Role of transporters in thyroid hormone trafficking in the developing brain

Friesema ECH, Jansen J, Kester MHA, Hume R*, Visser TJ
Dept of Internal Medicine, Erasmus MC, Rotterdam, *Maternal and Child Health Sciences, University of Dundee, Dundee, Scotland, UK

Thyroid hormones are essential for the development of the brain and the nervous system. Cellular entry is required for conversion of thyroid hormones by intracellular enzymes and for binding of T_3 to its nuclear receptors. We have identified monocarboxylate transporter 8 (MCT8) is an active and specific thyroid hormone transporter, the gene of which is located on the X chromosome (Xq13.2). MCT8 is highly expressed in specific brain regions and also in some other tissues.
We have studied 5 unrelated young boys, which all have the same novel syndrome characterized by 1) severe psychomotor retardation, 2) truncal hypotonia and 3) high serum levels of T_3. As the serum T_3 levels are elevated in our patients it suggests that this syndrome may be due to an insensitivity of the developing brain for thyroid hormone. Investigation of the *MCT8* gene resulted in the identification of different mutations in all 5 boys. In 2 boys, major parts of the *MCT8* gene were deleted and in the other 3 boys only different single nucleotides were mutated leading to changes in amino acid sequence. Quantitative mRNA studies on brain and liver samples from fetal (13-19 weeks of gestation) and neonatal (20-42 weeks of gestation) tissues showed that MCT8 expression in cerebellum decreases from 13 until 42 weeks of gestation, while the expression of MCT8 in liver remains constant during fetal development.
We conclude that because of the mutations in the MCT8 transporter the developing brain is deprived of the essential actions of thyroid hormones, resulting in a major defect in the development of the central nervous sytem. Because of the inhibited T_3 uptake and metabolism in brain cells, this syndrome is also characterized by the accumulation of circulation T_3.

Edith CH Friesema, Department of Internal Medicine, Erasmus MC, PO Box 1738, 3000 DR Rotterdam, The Netherlands, t 010-4087209, e-mail e.friesema@erasmusmc.nl

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