Role of Monocarboxylate Anion Transporter 8 (MCT8) in Thyroid Hormone Transport: Answers from Mice

The physiological significance of thyroid hormone transporters in the cell membrane has been demonstrated recently with the identification of mutations in the human monocarboxylate anion transporter 8 (MCT8) (1) (2). Mutations of this transporter are associated with a form of X-linked mental retardation, severe neurological impairment, and an unusual pattern of thyroid hormone concentrations in blood. As described by Dumitrescu et al. in this issue of Endocrinology (3), deletion of the Mct8 gene in mice faithfully reproduces the altered thyroid hormone concentrations observed in patients, although no obvious signs of neurological impairment are observed in the mutant mice. The altered thyroid hormone concentrations in blood and tissues seem to be due to the simultaneous elevation in the activity of deiodinases type 1 (D1) and 2 (D2) as a consequence of tissue-specific thyroid hormone availability consequent to different dependency on Mct8 for thyroid hormone uptake.

Until recently, the mechanism of thyroid hormone entry into cells was not clear. It was assumed that the lipophilic nature of thyroid hormones facilitated passive diffusion through the lipid bilayer. In support of this idea was the lack of evidence for saturable transport after administration of graded doses of thyroid hormones in vivo. However, specific transport mechanisms could be demonstrated for T3 and T4 in a variety of cultured cellular systems. Kinetic properties of high-affinity membrane transporters were described and later on characterized as distinct molecular entities (for a review see Ref. 4). The membrane transporters for thyroid hormones belong to several families including the Na+/H+-independent organic anion transporting polypeptides family. However, MCT8 is expressed in neurons and, therefore, neuronal uptake of T3 is likely to be impaired in the patients (9). In addition, because neurons express the inactivating type 3 deiodinase (D3), which degrades T3 to T2, decreased degradation of T3 could also account for the elevated blood levels of this hormone.

The Mct8 knockout mice generated by Dumitrescu et al. and reported in this issue (3) are an excellent tool to analyze the pathophysiology of the syndrome. The most important observation is that, indeed, deletion of the Mct8 gene leads to thyroid function abnormalities similar to those observed in the humans. Male mice with the genotype Mct8<sup>−/−</sup> have elevated T3 and reduced T4 and rT3 in blood. Importantly, Mct8<sup>−/−</sup> females present similar abnormalities, discarding any gender-specific differences that could influence the phenotype. The authors compare the effect of different doses of T3 administered to the wild-type and the mutant mice. Several conclusions could be drawn from these experiments. First, the authors demonstrate a relative pituitary resistance to thyroid hormone, because a higher dose of T3 was needed to suppress TSH in the mutant mice than in the wild-type mice. This experiment indicates that the effect of T3 on TSH suppression requires transport through Mct8. Actually the transporter is expressed in the anterior pituitary, though not in hormone producing, but in stellate cells (10). Second, they showed that the elevated T3 levels are due primarily to increased production from T4. The reason is that, in the T3<sup>-</sup> treated mice, basal concentrations of T3 and the disappear-

Abbreviations: D1, Deiodinase type 1; D2, deiodinase type 2; D3, deiodinase type 3; MCT-8, monocarboxylate anion transporter 8.

Endocrinology is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.
ance rate of the hormone in serum and liver were similar in mutant and wild-type mice, in a situation where \( T_4 \) was undetectable in both strains of mice. Therefore, \( T_4 \) is needed to maintain the high \( T_3 \) concentration in the mutant mice.

Indeed, a crucial aspect of the thyroid phenotype of the mutant mice is the coexistence of “hyperthyroid” and “hypothyroid” tissues, leading to a simultaneous elevation of \( D_1 \) and \( D_2 \) activities, respectively, in those tissues. In the liver, where transporters other than \( Mct8 \) are expressed, the elevation of circulating \( T_3 \) induces a clear thyrotoxic state, as shown by markers of thyroid hormone action in this organ. \( D_1 \), a sensitive marker of thyroid status in the liver, was up-regulated. The elevated activity of this enzyme further contributes to the syndrome by increasing conversion of \( T_4 \) to \( T_3 \) and increasing degradation of \( rT_3 \).

\( D_2 \) activity was highly increased in the brain, as a response to cellular hypothyroidism. The highly increased \( D_2 \) activity in brain is likely due to the decreased availability of \( T_4 \) to the astrocytes secondary to a decreased circulating \( T_4 \). The contribution of the brain to the thyroid syndrome is complex. \( D_2 \) and \( Mct8 \) are expressed in different cells (9), and entry of \( T_4 \) and \( T_3 \) to \( D_2 \)-expressing astrocytes through the blood-brain barrier should, in principle, not be compromised, as it takes place through a different transporter. An elevation of \( D_2 \) activity in these cells should be a late event in the syndrome, following the decreased \( T_4 \) supply. Another type of \( D_2 \)-expressing cells, the tanycytes, also express \( Mct8 \). These cells presumably get \( T_4 \) from the cerebrospinal fluid, via the choroid plexus, a site of prominent \( Mct8 \) expression. Therefore, it is likely that tanycyte \( D_2 \) is increased in the early phases of the syndrome, but its possible contribution to the syndrome is unknown.

The contribution of \( D_2 \) expressed in other tissues such as the heart, muscle, or skin is probably also relevant to explain the role played by \( D_2 \) in the initial phases of the syndrome, but its possible contribution to the syndrome is unknown.

Despite the \( Mct8 \) deletion reproduced the thyroid phenotype in mice, no obvious signs of neurological disturbances were observed. The mice seem to behave normally, without obvious motor abnormalities. Of course, a more detailed behavioral evaluation is needed. As pointed out by the authors (3), in mice it is difficult to reproduce other situations resulting from decreased thyroid hormone supply to the human brain. In terms of basal \( T_3 \) concentration, the brains of the mutant mice are probably not as strongly hypothyroid, as in other situations such as Pax8 deletion (11).

The secondary increase in \( D_2 \) activity may provide sufficient \( T_3 \) to normalize basal expression of \( T_3 \)-regulated genes and prevent the harmful effects of unliganded \( T_3 \) nuclear receptor (12, 13).

In conclusion, the findings by Dumitrescu et al. (3) represent an important step forward in understanding the role of the transporters in thyroid hormone distribution and action and the pathogenesis of the X-linked mental retardation syndrome caused by \( MCT8 \) mutations in humans.

Juan Bernal
Instituto de Investigaciones Biomédicas
Consejo Superior de Investigaciones Científicas
Universidad Autónoma de Madrid
28029 Madrid, Spain

Acknowledgments

Received May 23, 2006. Accepted May 25, 2006.
Address all correspondence and requests for reprints to: Prof. Juan Bernal, Instituto de Investigaciones Biomédicas, Arturo Duperier 4, 28029 Madrid, Spain. E-mail: jbernal@ib.uma.es.

The author is supported by a grant from the Ministry of Education and Science of Spain, BFU2005-01740.

Disclosure summary: J.B. has nothing to declare.

References

12. Morte B, Manzano J, Scanlan T, Vennstrom B, Bernal J 2002 Deletion of the thyroid hormone receptor r1 prevents the structural alterations of the cerebellum induced by hypothyroidism. Proc Natl Acad Sci USA 99:3985–3989

Endocrinology is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.