The Significance of Thyroid Hormone Transporters in the Brain

The developing brain is an important target of thyroid hormones. A complex regulatory network involving transfer of thyroid hormones through the brain barriers, interactions between neurons and glial cells, and deiodinase expression, works to deliver the appropriate amount of T₃ to the nuclear receptors. The data provided by Heuer et al. (1) in this issue indicates that specific thyroid hormone transporters may also be an essential part of this regulatory system.

Thyroid hormones influence brain development from about the end of the first trimester of fetal life. The human fetal brain expresses nuclear T₃ receptors at least from the 10th week of gestation, and receptor concentration increases 10-fold during the second trimester in brain and other tissues (2). T₄ is present in brain and other tissues, such as liver, kidney, and lung, but T₃ is detectable only in brain, at concentrations that result in an occupancy of brain T₃ receptors around 25%. The source of T₄ reaching the fetal brain up to midgestation is mostly of maternal origin (3). Both T₄ and T₃ cross the placenta and reach the fetal organs, but only T₄ appears to cross the fetal blood-brain barrier. Thus, the administration of T₃ by constant infusion to pregnant rat dams increased T₃ concentrations in all maternal and fetal tissues except the fetal brain (4). In contrast, the administration of T₄ increased T₃ content in fetal brain as well as in other tissues. There was also a very important difference between the brain and the rest of the tissues. When increasing amounts of T₄ were administered to pregnant dams maintained on methimazole, normal concentrations of T₃ in the fetal brain were kept over a much wider range of T₄ doses than in other tissues.

In adult rats, both T₄ and T₃ reach the brain from blood, but it was estimated that as much as 80% of the T₃ bound to the nuclear receptors was produced locally by type 2 deiodinase (D2) activity (5). As in fetal brain, when either T₄ or T₃ was administered to hypothyroid rats, the T₃ content of the brain was maintained within control values only by T₄, but not by T₃, infusion (6). Homeostasis of T₃ within the brain is maintained within narrow limits by a complex mechanism involving D2 and D3. Several years ago we reported that D2 was predominantly expressed in glial cells of two types, tanyctyes and astrocytes (7) (Fig. 1). Tanyctyes, in which expression of D2 was also reported by Tu et al. (8), are specialized ependymal cells lining the third ventricle and extending processes to the adjacent hypothalamus and the median eminence. The T₃ generated by these cells from cerebrospinal T₄ could play a role in TRH-TSH regulation. On the other hand, expression of D2 in the astrocytes suggested to us the existence of interplay between astrocytes and neurons on T₃ homeostasis similar to the metabolic coupling between the two cells concerning the glutamate-glutamine cycle or glucose use (9). Astrocytes would produce T₃ for neuronal use. As an additional control of neuronal T₃ concentration, D3, which degrades T₃ to the inactive metabolite diiodothyronine, is expressed in neurons. In this issue, Heuer et al. (1) confirm expression of D2 in the astrocytes and suggest important roles in T₃ homeostasis for recently characterized thyroid hormone transporters (Fig. 1).

The entry of thyroid hormones into the cells has for a long time been assumed to be by passive diffusion, because thyroid hormones are lipophilic molecules and as such could easily enter the membrane lipid bilayer. Experiments in vivo hardly gave any hint of a saturable process, as was, for example, the binding of T₃ to the nucleus, an observation that facilitated the discovery of nuclear receptors. However, in isolated hepatocytes and other cell types, the demonstration of relatively high-affinity sites for both T₄ and T₃, and the inhibition of cellular uptake by metabolic inhibitors, amino

Abbreviations: D2, Type 2 deiodinase; MCT, monocarboxylate anion transporters; OATP, organic anion-transporting polypeptides.

Endocrinology is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.
acids, and other chemicals, gave evidence for the physiological significance of thyroid hormone transporters (10). Several molecular entities have been identified as transporters for thyroid hormone (11). They belong to three main families: the organic anion transporting polypeptides (OATP), the L-amino acid transporters, and the monocarboxylate anion transporters (MCT).

Among the many members of the OATP family, human OATP-F (12) and rat Oatp14 (13) are preferentially expressed in the brain. The Oatp14 protein is localized in the border of brain capillary endothelial cells and in the choroid plexus. OATP-F/Oatp14 transports T₄ and rT₃ much more efficiently than T₃, and might be involved in the transport of T₄ through the blood-brain barrier and through the choroid plexus, and also in rT₃ clearance. The blood-brain barrier is the route by which thyroid hormone is preferentially distributed throughout the brain, and this transporter could facilitate uptake of T₄ by the astrocytes. Transfer of thyroid hormone through the choroid plexus achieves only limited diffusion to the brain parenchyma after passage to the cerebrospinal fluid but would allow uptake of T₃ by tanyocytes and subsequent T₃ generation in these cells.

The MCT family comprises up to 14 members, some of which are involved in the transport of important substrates for the brain such as lactate and pyruvate. MCT8 has been shown to act as a specific transporter for T₃ and T₄ and displays slightly higher affinity for T₃ (14). Heuer et al. (1) have also studied the regional expression of MCT8 mRNA. In addition to high expression levels in the choroid plexus, they found that MCT8 is expressed in neurons of the neocortex, hippocampus, basal ganglia, amygdala, hypothalamus, and the Purkinje cells of the cerebellum, all regions known to be sensitive to thyroid hormones (15). Expression of MCT8 in neurons suggests that neuronal uptake of the T₃ produced in astrocytes is facilitated by this transporter.

The physiological significance of MCT8 as a transporter for thyroid hormone is supported by the finding of mutations in humans by Dumitrescu et al. (16) and Friesema et al. (17). The syndrome affects children from an early age and consists of severe developmental delay and neurological damage together with an unusually altered pattern of thyroid hormone levels in blood. The patients presented low total and free T4, high total and free T₃, and low rT₃. TSH was moderately elevated in two of the patients and normal or slightly elevated in the other five. Inactivating mutations of the MCT8 transporter could result in the altered thyroid hormone levels. In vitro uptake of T₄ and T₃ by fibroblasts isolated from affected males was strongly reduced, and intracellular D2 was increased 6- to 8-fold (17). It is thus hypothesized that the resulting increase in intracellularly generated T₃ accumulates in blood because of its poor reuptake into cells. In addition, deficient uptake of T₄ and T₃ by neurons could reduce degradation by neuronal D3 to rT₃ and diiodothyronine, respectively, with increased T₃ and decreased rT₃. The brain and skin are predominant sites of D3 expression, but their contribution to T₃ degradation and to blood rT₃ is difficult to estimate (18).

The neurological syndrome caused by MCT8 mutations consists of developmental delays, rotary nystagmus, severe proximal hypotonia with poor head control, spastic quadriplegia, dystonic movements, and impaired gaze and hearing. More recently, a syndrome of paroxysmal dyskinesia has been recognized by Brockmann et al. (19) in the two patients originally described by Dumitrescu et al. (16). The whole clinical picture is so severe that it is pertinent to ask the question of whether the impaired uptake and action of thyroid hormone on neurons could cause such a syndrome. The neurological disorder of endemic cretinism (neurological cretinism) consists of variable degrees of neuromotor affection with proximal limb girdle spasticity and rigidity, more often affecting the lower extremities, extrapyramidal disorders of rigidity and bradykinesia, deaf-mutism, strabismus, dysarthria, and mental deficiency (20). Epidemiological and physiopathological considerations indicate that this syndrome is most probably a result of lack of thyroid hormone during fetal development, especially before midgestation. This is the period of neuroblast proliferation and maturation of the basal ganglia and cerebral cortex. In the postmortem examination of the maternal uncle of one of the patients, also affected males was strongly reduced, and intracellular D2 was increased 6- to 8-fold (17). It is thus hypothesized that the second trimester is also the period when thyroid hormone receptors increase in concentration in the brain. If MCT8 is needed at this stage of development for T₃ entry into neurons, mutations of the transporter could also interfere with T₃-dependent developmental processes. Knowledge of the ontogenetic patterns of MCT8 in the human fetal brain would certainly be helpful. On the other hand, there is also the possibility that MCT8 mutations interfere with transport of other substrates for brain metabolism that could be even more important than T₃ in determining the severity and outcome of the syndrome. Other members of the family transport metabolic substrates such as pyruvate and lactate, but MCT8 so far appears to be specific for iodothyronines (14).

Juan Bernal
Instituto de Investigaciones Biomedicas
28029 Madrid, Spain

Acknowledgments

Received February 2, 2005. Accepted February 4, 2005.
Address all correspondence and requests for reprints to: Prof. Juan Bernal, Instituto de Investigaciones Biomedicas, Arturo Duperier 4, 28029 Madrid, Spain.

References

studied in thyroidectomized rats infused with thyroxine or triiodothyronine.

Endocrinology 138:2559–2568


Bates JM, St Germain DL, Galton VA 1999 Expression profiles of the three iodothyronine deiodinases D1, D2, and D3, in the developing rat. Endocrinology 140:844–851


DeLong GR 1984 The effect of iodine deficiency on neuromuscular development. IDD Newslett 6:1–9

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