

The Elemental Importance of Sufficient Iodine Intake: A Trace Is Not Enough

Thyroid hormone is an important regulator of energy metabolism and crucial for the development of different tissues, in particular the brain (1, 2). Iodine is an essential trace element for the synthesis of thyroid hormone; as their names indicate, the prohormone T_4 contains four iodine atoms, and the principal bioactive hormone T_3 contains three iodine atoms. If iodine intake is sufficient, the normal human thyroid gland secretes predominantly T_4 and only about 20% of daily T_3 production (3). Most T_3 is generated outside the thyroid gland by enzymatic outer ring deiodination (ORD) of T_4 in different tissues. T_4 and T_3 are converted by inner ring deiodination to the receptor-inactive metabolites rT_3 and 3,3'-diiodothyronine.

The peripheral metabolism of thyroid hormone involves three deiodinases (3). Two deiodinases (D1 and D2) have ORD activity and are thus capable of producing T_3 from T_4 . Conversion of T_4 to T_3 is the most efficient reaction catalyzed by D2, but this is far from true for D1, which is much more effective in the ORD of rT_3 (4). In addition to expression of D1 in the thyroid gland, the enzyme is particularly abundant in liver and kidney (3). Hepatic and renal D1 are important sources of circulating T_3 .

D2 is expressed in human brain, pituitary, thyroid, and skeletal muscle (3). In particular in the brain and also in the anterior pituitary, D2 is extremely important for local T_3 production (3). Although modest levels of D2 are found in the normal human skeletal muscle, they appear sufficient to contribute a major part of peripheral T_3 production in view of the large size of this tissue (5). The relative importance of skeletal muscle D2 for plasma T_3 production increases in hypothyroidism because this is associated with a decrease in D1 expression in liver and kidney and an increase in D2 expression in skeletal muscle and other tissues (6). The opposite is true for hyperthyroidism. D1 expression is stimulated by its product T_3 at the transcriptional level (3). Conversely, D2 activity is under negative control of its substrates T_4 and rT_3 , which induce the ubiquitination and degradation of the enzyme (3).

Although D1 also has inner ring deiodination activity, a third deiodinase (D3) is the major player in the degradation of thyroid hormone, showing preference for T_3 over T_4 as the substrate (3). In adults, the brain may be the major site of D3 expression, although normal skin also contains substantial D3 activity (7, 8). Even higher D3 levels are expressed in fetal tissues, in particular brain and liver (9, 10).

The role of D3 in fetal development is intriguing. In addition to different fetal tissues, very high D3 activities are

expressed in the placenta and the pregnant uterus (11–13). Despite this high D3 expression, placental transfer of maternal T_4 represents the only source of fetal plasma T_4 in the first half of gestation (1, 2). In the second half of gestation, the fetal thyroid gland becomes an ever more important source of circulating T_4 (1, 2). The high D3 activities expressed in the fetoplacental unit are probably important to prevent premature exposure of growing tissues to bioactive T_3 , which induces cellular differentiation. Nevertheless, sufficient fetal plasma T_4 accumulates to supply the brain with substrate for local T_3 production (10).

A recent extensive study of fetal and neonatal human brain development has demonstrated region-specific temporary profiles of tissue T_4 , T_3 , and rT_3 levels, and D2 and D3 activities (10). These findings support the view that normal brain development requires the coordinated expression of D2 and D3 to secure intracellular T_3 levels that are optimal for the particular brain region and stage of development. From recent work in different laboratories, a picture has emerged emphasizing the interaction between astrocytes and neurons in the local regulation of T_3 levels in the brain (14, 15). Neurons are thought to be the major target cells for T_3 in the developing brain, and this T_3 is supplied by neighboring astrocytes (14, 15).

Several steps are required to use plasma T_4 and make it available as bioactive T_3 to central neurons (Fig. 1). In addition to transfer of T_4 at the choroid plexus from plasma to CSF and subsequently to periventricular cells, T_4 supply to the brain requires its transport across the blood-brain barrier, but little is known about this process (16–18). Recently, one member of the organic anion transporting polypeptide family, OATP1C1, was shown to be highly specific for T_4 and expressed almost exclusively in brain capillaries, suggesting that it is important for T_4 transport across the blood-brain barrier (19, 20).

Also the transporters involved in T_4 uptake in astrocytes and T_3 release from these cells have not been identified. However, recent findings suggest that a member of the monocarboxylate transporter family, MCT8, is extremely important for neuronal T_3 uptake (15, 21). The *MCT8* gene is located on the X chromosome, and males with an inactivating *MCT8* mutation show a distinct phenotype of severe psychomotor retardation in combination with high serum T_3 levels (22–24). This syndrome is explained by the impaired neuronal T_3 uptake if MCT8 is inactivated, preventing T_3 access to its nuclear receptor as well as to D3 also present in these cells, with a consequent defect in neuronal T_3 action and metabolism (25).

The clinical features of patients with *MCT8* mutations dramatically underscore the crucial role of thyroid hormone in brain development. This has been known for a long time from the severe neurological deficits in subjects that have

Abbreviations: D1–D3, Deiodinases 1–3; ORD, outer ring deiodination. *Endocrinology* is published monthly by The Endocrine Society (<http://www.endo-society.org>), the foremost professional society serving the endocrine community.

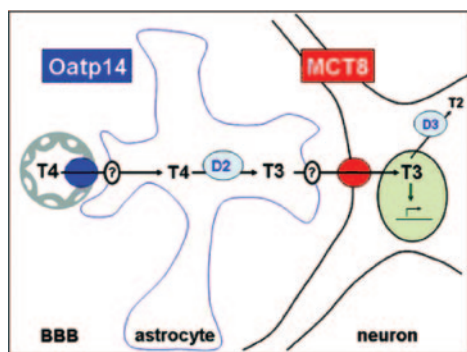


FIG. 1. A schematic model showing thyroid hormone trafficking in the brain. OATP1C1 (OATP14) in capillaries transports T_4 from blood into extracellular fluid in the CNS. T_4 then enters astrocytes by an as yet unknown transporter to be converted by D2 to bioactive T_3 . After release from these cells, T_3 is taken up via MCT8 by neurons, where it regulates gene expression and is finally inactivated by D3. BBB, Blood-brain barrier. Reproduced with permission from Heuer *et al.* (15).

been deprived of sufficient thyroid hormone supply during fetal and neonatal development (1, 2). In most Western societies, neonatal screening programs for congenital hypothyroidism have been established, which has led to an almost complete prevention of major neurological problems due to delayed T_4 substitution therapy of affected infants. In many developing countries, such neonatal screening programs have not been introduced. Another major problem is the endemic iodine deficiency that still exists in many areas around the world, especially in Africa (26). Iodine deficiency is the major preventable cause of mental retardation, and it is a great shame that still today the neurological development of millions of people is impaired because of insufficient iodine intake during the fetal and/or neonatal periods (26). Compared with these severe health problems, the negative effects of the mild iodine deficiency that exists in some Western countries as well as those of maternal hypothyroidism on the neurological development of the offspring are milder but significant (27, 28).

The group of Morreale de Escobar in Madrid has produced overwhelming scientific evidence showing the severe effects of thyroid hormone deprivation on brain development in rats (1, 2). These studies addressed the migration and differentiation of neurons in different brain areas to assess thyroid hormone-sensitive brain development. Dramatic effects have been documented of overt hypothyroidism and severe iodine deficiency at various stages of development, but significant deficits have also been reported for transient and mild thyroid hormone deficiency (1, 2). The paper published by the Madrid group in this issue of *Endocrinology* goes a long way to show tissue-specific responses of local T_4 and T_3 levels and deiodinase expression in rats exposed to varying degrees of iodine deficiency (29). Even in mild iodine deficiency, which may represent the situation in different Western societies, abnormal thyroid hormone levels were determined in different tissues. The main message of this study is that even mild iodine deficiency should be avoided, in particular during the fetal and neonatal periods.

During iodine deficiency, various adaptations take place regarding the sources of plasma and tissue T_3 . Thyroidal

production of T_4 decreases, whereas that of T_3 increases. A lesser degree of thyroglobulin iodination favors *de novo* production of T_3 at the expense of T_4 production. In addition, increased thyrocyte expression of D1 by TSH results in increased intrathyroidal T_4 to T_3 conversion and thus increased T_3 and decreased T_4 secretion. Prolonged iodine deficiency of course also results in goiter formation. These intrathyroidal adaptations contribute importantly to the maintenance of plasma T_3 at the expense of decreasing plasma T_4 with increasing iodine deficiency. In mild iodine deficiency, plasma T_3 may actually be increased.

Also in peripheral tissues, adaptations take place that affect local thyroid state. This is particularly true for tissues, such as the brain, which show an increase in D2 activity in response to the decrease in plasma T_4 (29). Apparently, this increased D2 activity not always fully compensates for the decrease in plasma T_4 because brain T_3 levels in iodine-deficient rats are lower than in iodine-sufficient rats. In other tissues, which derive their T_3 largely from plasma, T_3 levels are maintained even in moderate to severe iodine deficiency. Because T_3 is an important factor in the regulation of D1 expression, it is not surprising that hepatic D1 activities remain normal as long as plasma T_3 is normal (29).

The study of Pedraza *et al.* (29) also brings some surprises, especially regarding the regulation of adrenal and ovarian T_3 levels. With increasing iodine deficiency, the adrenals show a remarkable steep decrease in local T_3 levels, whereas T_3 levels in the ovaries are maintained well above control levels. The reasons for the extraordinary responses of adrenal and ovarian T_3 levels to iodine deficiency remain to be explained. Little is known about expression of deiodinases in these tissues.

Another remarkable finding in the Pedraza study (29) is the smaller increase in plasma TSH in iodine-deficient rats in comparison with that observed previously in T_4 -substituted thyroidectomized rats at comparable plasma T_4 levels. The main difference between the two situations is that plasma T_3 is much higher in the iodine-deficient than in the hypothyroid rats. Therefore, these data confirm that plasma T_3 exerts an important direct negative feedback action at the hypothalamic and/or hypophyseal level. However, the findings also confirm that plasma T_4 plays an important role in this respect through local conversion to T_3 in the hypothalamus and the anterior pituitary because plasma TSH increases reciprocally with the decrease in plasma T_4 at increasing iodine deficiency. It is common clinical knowledge that, in patients with primary thyroid disease and in subjects with insufficient iodine intake, plasma TSH shows a much better negative correlation with plasma (F) T_4 than with plasma T_3 . Also in the anterior pituitary, D2 is increased in hypothyroidism, which is not logical because it would dampen down the response of the thyrotrope to the decrease in plasma T_4 . However, the capacity for regulation of D2 by substrate-induced degradation of the enzyme appears to be limited in the thyrotrope so that it still responds with an increased TSH secretion when plasma T_4 is low (30).

Pedraza *et al.* (29) have studied the role of changes in tissue D1 and D2 expression in the regulation of local T_3 levels in iodine-deficient rats. No information is available about the role of D3 in the adaptation of tissues to a decrease in iodine

intake. It has become increasingly clear in recent years that D3 plays a prominent role in the regulation of local and systemic thyroid hormone levels, for instance during fetal and neonatal development and severe illness (10, 31). Because at least in brain D3 expression is dependent on thyroid state (6), changes in D3 activity may well contribute to differences in local T₃ levels between iodine-deficient and sufficient subjects.

The important message of the Madrid group is that sufficient iodine intake is required for optimal neurological development of the fetus and neonate. Recommended daily iodine intake amounts to 90 µg for infants (0–6 yr), 120 µg for children (6–12 yr), 150 µg for adults, and 200 µg for pregnant and lactating women (32). It is part of normal public health care to make sure that iodine intake meets these recommendations in particular for pregnant women and infants.

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References

- Morreale de Escobar G, Obregon MJ, Escobar del Rey F 2000 Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? *J Clin Endocrinol Metab* 85:3975–3987
- Morreale de Escobar G, Obregon MJ, Escobar del Rey F 2004 Role of thyroid hormone during early brain development. *Eur J Endocrinol* 151(Suppl 3):U25–U37
- Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR 2002 Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev* 23:38–89
- Visser TJ 1994 Role of sulfation in thyroid hormone metabolism. *Chem Biol Interact* 92:293–303
- Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR 2005 Type 2 iodothyronine deiodinase is the major source of plasma T₃ in euthyroid humans. *J Clin Invest* 115:2524–2533
- Bianco AC, Larsen PR 2005 Cellular and structural biology of the deiodinases. *Thyroid* 15:777–786
- Santini F, Pinchera A, Ceccarini G, Castagna M, Rosellini V, Mammoli C, Montanelli L, Zucchi V, Chopra IJ, Chiovato L 2001 Evidence for a role of the type III-iodothyronine deiodinase in the regulation of 3,5,3'-triiodothyronine content in the human central nervous system. *Eur J Endocrinol* 144:577–583
- Santini F, Vitti P, Chiovato L, Ceccarini G, Macchia M, Montanelli L, Gatti G, Rosellini V, Mammoli C, Martino E, Chopra IJ, Safer JD, Braverman LE, Pinchera A 2003 Role for inner ring deiodination preventing transcutaneous passage of thyroxine. *J Clin Endocrinol Metab* 88:2825–2830
- Richard K, Hume R, Kaptein E, Sanders JP, van Toor H, De Herder WW, den Hollander JC, Krenning EP, Visser TJ 1998 Ontogeny of iodothyronine deiodinases in human liver. *J Clin Endocrinol Metab* 83:2868–2874
- Kester MH, Martinez de Mena R, Obregon MJ, Marinkovic D, Howatson A, Visser TJ, Hume R, Morreale de Escobar G 2004 Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas. *J Clin Endocrinol Metab* 89:3117–3128
- Koopdonk-Kool JM, de Vijlder JJ, Veenboer GJ, Ris-Stalpers C, Kok JH, Vulsma T, Boer K, Visser TJ 1996 Type II and type III deiodinase activity in human placenta as a function of gestational age. *J Clin Endocrinol Metab* 81:2154–2158
- Galton VA 2005 The roles of the iodothyronine deiodinases in mammalian development. *Thyroid* 15:823–834
- Huang SA, Dorfman DM, Genest DR, Salvatore D, Larsen PR 2003 Type 3 iodothyronine deiodinase is highly expressed in the human uteroplacental unit and in fetal epithelium. *J Clin Endocrinol Metab* 88:1384–1388
- Bernal J 2005 Thyroid hormones and brain development. *Vitam Horm* 71:95–122
- Heuer H, Maier MK, Iden S, Mittag J, Friesema EC, Visser TJ, Bauer K 2005 The monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations. *Endocrinology* 146:1701–1706
- Bernal J 2005 The significance of thyroid hormone transporters in the brain. *Endocrinology* 146:1698–1700
- Hennemann G, Docter R, Friesema EC, de Jong M, Krenning EP, Visser TJ 2001 Plasma membrane transporter of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. *Endocr Rev* 22:451–476
- Robbins J, Lakshmanan M 1992 The movement of thyroid hormones in the central nervous system. *Acta Med Austriaca* 19(Suppl 1):21–25
- Pizzagalli F, Hagenbuch B, Stieger B, Klenk U, Folkers G, Meier PJ 2002 Identification of a novel human organic anion transporting polypeptide as a high affinity thyroxine transporter. *Mol Endocrinol* 16:2283–2296
- Sugiyama D, Kusuohara H, Taniguchi H, Ishikawa S, Nozaki Y, Aburatani H, Sugiyama Y 2003 Functional characterization of rat brain-specific organic anion transporter (Oatp14) at the blood-brain barrier: high affinity transporter for thyroxine. *J Biol Chem* 278:43489–43495
- Friesema EC, Ganguly S, Abdalla A, Manning Fox JE, Halestrap AP, Visser TJ 2003 Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. *J Biol Chem* 278:40128–40135
- Friesema EC, Grueters A, Biebrermann H, Krude H, von Moers A, Reeser M, Barrett TG, Mancilla EE, Svensson J, Kester MH, Kuiper GG, Balkassmi S, Uitterlinden AG, Koehle J, Rodien P, Halestrap AP, Visser TJ 2004 Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* 364:1435–1437
- Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S 2004 A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *Am J Hum Genet* 74:168–175
- Schwartz CE, May MM, Carpenter NJ, Rogers RC, Martin J, Bialer MG, Ward J, Sanabria J, Marsa S, Lewis JA, Echeverri R, Lubs HA, Voeller K, Simensen RJ, Stevenson RE 2005 Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. *Am J Hum Genet* 77:41–53
- Jansen J, Friesema EC, Milici C, Visser TJ 2005 Thyroid hormone transporters in health and disease. *Thyroid* 15:757–768
- De Benoist B, Andersson M, Egli I, Takkouche B, Allen H 2004 Iodine status worldwide. WHO database on iodine deficiency.
- Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 341:549–555
- Glinoe D 2004 The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. *Best Pract Res Clin Endocrinol Metab* 18:133–152
- Pedraza PE, Obregon M-J, Escobar-Morreale HF, Escobar del Rey F, Morreale de Escobar G 2006 Mechanisms of adaptation to iodine deficiency in rats: thyroid status is tissue specific. Its relevance for man. *Endocrinology* 147:2098–2108
- Christoffoleta M, Ribeiro R, Singru P, Fekete C, da Silva WS, Gordon DE, Huang SA, Crescenzi A, Harney JW, Ridgway EC, Larsen PR, Lechan RM, Bianco AC 2006 Atypical expression of type 2 iodothyronine deiodinase in thyrotrophs explains the thyroxine-mediated pituitary thyrotropin feedback mechanism. *Endocrinology* 147:1735–1743
- Peeters RP, van der Geyten S, Wouters PJ, Darras VM, van Toor H, Kaptein E, Visser TJ, Van den Berghe G 2005 Tissue thyroid hormone levels in critical illness. *J Clin Endocrinol Metab* 90:6498–6507
- 2001 Assessment of iodine deficiency disorders and monitoring their elimination. Geneva: WHO, UNICEF, ICCIDD; 1–107

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