

# Thyroid physiology becomes more complicated

P Reed Larsen

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.