Topic: **PLASMA MEMBRANE TRANSPORTERS OF THYROID HORMONES**

**Title**: Effective cellular uptake & efflux of thyroid hormone by human monocarboxylate transporter 10.

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**SUMMARY**

**Context**: Cellular entry of thyroid hormone is mediated by plasma membrane transporters, among others a T-type (aromatic) amino acid transporter. Monocarboxylate transporter 10 (MCT10) has been reported to transport aromatic amino acids but not iodothyronines. Within the MCT family, MCT10 is most homologous to MCT8, which is a very important iodothyronine transporter but does not transport amino acids.

**Objective**: The authors decided to reinvestigate the possible transport of thyroid hormone by human (h) MCT10 in comparison with hMCT8.

**Results**: Transfection of COS1 cells with hMCT10 cDNA resulted in: a) production of an approximately 55 kDa protein located to the plasma membrane as shown by immunoblotting and confocal microscopy; b) a strong increase in the affinity labelling of intracellular type I deiodinase by N-bromoacetyl-[125I]-T³; c) a marked stimulation of cellular T₄ and, particularly, T₃ uptake; d) a significant inhibition of T₃ uptake by phenylalanine, tyrosine, and tryptophan of 12.5%, 22.2%, and 51.4%, respectively; and e) a marked increase in the intracellular deiodination of T₄ & T₃ by different deiodinases. Cotransfection studies using the cytosolic thyroid hormone-binding protein microcrystallin (CRYM) indicated that hMCT10 facilitates both cellular uptake and efflux of T₄ and T₃. In the absence of CRYM, hMCT10 and hMCT8 increased T₃ uptake after 5 min incubation up to 4.0- and 1.9-fold, and in the presence of CRYM up to 6.9- and 5.8-fold, respectively. Human MCT10 was less active toward T₄ than human MCT8.

**Conclusions**: These findings establish that human MCT10 is at least as active a thyroid hormone transporter as human MCT8, and that both transporters facilitate iodothyronine uptake as well as efflux.

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**COMMENT**

Thyroid hormone is metabolized and exerts its actions intracellularly, processes that require first the transport of extracellular iodothyronines across plasma membrane. Different types of transporters are likely to be involved in thyroid hormone (TH) uptake in different tissues. A number of these have recently been characterized at the molecular level, among which several members of the ‘MCT’ family of proteins.

Human MCT8 has been shown to be an active & specific iodothyronine transporter (for further reading on this topic, see the recent review by the same group in Trends in Endocrinology & Metabolism, March 2008). Furthermore, the pathophysiological relevance of MCT8 has been demonstrated in male patients with a syndrome of elevated serum T₃ concentrations combined with severe psycho-motor retardation.
(the “Allan-Herndon-Dudley syndrome”, first described in 1944), due to a mutation in MCT8.

Human MCT8 gene is located on the X chromosome and human MCT10 gene on chromosome 6: the structure of both genes is very similar. The lack of iodothyronine transport (so far reported) for MCT10 is surprising in view of the homology between both proteins. The authors decided, therefore, to reinvestigate possible TH transport by human MCT10 in comparison with human MCT8.

The results showed for the first time that both human MCTs facilitate the bidirectional transport of T$_4$ and, in particular, T$_3$ across plasma membrane, and that human MCT10 transports T$_3$ even better than human MCT8.

With regard to the possible physiological relevance of these findings, the authors indicate that this transporter facilitates TH cellular entry, perhaps allowing the access of TH to intracellular deiodination and metabolism. MCT10 could also facilitate the access of T$_3$ to its nuclear receptors, although further studies are required to establish more firmly the role of both MCTs in TH action. Since both MCTs mediate the bidirectional transport of iodothyronines, they may also be important for the release of T$_3$ from cells in which the hormone is produced locally by T$_4$ deiodination. Finally, particularly interesting is the high expression of MCT10 mRNA in placenta, since placental transport of maternal TH is essential for fetal development in the early stages of gestation.

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See Figure below