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5

Inherited defects in thyroid hormone cell-membrane transport and metabolism

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The description of two novel human defects in the last ten years has uncovered new aspects of thyroid hormone physiology with regard to cell-membrane transport and intracellular metabolism. Mutations in the X-linked monocarboxylate transporter 8 (MCT8) gene result in an invalidating neurodevelopmental phenotype in males and pathognomonic thyroid functions tests with high T_3, low rT_3, low or low normal T_4, and normal or slightly high TSH. Recessive mutations in the selenocysteine insertion sequence binding protein 2 (SBP2) gene present a variable clinical phenotype depending on the severity of the defect and its consequences on the selenoprotein hierarchy. Most characteristic is the thyroid phenotype of low serum T_3, high T_4, high rT_3, and slightly elevated TSH levels. Herein we review all known cases of MCT8 and SBP2 deficiency and describe each disease in terms of the clinical, biochemical, genetic, and therapeutic aspects.

Introduction and thyroid physiology

Thyroid hormone (TH) is essential for human development, growth and metabolism. The effects of TH deficiency and excess during development can be profound and permanent, especially with regards to the nervous system [1]. The feedback regulatory system involving the hypothalamus–pituitary–

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thyroid axis maintains the circulating TH available to tissues. Intracellular concentrations of T_3 are regulated by iodothyronine deiodinases (Ds), which provide a mechanism for local regulation of TH supply. These selenoenzymes convert the hormone precursor thyroxine (T_4) through outer-ring deiodination (5′-deiodination) by D1 and D2 to form the active 3,3′,5-triiodothyronine (T_3), or, inactivate T_4 and T_3 through inner-ring deiodination (5-deiodination) by D3, to form 3,3′,5′-triiodothyronine (reverse T_3; rT_3) and 3,3′-diiodothyronine (T_2), respectively [2]. Several classes of cell-membrane transporters mediate the influx and efflux of T_3 and T_4 into the cells [3].

TH cell-membrane transport defect

TH cell-membrane transporters

Several types of TH transporters located in cellular membranes have been recognized, including the Na^+/taurocholate cotransporting polypeptide [4], the Na^+-independent organic anion transporting polypeptide (OATP) family [5], the heterodimeric L-type amino acid transporters (LAT1, LAT2) [6], and the monocarboxylate transporter (MCT) family [7]. Among them, OATP1C1 [8], MCT8 [9] and MCT10 [10] have narrower substrate specificities, indicating their relatively important role in TH bioavailability.

OATP1C1, with preferential transport of T_4, is highly enriched in brain capillaries [8,11,12], which may act as a bridge between the circulating T_4 and astrocytes, where T_4 is deiodinated to active T_3. Accordingly, the unique role of OATP1C1 in T_4 transport in the brain is supported by the finding of central nervous system specific hypothyroidism in Oatp1C1 knockout (KO) mice [13]. However, no human with OATP1C1 deficiency has been identified.

MCT8 is an active and specific TH cell-membrane transporter expressed in many tissues [9], and its deficiency causes a severe complex phenotype in humans [14,15]. The human (*hMCT8*) gene is located on chromosome Xq13.2 and consists of six exons. It encodes two variant proteins of 613 and 539 amino acids translated from two putative in-frame start sites. There is a high degree of homology in amino acid sequences of MCT8 among different species. However, the non-primate MCT8 gene lacks the upstream translation start site [16]. Currently, the functional importance of the additional 75 amino acids located in the amino-terminus of hMCT8 remains unknown. The predicted structure contains 12 hydrophobic transmembrane domains (TMDs) with intracellular amino- and carboxyl-terminus [17]. In this review, the numbering of hMCT8 amino acids starts from the upstream translation start site. Both rat MCT8 (rMct8) and hMCT8 markedly stimulate the uptake of TH, but fail to influence the transport of other molecules such as aromatic amino acids. MCT8 is widely distributed in tissues, including brain, liver, kidney, heart, thyroid and placenta [9,18,19].

MCT10, initially characterized as a T-type amino acid transporter, has the highest homology to MCT8 within the MCT family. It was demonstrated as an alternative TH transporter with increased affinity for T_3 [10]. In both humans and rodents, MCT10 is widely expressed in tissues such as skeletal muscle, kidney, liver and intestine [20,21]. Mutations in the MCT10 gene have not been identified.

Patients with MCT8 deficiency

MCT8 gene defects were first reported in 2004. All affected males display severe neurodevelopmental deficits and pathognomonic thyroid tests including high serum T_3, low rT_3, low normal to reduced T_4, and normal or slightly elevated TSH [14,15]. MCT8 gene mutations were also found to be responsible for the Allan–Herndon–Dudley syndrome (AHDS), an X-linked mental retardation syndrome (XLMR) initially described in 1944 [22] that is now synonymous with MCT8 defect. To date, more than 100 families of all races and diverse ethnic origins harboring more than 70 different mutations have been described.

The defect has 100% penetrance in males. There is, however, one case of a female patient with typical features of MCT8 deficiency attributed to the disruption of MCT8 by a de novo translocation and unfavorable nonrandom X-inactivation [23]. MCT8 gene mutations are distributed throughout the coding region and form apparent clusters in the TMDs, which are highly conserved across species. Mutations range from single nucleotide substitutions to large deletions involving one or more exons.