to spasticity. In addition, AHDS patients display episodic involuntary movements, which occur spontaneously or are triggered by stimuli. Most of the patients are unable to sit upright, crawl, stand or walk. Development of speech is absent in most affected individuals. However, in a few families, motor and speech development are somewhat less impaired, resulting in limited walking and verbal communication. All patients have a severe mental retardation with IQs below 40. Females with heterozygous *MCT8* mutations do not express phenotypic abnormalities.

To date, mutations in *MCT8* have not been localized to hotspot regions but are spread over the entire coding region of the gene. The identification of more than 20 affected families in recent years indicates that mutations in *MCT8* are not an uncommon cause of X-linked mental retardation. It is clear that many of the mutations, such as

Table 1. Clinical, molecular and functional characteristics of MCT8 patients

Family	Gene mutation	Protein mutation	Serum T_3 (fold increase versus controls)	Axial hypotonia	Absent speech	Never walked	T_3 uptake (% versus controls)	T_3 metabolism (% versus controls)	Protein expression (% versus controls)	Refs
1	delEx1	Absent	3.1	1/1	1/1	1/1	0[a]	0[a]	0[a]	[34]
2	671C>T	Ala224Val	2.8	1/1	1/1	1/1	5.0	0.0	+	[34,39]
3	1412T>C	Leu471Pro	2.3	1/1	1/1	1/1	−0.1	3.1	0	[34,39]
4	delEx3–4	Truncated	2.6	1/1	1/1	1/1	0[a]	0[a]	0[a]	[34]
5	733C>T	Arg245X	3.7	1/1	1/1	1/1	−0.2	0.1	0	[34,39]
6	1535T>C	Leu512Pro	1.9	1/1	1/1	1/1	−4.8	−3.8	NR	[35]
7	delT1212	Truncated	1.9	1/1	1/1	1/1	0[a]	0[a]	0[a]	[35]
8	1703T>C	Leu568Pro	NR	12/12	0/12	1/12	15.3	28.0	NR	[37]
9	1301T>G	Leu434Trp	2.7	8/8	2/8	1/8	32.6	35.2	NR	[37]
10	703G>A	Val234Met	2.4	2/2	2/2	2/2	8.6	14.3	NR	[37]
11	1343C>A	Ser448X	1.0	1/1	1/1	1/1	−10.6	−5.9	NR	[37]
12	581C>T	Ser194Phe	2.5	4/4	0/4	4/4	22.8	25.2	NR	[37]
13	del683–685	delPhe230	NR	2/2	2/2	2/2	2.4	−3.5	NR	[37]
14	insGTG869	insVal235	2.1[b]	1/1	1/1	1/1	NR	NR	NR	[43]
15	insATC565	insIle189	NR	2/2	2/2	2/2	0[a]	−2.7	NR	[44]
16	delC1834	Pro612fs679X	2.0	6/6	6/6	6/6	NR	18	NR	[45]
17	1003C>T	Gln335X	2.2	1/1	NR	NR	NR	NR	NR	[46]
18	812G>A	Arg271His	2.5	1/1	1/1	1/1	19.7	17.0	++	[6,39]
19	del631–644	Truncated	1.8	1/1	1/1	1/1	0[a]	0[a]	0[a]	[6]
20	Ex3 −1G>C	del267–370	1.6	1/1	1/1	1/1	0[a]	0[a]	0	[6,39]
21	del683–685	delPhe230	2.8	1/1	1/1	1/1	2.4	−3.5	+	[6,39]

Abbreviations: del, deletion; Ex, exon; ins, insertion; NR, not reported; 0: absent; +: moderate; ++: normal; x/x: number affected/number with mutations.
[a]Presumed inactive.
[b]Free T_3.

large deletions and truncating mutations, are devastating for the function of the MCT8 protein. The effects on MCT8 function are less obvious with amino acid substitutions, deletions or insertions. Therefore, different mutations have been introduced into *MCT8* cDNA by site-directed mutagenesis and have been tested functionally [6,39]. This was done by (co)transfecting JEG3 cells, which show little expression of endogenous MCT8, with wild-type or mutant *MCT8* without or with *D3* cDNA. Subsequently, the cells were tested for T_3 transport and metabolism.

In contrast to wild-type *MCT8*, transport and metabolism of T_3 is absent completely with most *MCT8* mutants (Table 1). However, the Leu568Pro, Leu434Trp, Ser194Pro and Arg271His mutants show significant residual activity. Interestingly, most patients in the families with Leu568-Pro and Leu434Trp mutations had developed some walking and speech capacities. Additionally, males with the Ser194Pro mutation were able to walk. These observations suggest that diverse mutations affect MCT8 function differentially and might be the cause of minor phenotypic variations.

Patients with *MCT8* mutations have abnormal thyroid function tests. TSH levels are approximately doubled compared with non-carriers [6]. Mean serum T_4 and free T_4 levels show a 40% decrease compared with healthy controls and rT_3 values are diminished to 36% of control levels [6]. The most characteristic finding is markedly elevated T_3 levels. Table 1 shows a 2.3-fold increase in T_3 levels of studied MCT8 patients. In heterozygous (female) carriers, TSH levels are comparable to familial non-carriers [6,40]. However, other TH values seem to be intermediate between patients and non-carriers.

MCT8 KO mice

Recently, two different *MCT8* KO mouse models were generated to gain insight into the mechanisms underlying the neurological and endocrinological abnormalities in MCT8 patients [27,41]. The main findings of these studies are summarized in Table 2. Serum-thyroid parameters in the *MCT8* KO mice (both $MCT8^{-/y}$ males and $MCT8^{-/-}$ females) replicate the abnormalities seen in human patients. T_4 and rT_3 levels are decreased, TSH levels are increased modestly and T_3 levels are increased markedly in *MCT8* KO mice compared with wild-type mice. The liver content of T_3 is increased as well as the T_3-responsive D1 mRNA levels and D1 protein activity, supporting the observation that *MCT8* KO mice do not differ in hepatic T_3 uptake compared with controls.

Brains of the *MCT8* KO mice show a significantly lower content of T_4 in parallel with the decrease in serum T_4. This is underscored by the increased D2 mRNA levels and protein activity, which are regulated negatively by T_4 [1]. In *MCT8* KO mice, brain T_3 levels are also decreased markedly despite the strong increase in serum T_3. The cerebral uptake of T_3, but not of T_4, is impaired dramatically in these animals. The low brain T_3 content in *MCT8*

Table 2. Overview of findings in *MCT8* KO mice[a]

Tissue/serum	Measurement	Study	
		Dumitrescu *et al.* [41]	Trajkovic *et al.* [27]
Serum TH levels	T_3	1.50	2.10
	T_4	0.70	0.34
	rT_3	<0.16	ND
	TSH	1.80	ND
Liver	T_3 content	2.30	ND
	D1 mRNA	6.10	2.00
	D1 activity	3.10	3.50
Brain	T_3 content	0.56	0.59
	T_4 content	ND	0.48
	D2 mRNA	1.60	ND
	D2 activity	10.60	7.00
	D3 activity	ND	0.63

[a]All values represent significant fold changes in male *MCT8* KO mice compared with wild-type mice.

KO animals is associated with low brain D3 activity, which is regulated positively by TH. Trajkovic *et al.* also studied whether MCT8 inactivation results in neuronal abnormalities [27]. Although transcript levels of the TH-responsive *RC3* gene are decreased mildly in the striatum, histological examination of cerebellar Purkinje cells, which normally produce MCT8, did not detect any abnormalities.

Additionally, different aspects of the hypothalamus–pituitary–thyroid axis were investigated in *MCT8* KO mice. TRH transcript levels are increased strongly in the hypothalamic paraventricular nucleus (PVN) neurons in *MCT8* KO mice. The elevated TRH expression is suppressed by T_4 but not by T_3 administration, indicating that these neurons are able to respond to locally produced T_3. In contrast to the 'hypothyroid' state in the hypothalamus, the pituitary appears to be 'euthyroid' because transcript levels of TH-responsive genes were not altered in *MCT8* KO mice [27]. However, the pituitary in the *MCT8* KO animals is relatively insensitive to T_3. Only administration of high T_3 concentrations is able to suppress TSH in *MCT8* KO animals rendered hypothyroid.

The most remarkable finding in these *MCT8* KO animals is the absence of neurological disturbances, despite the low levels of T_4 and T_3 in the brain. This might be explained in different ways. First, brain development in mice might respond differently to TH deficiency than in humans. Second, the lack of MCT8 might be compensated sufficiently by other TH transporters in mouse brain but not in human brain, securing a relatively normal development in the mouse. Third, human MCT8 might transport other ligands, which are essential for normal human brain development. Fourth, the putative long MCT8 protein in humans might have other functions in addition to the short MCT8 protein, the only form present in mice.

Thus, although *MCT8* KO mice are a suitable tool with which to study TH abnormalities, it remains a challenge to unravel the precise mechanisms involved in the pathogenesis of the psychomotor retardation in human patients with *MCT8* mutations.

Pathophysiology of *MCT8* mutations

Integrating the findings in humans and mice with *MCT8* mutations might lead to the following considerations. The modestly increased serum TSH levels in patients seem to fit with the low free T_4 levels, although, in view of the strongly elevated serum T_3, the TSH levels appear inappropriately high. Studies in the *MCT8* KO mice indicate a relative TH insensitivity in the hypothalamus and pituitary. The inappropriate TSH levels in human MCT8 patients correspond with a partial hypothalamic and pituitary TH resistance. The presence of MCT8 in human hypothalamus and pituitary fit with this hypothesis [32,33].

In keeping with the assumed function of MCT8 in neuronal T_3 uptake, it is fully understandable that MCT8 mutations result in a diminished intracellular T_3 concentration. Considering the crucial role of TH in normal brain development, it is conceivable that neurological defects will be the consequence of this neuronal T_3 deprivation. It is unknown currently whether all T_3-dependent neurons express MCT8. Therefore, it cannot be excluded that certain types of neurons express other prominent T_3 transporters, instead of or in addition to MCT8. Depending on the presence of additional transporters, MCT8 might function primarily in the import or in the export of T_3. In the former case, inactivation of MCT8 will result in decreased intracellular T_3 levels and, in the latter case, in an increased intracellular T_3.

Changes in deiodinase activities contribute to the abnormal TH levels in subjects with *MCT8* mutations. The accumulation of T_3 might be the result of blocking T_3 entry into D3-expressing cells, which in turn leads to a decrease in T_3 clearance. This would be followed by an increase in renal and hepatic D1 activities and consequent T_3 production, which further stimulates T_4 to T_3 conversion. The increased D1 activity might also contribute to decreased circulating T_4 and rT_3 concentrations. Recently, it was shown that the T_3:T_4 ratio increases with age in *MCT8* KO mice, thereby underscoring the prominent role for D1 in the origin of the TH abnormalities [42].

It is feasible that the liver in MCT8 patients is in a hyperthyroid state, as is the case in *MCT8* KO mice, because sex hormone-binding globulin (SHBG) concentrations are increased markedly in serum [6]. Because SHBG production in the liver is regulated positively by T_3, SHBG levels are indicative for the TH status in the liver. The hyperthyroid state in the liver is explained by the elevated serum T_3 levels and a presumed lack of importance of MCT8 for hepatic T_3 uptake. If MCT8 in liver is more important for T_3 efflux, its inactivation might further increase intracellular T_3. The low muscle and fat mass in MCT8 patients might be the result of tissue 'wasting' because these tissues are in a hypermetabolic state owing to their exposure to high T_3 levels. Apparently, muscle and fat do not require MCT8 for TH uptake.

In conclusion, although it is apparent that MCT8 has a crucial role in proper brain development, the contribution of MCT8 to TH transport in other tissues is less clear. The exact mechanisms that have a role in the generation of tissue-specific hypo- or hyperthyroidism remain to be elucidated.

Treatment of MCT8 patients

Currently, the therapeutic options for MCT8 patients are limited. The harmful effects of TH deprivation on early brain development are almost certainly irreversible. Therefore, postnatal TH treatment is expected to have limited positive consequences. Only mutations that inactivate MCT8 partially might benefit from TH therapy. Theoretically, T_3 analogues that are taken up by cells in which MCT8 is disrupted might also have a place in the treatment of MCT8 patients. Supportive therapy, such as appropriate diet to prevent aspiration, as well as anticonvulsant therapy, might alleviate some of the secondary somatic problems. Although treatment options are limited in MCT8 patients, the detection of *MCT8* mutations is important for providing a diagnosis to family members, carrier identification and prenatal diagnosis.

Conclusion

TH is essential for the normal development of various tissues, especially the brain. Proper intracellular TH concentrations are required for normal TH action and

metabolism. Therefore, TH transport across the plasma membrane is crucial. Several TH transporter families have been identified, however, only MCT8, MCT10 and OATP1C1 have been shown to be specific TH transporters so far.

Whereas the physiological significance of MCT10 and OATP1C1 remains to be further investigated, an important function of MCT8 in normal brain development has been established in recent years. Mutations in MCT8 are associated with high T_3 levels and severe psychomotor retardation. *MCT8* KO mice have been generated, which lack neurological abnormalities but imitate the TH abnormalities in MCT8 patients perfectly. Although the *MCT8* KO mice have provided interesting insights, the precise mechanisms underlying this dramatic disorder in humans need to be clarified.

The progress made in the molecular identification of TH transporters in recent years should be continued by investigating cellular TH transport processes. Not only TH influx, but also export, deserves attention in the forthcoming years. Undoubtedly, novel syndromes caused by defects in TH transporters will be recognized and linked to TH insensitivity. Continuing research in the complex world of TH transport in and out of cells promises a fascinating future.

References

1 Bianco, A.C. and Kim, B.W. (2006) Deiodinases: implications of the local control of thyroid hormone action. *J. Clin. Invest.* 116, 2571–2579
2 Yen, P.M. *et al.* (2006) Thyroid hormone action at the cellular, genomic and target gene levels. *Mol. Cell. Endocrinol.* 246, 121–127
3 Hennemann, G. *et al.* (2001) Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. *Endocr. Rev.* 22, 451–476
4 Abe, T. *et al.* (2002) Thyroid hormone transporters: recent advances. *Trends Endocrinol. Metab.* 13, 215–220
5 Jansen, J. *et al.* (2005) Thyroid hormone transporters in health and disease. *Thyroid* 15, 757–768
6 Friesema, E.C. *et al.* (2006) Mechanisms of disease: psychomotor retardation and high T3 levels caused by mutations in monocarboxylate transporter 8. *Nat. Clin. Pract. Endocrinol. Metab.* 2, 512–523
7 Friesema, E.C. *et al.* (1999) Identification of thyroid hormone transporters. *Biochem. Biophys. Res. Commun.* 254, 497–501
8 van der Putten, H.H. *et al.* (2003) Thyroid hormone transport by the rat fatty acid translocase. *Endocrinology* 144, 1315–1323
9 Mitchell, A.M. *et al.* (2005) Thyroid hormone export from cells: contribution of P-glycoprotein. *J. Endocrinol.* 185, 93–98
10 Taylor, P.M. and Ritchie, J.W. (2007) Tissue uptake of thyroid hormone by amino acid transporters. *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 237–251
11 Hagenbuch, B. (2007) Cellular entry of thyroid hormones by organic anion transporting polypeptides. *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 209–221
12 Visser, W.E. *et al.* (2007) Thyroid hormone transport by monocarboxylate transporters. *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 223–236
13 Pizzagalli, F. *et al.* (2002) Identification of a novel human organic anion transporting polypeptide as a high affinity thyroxine transporter. *Mol. Endocrinol.* 16, 2283–2296
14 Sugiyama, D. *et al.* (2003) Functional characterization of rat brain-specific organic anion transporter (Oatp14) at the blood–brain barrier: high affinity transporter for thyroxine. *J. Biol. Chem.* 278, 43489–43495
15 Tohyama, K. *et al.* (2004) Involvement of multispecific organic anion transporter, Oatp14 (Slc21a14), in the transport of thyroxine across the blood–brain barrier. *Endocrinology* 145, 4384–4391
16 Friesema, E.C. *et al.* (2003) Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. *J. Biol. Chem.* 278, 40128–40135
17 Friesema, E.C. *et al.* (2006) Human monocarboxylate transporter 10 does transport thyroid hormone. *Thyroid* 16, 913
18 Chu, C. *et al.* (2007) Blood–brain barrier genomics and cloning of a novel organic anion transporter. *J. Cereb. Blood Flow Metab.*, DOI: 10.1038/sj.jcbfm.9600538
19 Zhou, Y. *et al.* (1990) Evidence for a close link between the thyroid hormone transport system and the aromatic amino acid transport system T in erythrocytes. *J. Biol. Chem.* 265, 17000–17004
20 Zhou, Y. *et al.* (1992) Thyroid hormone concentrative uptake in rat erythrocytes. Involvement of the tryptophan transport system T in countertransport of tri-iodothyronine and aromatic amino acids. *Biochem. J.* 281, 81–86
21 Kim, D.K. *et al.* (2001) Expression cloning of a Na^+-independent aromatic amino acid transporter with structural similarity to H^+/monocarboxylate transporters. *J. Biol. Chem.* 276, 17221–17228
22 Kim, D.K. *et al.* (2002) The human T-type amino acid transporter-1: characterization, gene organization, and chromosomal location. *Genomics* 79, 95–103
23 Ramadan, T. *et al.* (2006) Basolateral aromatic amino acid transporter TAT1 (Slc16a10) functions as an efflux pathway. *J. Cell. Physiol.* 206, 771–779
24 van der Deure, W.M. *et al.* (2007) Genetic variation in thyroid hormone transporters. *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 339–350
25 Rechsteiner, M. and Rogers, S.W. (1996) PEST sequences and regulation by proteolysis. *Trends Biochem. Sci.* 21, 267–271
26 Friesema, E.C. *et al.* (2006) Thyroid hormone transport by the human monocarboxylate transporter 8 and its rate-limiting role in intracellular metabolism. *Mol. Endocrinol.* 20, 2761–2772
27 Trajkovic, M. *et al.* (2007) Abnormal thyroid hormone metabolism in mice lacking the monocarboxylate transporter 8. *J. Clin. Invest.* 117, 627–635
28 Heuer, H. *et al.* (2005) The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations. *Endocrinology* 146, 1701–1706
29 Bonen, A. *et al.* (2006) Distribution of monocarboxylate transporters MCT1–MCT8 in rat tissues and human skeletal muscle. *Appl. Physiol. Nutr. Metab.* 31, 31–39
30 Price, N.T. *et al.* (1998) Cloning and sequencing of four new mammalian monocarboxylate transporter (MCT) homologues confirms the existence of a transporter family with an ancient past. *Biochem. J.* 329, 321–328
31 Chan, S.Y. *et al.* (2006) Monocarboxylate transporter 8 expression in the human placenta: the effects of severe intrauterine growth restriction. *J. Endocrinol.* 189, 465–471
32 Alkemade, A. *et al.* (2005) Neuroanatomical pathways for thyroid hormone feedback in the human hypothalamus. *J. Clin. Endocrinol. Metab.* 90, 4322–4334
33 Alkemade, A. *et al.* (2006) Novel neuroanatomical pathways for thyroid hormone action in the human anterior pituitary. *Eur. J. Endocrinol.* 154, 491–500
34 Friesema, E.C. *et al.* (2004) Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* 364, 1435–1437
35 Dumitrescu, A.M. *et al.* (2004) A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *Am. J. Hum. Genet.* 74, 168–175
36 Sugiura, M. *et al.* (2007) Overexpression of MCT8 enhances the differentiation of ES cells into neural progenitors. *Biochem. Biophys. Res. Commun.* 360, 741–745
37 Schwartz, C.E. *et al.* (2005) Allan–Herndon–Dudley syndrome and the monocarboxylate transporter 8 (*MCT8*) gene. *Am. J. Hum. Genet.* 77, 41–53
38 Schwartz, C.E. and Stevenson, R.E. (2007) The MCT8 thyroid hormone transporter and Allan–Herndon–Dudley syndrome. *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 307–321
39 Jansen, J. *et al.* (2007) Functional analysis of monocarboxylate transporter 8 mutations identified in patients with X-linked

psychomotor retardation and elevated serum triiodothyronine. *J. Clin. Endocrinol. Metab.* 92, 2378–2381
40 Refetoff, S. and Dumitrescu, A.M. (2007) Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. *Best Pract. Res. Clin. Endocrinol. Metab.* 21, 277–305
41 Dumitrescu, A.M. *et al.* (2006) Tissue-specific thyroid hormone deprivation and excess in monocarboxylate transporter (mct) 8-deficient mice. *Endocrinology* 147, 4036–4043
42 Dumitrescu, A.M. *et al.* (2007) High circulating T3 in *Mct8* deficient mice is an age related postnatal event dependent on the ontogeny of deiodinases. *The Endocrine Society's 89th annual meeting Toronto, Canada*, [OR52-52]
43 Kakinuma, H. *et al.* (2005) A novel mutation in the monocarboxylate transporter 8 gene in a boy with putamen lesions and low free T4 levels in cerebrospinal fluid. *J. Pediatr.* 147, 552–554
44 Holden, K.R. *et al.* (2005) X-linked *MCT8* gene mutations: characterization of the pediatric neurologic phenotype. *J. Child Neurol.* 20, 852–857
45 Maranduba, C.M. *et al.* (2006) Decreased cellular uptake and metabolism in Allan–Herndon–Dudley syndrome (AHDS) due to a novel mutation in the MCT8 thyroid hormone transporter. *J. Med. Genet.* 43, 457–460
46 Herzovich, V. *et al.* (2006) Unexpected peripheral markers of thyroid function in a patient with a novel mutation of the *MCT8* thyroid hormone transporter gene. *Horm. Res.* 67, 1–6