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Thyroid physiology becomes more complicated

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Rare clinical syndromes often lead to new insights, sometimes requiring modifications even in 'classical' physiological concepts. If such a condition is a result of a gene mutation, our capacity to reproduce it in mouse models can facilitate this process. A striking example is the X-linked psychomotor retardation syndrome first identified by Allan, Herndon and Dudley (AHDS) over 50 years ago. As reviewed last year in this journal, AHDS has now been linked to a defect in the gene encoding a thyroid hormone transporter, monocarboxylate transporter 8 (MCT8) (Friesema ECH *et al*. [2006] *Nat Clin Pract Endocrinol Metab* 2: 512–523). Males with AHDS have severe mental retardation and speech difficulties accompanied by hypotonia of truncal musculature. Although it is well known that thyroid hormone is required for normal central nervous system (CNS) development, this phenotype is not typical of congenital hypothyroidism. Nor do the laboratory abnormalities—a mild decrease in serum T_4, a modestly elevated serum T_3 and a high-normal serum TSH level—suggest thyroid hormone deficiency.

Two groups have recently created mouse models of this disorder by targeting the gene encoding MCT8 (Dumitrescu AM *et al*. [2006] *Endocrinology* 147: 4036–4043; Trajkovic M *et al*. [2007] *J Clin Invest* 117: 627–635). Analyses of these animals reveal surprising new insights into the complexity of thyroid hormone transport into different cells. MCT8 is widely expressed in the CNS, especially in the hippocampus and the cerebral cortex, as well as in liver, kidney and thyroid. MCT8-null male mice have thyroid function tests similar to patients with AHDS. Heterozygous females are not affected.

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Strikingly, in MCT-null mice there is no uptake of circulating T_3 into the brain but, despite this, brain T_4 uptake is normal as is T_3 uptake into the liver. MCT8 is thus required for T_3 (but not T_4) uptake by brain but not by liver.

Because T_3 cannot enter the hypothalamic neurons in the mouse model, levels of TSH-releasing hormone mRNA rise, causing mild TSH elevation and increased thyroid hormone secretion (Trajkovic M *et al*. [2007] *J Clin Invest* 117: 627–635). Despite its expression in liver, MCT8 is not required for hepatic T_3 uptake. The hepatocytes therefore become thyrotoxic because of the elevated serum T_3 levels, thereby increasing hepatic type 1 deiodinase levels. This increase accelerates the conversion of T_4 to T_3, further elevating the serum T_3 and reducing serum T_4 levels. Since MCT8 is not expressed in mouse thyrotrophs, TSH secretion is attenuated by the elevated T_3 levels.

This complex mixture of T_3 deficiency in some cells and T_3 excess in others would have been very difficult to identify without this animal model. Despite the above mentioned similarities to AHDS patients in the pattern of serum hormones, the mice appear to have normal motor function. It is not yet clear whether this reflects differences in the developmental requirements for T_3 of the CNS of mice versus humans or merely that further testing is required.

This fascinating model provides only our first glimpse into the complexities of cellular thyroid hormone uptake, which only a few years ago was thought to occur by passive diffusion. One suspects that similar surprises might be in store for us in other hormone systems.