

Topic: **INTRACELLULAR TRANSPORT OF THYROID HORMONES**

Title: **Thyroid hormone transport by the human monocarboxylate transporter 8 and its rate-limiting role in intracellular metabolism.**

Authors: **Friesema EC, Kuiper GG, Jansen J, Visser TJ, & Kester MH (Rotterdam, Netherlands)**

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**SUMMARY**

**Background:** Cellular entry of thyroid hormones is mediated by plasma membrane transporters. The authors have identified rat monocarboxylate transporter (MCT8) as an active and specific thyroid hormone transporter.

**Human relevance:** The MCT8 gene is located on the X-chromosome. The physiological relevance of MCT8 has been demonstrated by the identification of hemizygous mutations in this gene in males who present extremely severe mental retardation and elevated serum T<sub>3</sub> levels.

**Study and Results:** The authors have characterized human (h) MCT8 by analysis of iodothyronine uptake and metabolism in cell lines transiently transfected with hMCT8 cDNA alone or together with iodothyronine deiodinase D1, D2, or D3. MCT8 mRNA was detected by RT-PCR in a number of human cell lines as in COS1 cells but was low to undetectable in other cell lines, including JEG3 cells. MCT8 protein was not detected in nontransfected cell lines tested by immunoblotting using a polyclonal C-terminal hMCT8 antibody but was detectable in transfected cells. Transfection of COS1 and JEG3 cells with hMCT8 cDNA resulted in 2- to 3-fold increases in uptake of T<sub>3</sub> and T<sub>4</sub>, but little or no increase in reverse-T<sub>3</sub> (rT<sub>3</sub>) or 3, 3'-T<sub>2</sub>. The expression of MCT8 produced large increases in T<sub>4</sub> metabolism when co-transfected with D2 or D3, T<sub>3</sub> metabolism by D3, rT<sub>3</sub> metabolism by D1 or D2, and 3, 3'-T<sub>2</sub> metabolism by D3. Affinity labeling of hMCT8 protein was observed after incubation of intact transfected cells with N-bromoacetyl-radiolabelled-T<sub>3</sub>. Human MCT8 also facilitated the affinity labeling of co-transfected D1 by bromoacetyl-T<sub>3</sub>.

**Conclusions:** The present findings indicate that hMCT8 mediates plasma membrane transport of iodothyronines, thus increasing their intracellular availability for further metabolic events.

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**COMMENT**

The biological activity of thyroid hormone is determined by the intracellular concentration of T<sub>3</sub> which, among other factors, depends of circulating T<sub>3</sub> concentrations and its prohormone precursor (T<sub>4</sub>). T<sub>4</sub> only becomes an active hormone after entering the cells and transformation into T<sub>3</sub>, under the catalytic action of deiodinases (D1 & D2). During

the last three decades, studies have demonstrated the importance of transporters for thyroid hormone to be taken up by target cells. Such transporters have only been recently identified at the molecular level, including several members of the Na-independent organic anion-transporting polypeptide family (OATPs). MCT8 is a member of the

monocarboxylate transporter family and has been characterized to be an active iodothyronine transporter, whereas it does not transport the aromatic amino-acids or the typical monocarboxylate ligands (such as lactate and pyruvate).

In man, a novel syndrome of severe X-linked mental retardation with elevated serum T<sub>3</sub> levels has been described in 2004 and is associated with mutations in the monocarboxylate transporter gene (MCT8). The severity of the phenotype is best explained by the recent demonstration that MCT8 is localized in different tissues such as the brain, where it is expressed in specific thyroid hormone-sensitive neuronal populations. Thus, mutations of MCT8 in the developing brain would deprive neurons of essential local presence of T<sub>3</sub> and hence result in psychomotor retardation.

In the present study, the authors aimed at characterizing human MCT8 as a thyroid hormone transporter. They transfected cell lines without hMCT8 expression with its cDNA and showed that the transfected cells had higher T<sub>4</sub> and T<sub>3</sub> transport rates. Furthermore, the metabolism of all iodothyronines was markedly stimulated in cells with iodothyronine deiodinase activities if these cells were also transfected with hMCT8. Most remarkable are the results showing that transfection of cells with hMCT8 in addition to that of the deiodinases facilitated the intracellular metabolism of the different iodothyronines. This represents the most direct evidence that hMCT8 increased the intracellular availability of these substrates for deiodination.

***(Daniel Glinde, M.D.; Ph.D.)***