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 T4 contains four iodine atoms, and the principal bioactive hormone T3 contains three iodine atoms. If iodine intake is sufficient, the normal human thyroid gland secretes predominantly T4 and only about 20% of daily T3 production (3). Most T3 is generated outside the thyroid gland by enzymatic outer ring deiodination (ORD) of T4 in different tissues. T4 and T3 are converted by inner ring deiodination to the receptor-inactive metabolites rT3 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 T3 from T4. Conversion of T4 to T3 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 rT3 (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 T3.

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 T3 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 T3 production in view of the large size of this tissue (5). The relative importance of skeletal muscle D2 for plasma T3 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 T3 at the transcriptional level (3). Conversely, D2 activity is under negative control of its substrates T4 and rT3, 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 T3 over T4 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 T4 represents the only source of fetal plasma T4 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 T4 (1, 2). The high D3 activities expressed in the fetoplacental unit are probably important to prevent premature exposure of growing tissues to bioactive T3, which induces cellular differentiation. Nevertheless, sufficient fetal plasma T4 accumulates to supply the brain with substrate for local T3 production (10).

A recent extensive study of fetal and neonatal human brain development has demonstrated region-specific temporary profiles of tissue T4, T3, and rT3 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 T3 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 T3 levels in the brain (14, 15). Neurons are thought to be the major target cells for T3 in the developing brain, and this T3 is supplied by neighboring astrocytes (14, 15).

Several steps are required to use plasma T4 and make it available as bioactive T3 to central neurons (Fig. 1). In addition to transfer of T4 at the choroid plexus from plasma to CSF and subsequently to periventricular cells, T4 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 T4 and expressed almost exclusively in brain capillaries, suggesting that it is important for T4 transport across the blood-brain barrier (19, 20).

Also the transporters involved in T4 uptake in astrocytes and T3 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 T3 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 T4 levels (22–24). This syndrome is explained by the impaired neuronal T3 uptake if MCT8 is inactivated, preventing T3 access to its nuclear receptor as well as to D3 also present in these cells, with a consequent defect in neuronal T3 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.
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 T4 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 T4 and T3 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 T3. Thyroidal production of T4 decreases, whereas that of T3 increases. A lesser degree of thyroglobulin iodination favors de novo production of T3 at the expense of T4 production. In addition, increased thyroidal expression of D1 by TSH results in increased intrathyroidal T4 to T3 conversion and thus increased T3 and decreased T4 secretion. Prolonged iodine deficiency of course also results in goiter formation. These intrathyroidal adaptations contribute importantly to the maintenance of plasma T3 at the expense of decreasing plasma T4 with increasing iodine deficiency. In mild iodine deficiency, plasma T3 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 T4 (29). Apparently, this increased D2 activity not always fully compensates for the decrease in plasma T4 because brain T3 levels in iodine-deficient rats are lower than in iodine-sufficient rats. In other tissues, which derive their T3 largely from plasma, T3 levels are maintained even in moderate to severe iodine deficiency. Because T3 is an important factor in the regulation of D1 expression, it is not surprising that hepatic D1 activities remain normal as long as plasma T3 is normal (29).

The study of Pedraza et al. (29) also brings some surprises, especially regarding the regulation of adrenal and ovarian T3 levels. With increasing iodine deficiency, the adrenals show a remarkable steep decrease in local T3 levels, whereas T3 levels in the ovaries are maintained well above control levels. The reasons for the extraordinary responses of adrenal and ovarian T3 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 T4-substituted thyroidectomized rats at comparable plasma T4 levels. The main difference between the two situations is that plasma T3 is much higher in the iodine-deficient than in the hypothyroid rats. Therefore, these data confirm that plasma T3 exerts an important direct negative feedback action at the hypothalamic and/or hypophyseal level. However, the findings also confirm that plasma T4 plays an important role in this respect through local conversion to T3 in the hypothalamus and the anterior pituitary because plasma TSH increases reciprocally with the decrease in plasma T4 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 (FT)4 than with plasma T3.

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 T4. 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 T4 is low (30).

Pedraza et al. (29) have studied the role of changes in tissue D1 and D2 expression in the regulation of local T3 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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