MCT8: From gene to disease and therapeutic approach

MCT8 : du gène à la maladie, une approche thérapeutique

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Résumé

Le métabolisme et l’action des hormones thyroïdiennes constituent des processus essentiellement intracellulaires. Ils requièrent un transfert transmembranaire de l’hormone qu’assurent différents transporteurs. Plusieurs d’entre eux (MCT8, MCT10) sont exprimés dans de nombreux tissus dont le foie, le rein, la thyroïde et le cerveau. Le gène MCT8 est localisé sur le chromosome X. Les mutations de MCT8 déterminent un retard psychomoteur sévère, une concentration de T4 abaissée, de T3 accrue, chez les sujets masculins qui en sont atteints. On pense que le retard psychomoteur s’explique par un défaut de captage neuronal de la T3 durant la période du développement cérébral. Les anomalies des concentrations hormonales apparaissent liées, d’une part, à une augmentation de la conversion rénale de T4 en T3, d’autre part, à une altération de la sécrétion hormonale par la glande thyroïde. Les choix thérapeutiques s’orientent vers l’utilisation précoce d’analogues de la T3 qui ne requièrent pas l’expression de MCT8 pour le captage neuronal.

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Mots clés : MCT8 ; Transporteurs des hormones thyroïdiennes ; T3 ; Retard psychomoteur ; Syndrome d’Allan-Herndon-Dudley

Abstract

Thyroid hormone metabolism and action are largely intracellular processes that require transport of the hormone across the plasma membrane by different transporters. Two of these, MCT8 and MCT10, are close members of the monocarboxylate transporter family. MCT8 is expressed in a variety of tissues, including liver, kidney, thyroid and brain. The MCT8 gene is located on the X chromosome, and mutations in MCT8 result in severe psychomotor retardation and low serum T4 and high T3 levels in affected males. The psychomotor retardation is thought to be caused by impaired neuronal T3 uptake during brain development. The abnormal thyroid hormone levels appear to result from an increased T4 to T3 conversion in the kidney as well as altered hormone secretion from the thyroid gland. Options for therapy aim at early treatment with T3 analogues, neuronal uptake of which does not require MCT8.

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1. Introduction

Under normal conditions, the thyroid produces predominantly the prohormone thyroxine (3,3′,5,5′-tetraiodothyronine, T4) and only a small amount of the active hormone 3,3′,5-triiodothyronine (T3). Most T3 is generated by outer ring deiodination (ORD) of T4 in peripheral tissues [1]. In contrast to the activating pathway, thyroid hormone (TH) is inactivated by inner ring deiodination (IRD), which converts T4 and T3 into the metabolites 3,3′,5′-triiodothyronine (rT3) and 3,3′-diodothyronine (T2), respectively [1].

Three iodothyronine deiodinases (D1-3) are involved in these different deiodination reactions [1]. D1 is expressed in liver, kidneys and thyroid and has both ORD and IRD activity. It is thought to contribute importantly to production of serum T3, in particular in eu- and hyperthyroid conditions. D2 has only ORD activity and is expressed in brain, pituitary, brown adipose tissue (BAT), thyroid and skeletal muscle. It is essential for local production of T3 in brain pituitary and BAT, but the enzyme in thyroid and muscle may be an important site for production of serum T3 in eu- and hypothyroid subjects. D3 is highly expressed in different fetal tissues, placenta and pregnant uterus, and also in adult...
brain and skin. It has only IRD activity and thus, catalyzes the inactivation of TH. Together with D2, D3 has a crucial role in the region-specific and time-dependent regulation of T3 in the developing brain. The deiodinases are homologous selenoproteins embedded in the membrane of the endoplasmic reticulum or the plasma membrane, such that the active sites are located in the cytoplasm [1].

Most but not all actions of TH are exerted by binding of T3 to its nuclear receptors. This results in a change in the composition of the transcription machinery and thus, in an increase or decrease in expression of T3 responsive genes [2]. Therefore, TH metabolism and action require transport of iodothyronines across the cell membrane. This does not take place by passive diffusion but requires the involvement of specific transporters [3]. Two of these, MCT8 and MCT10, have been characterized as effective TH transporters in our laboratory [4–7]. Studies by our group and by others have also demonstrated that mutations in MCT8 result in a syndrome combining severe psychomotor retardation and abnormal serum TH levels [8–12].

2. MCT8 and MCT10

The TH transporters MCT8 and MCT10 are members of the monocarboxylate transporter family, named such because MCT1-4 was shown to transport monocarboxylates like lactate and pyruvate [13]. However, the function of most of the 14 members of this family is still enigmatic. In 2001, MCT10 was identified as an aromatic amino acid transporter, apparently without activity toward iodothyronines [14]. This led us to test its close homolog MCT8 for possible TH transport, which was indeed found to be the case [4,6]. We have latter also shown that – in contrast to the initial negative results – MCT10 is also a very effective TH transporter [5].

MCT8 and MCT10 are encoded by genes of similar structures. The MCT8 gene is located on human chr X13.2 and the MCT10 gene on chr 6q21-q22. Both genes have six exons and thus, five introns of which intron 1 is ~100 kb in size. MCT8 has two possible translation start sites (TLSs), yielding proteins of 613 or 539 amino acids (Fig. 1). In many animals, MCT8 lacks the first TLS, giving rise to only the short MCT8 protein. If the N-terminal extension of the long human MCT8 protein has specific functions remains to be determined. In all species, MCT10 has only one TLS, corresponding to the second TLS of human MCT8.

MCT8 and MCT10 have 12 putative transmembrane domains (TMDs) and both N-and C-terminal domains are located intracellularly [4–6]. There is a high degree of homology between the MCT8 and MCT10 proteins, in particular in the TMDs, which fits with the similar functions of these proteins as TH transporters. Both MCT8 and MCT10 facilitate transport of different iodothyronines although T3 appears to be transported somewhat better by MCT10 than by MCT8, whereas T4 appears to be a better ligand for MCT8 than for MCT10 [5,6]. Both MCT8 and MCT10 facilitate cellular uptake as well as efflux of iodothyronines. Therefore, transfection with MCT8 or MCT10 may induce only a modest increase in steady-state intracellular hormone levels. This is potentiated if efflux is inhibited, e.g. by co-transfection with the high-affinity cytoplasmic TH-binding protein CRYM [5]. That MCT8 and MCT10 indeed increase intracellular TH availability is demonstrated by the marked increase in TH metabolism if D1, D2 or D3-expressing cells are transfected with these transporters [5,6].

MCT8 and MCT10 are expressed in many human tissues. MCT10 shows particularly high expression in skeletal muscle, intestine and kidney, while MCT8 is highly expressed in liver, kidney, adrenal, ovary and thyroid [15]. As studied in mice, MCT8 is also expressed importantly in brain, in particular in neurons in different brain regions, including cerebral cortex and cerebellum, but also in the choroid plexus, in capillaries and in tanycytes lining the third ventricle [16].

3. Patients

The pathophysiological importance of MCT8 has been demonstrated by the identification of mutations in MCT8 in male patients with severe psychomotor retardation and abnormal serum TH levels [8–12]. The neurological syndrome has already been described in 1944 by Allan, Herndon and Dudley [17], and since then referred to as the Allan-Herndon-Dudley syndrome (AHDS). AHDS comprises central hypotonia associated with poor head control and initially also peripheral hypotonia that progresses to spasticity. Most AHDS patients are unable to sit, stand or walk independently and have not developed speech, although patients with a milder phenotype who can walk and/or talk with great difficulty have been reported. All patients have severe mental retardation [18]. AHDS patients are born without apparent abnormality and the disease appears to develop progressively, often associated with macrocephaly. MRI of the brain usually shows delayed myelination before the age of 2 years, which apparently normalizes with increasing age [12].

In addition to the psychomotor retardation, AHDS patients also exhibit abnormal thyroid parameters [7–12]. Serum T4 and FT4 levels vary from low-normal to truly decreased, whereas serum T3 levels are invariably increased. Like T4, serum rT3 is usually decreased, and the serum T3/rT3 ratio is markedly elevated. Serum TSH varies between normal and elevated with mean TSH levels being about twice the normal mean. In view of the low (F)T4 and somewhat higher TSH levels, many AHDS patients have been treated with T4 substitution without any obvious benefit.

TH is crucial for brain development. In AHDS patients, brain development is impaired despite the presence of elevated serum T3 levels, suggesting some form of TH resistance. After exclusion of mutations in the T3 receptors and the deiodinases, it was hypothesized that this TH resistance could be caused by impaired TH uptake in target cells due to mutations in a TH transporter. Since AHDS only occurs in males and the MCT8 gene is located on the X chromosome, the hypothesis was tested by testing this gene for possible mutations. Indeed, in over 50 families with AHDS studied so far, various mutations in MCT8 have been identified [19].

These mutations include large deletions, frame-shift mutations and non-sense mutations, which are obviously deleterious for MCT8 function. However, this is not so obvious for mutations
that result in the deletion, insertion or substitutions of single amino acids. Therefore, cells have been transfected with wild-type MCT8 or with the various mutants, and subsequently tested for TH uptake or, after co-transfection of D3, for TH metabolism. All mutations resulted in a marked decrease in TH transport, although the magnitude of this impairment was dependent on the cell type used for transfection [20–22]. The results suggested some correlation between the severity of the clinical phenotype, the changes in serum TH levels and the defect in TH transport.

The pathogenic mechanism of AHDS involves an important role of MCT8 in T3 uptake in central neurons and, hence, in the crucial action of T3 in this important target cell during brain development. Inactivation of MCT8 results in the lack of T3 supply to its nuclear receptor in these neurons and thus, in impaired differentiation of these cells, with dramatic consequences for brain development [11].

4. Animal model

To study the pathogenic mechanism of MCT8 mutations in more detail, Mct8 knockout (ko) mice have been generated and studied in different laboratories [23,24]. Surprisingly, Mct8 ko mice do not show any remarkable neurological phenotype. They do show, however, the same changes in serum TH levels as AHDS patients, including a marked decrease in serum T4 and a marked increase in serum T3. Studies aimed to reveal the mechanism(s) of these altered serum TH levels have indicated:

- increased D1 expression in liver and kidney;
- increased D2 activity in brain and pituitary;
- decreased D3 activity in brain of Mct8 ko versus wild-type (wt) animals [24,25].

The important role of MCT8 in brain TH transport is evident from the almost complete block in T3 uptake in Mct8 ko mice, whereas T4 uptake is not affected [24]. T4 and T3 uptake in liver is not inhibited in Mct8 ko mice, while unexpectedly T4 and T3 appear to accumulate at higher levels in kidneys form Mct8 ko mice than in wt mice [24,25]. The reason for this remains to be established but may be explained if MCT8 is more important for TH efflux than for TH uptake in the kidney. The increase renal T4 content in combination with the higher D1 activity in this tissue may contribute to a strong increase in peripheral T4 to T3 conversion, and thus, to the low T4 and high serum T3 levels in Mct8 ko mice and AHDS patients [25].

Further studies in Mct8 ko mice have indicated an important role of this transporter in TH secretion [26,27]. Thyroidal T4 and T3 content is increased in Mct8 ko vs wt mice. Furthermore, after stimulation of mice with TSH, the increase in serum T4 is lower, whereas the increase in serum T3 is higher in Mct8 ko vs wt mice [27]. This suggests that T4 secretion from thyroid cells is mediated importantly by MCT8. If MCT8 is inactivated, T4 accumulates in the thyrocyte, leading to increased intra-thyroidal T4 to T3 conversion, and thus, an increase in the ratio of secreted T3 vs T4.

5. Treatment

One of the disappointing consequences of the lack of a neurological phenotype in Mct8 ko mice is that these animals cannot
be used as a model for the development of an effective treatment of patients with AHDS. The possible success of such a treatment will depend on:

- the extent to which irreversible damage in brain development has occurred at the time the disease is diagnosed;
- the possibility to supply active hormone to important brain targets in the absence of functional MCT8.

TH is essential for prenatal brain development, but TH-dependent brain maturation continues after birth [28]. The lack of obvious abnormalities at birth and the progressive nature of AHDS may suggest that early postnatal instalment of an effective therapy may have substantial beneficial effect.

Because of the low serum T4 in combination with a somewhat increased serum TSH, many AHDS patients have been treated with LT4 without obvious benefit. In fact, such treatment may have detrimental effects as it may further increase T3 exposure of tissues, which do not depend on MCT8 for TH uptake. It could also be hypothesized that the abnormal serum T4 and T3 levels contribute importantly to the clinical phenotype and that their normalization may have beneficial therapeutic effects. Such a study has been carried out in an adolescent AHDS patient in whom serum TH levels were normalized by block-and-replace therapy with PTU plus LT4. This produced favourable effects on body weight and heart rate but – as expected – did not result in an obvious mental improvement [29].

Obvious possibilities for effective therapy include early treatment of AHDS patients with a thyromimetic compound that is effectively transported in the brain even if MCT8 is mutated. One such compound is DITPA, which is currently tested clinically in MCT8 patients [30]. Studies are also going on in cell models and in mice to explore if the bioactive TH metabolite Triac or its precursor Tetrac may be used for effective treatment of AHDS patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


