Crucial role for type II iodothyronine deiodinase in the metabolic coupling between glial cells and neurons during brain development

C Asteria

Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, University of Milan, Milan, Italy

(Received should be addressed to C Asteria, Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, University of Milan, Via F Sforza 35, I-20122 Milan, Italy)

Mammalian brain maturation and function are under the control of thyroid hormones which regulate and synchronize several developmental processes in the central nervous system (CNS), such as cell migration, neuronal differentiation, outgrowth of neuronal processes, acquisition of neuronal polarity, synaptogenesis and myelin formation. Moreover, thyroid hormones seem to be crucial for the cytoarchitecture of the neocortex and the cerebellum. In recent years it has been demonstrated that both the neurons and the oligodendrocytes are direct cellular targets of thyroid hormones during brain development. These cell types express thyroid hormone receptors which bind the active hormone 3,5,3'-triiodothyronine (T3), leading to the expression of specific neuronal genes. Therefore, T3 exerts an important role in the control of the timed coordination of different developmental events in the central nervous system, in large part by regulating gene expression and cell differentiation. As a consequence, it is not surprising that tightly controlled amounts of T3 are required during the critical period of construction of the neuronal network. In effect, thyroid hormone deficiency during this period leads to severe alterations in the anatomy and function of the brain (cretinism) if replacement therapy is not performed soon after birth.

Although thyroxine (T4) is about 8- to 10-fold more abundant than T3 in the thyroidal secretion, the latter is the active hormone accounting for most of the biological potency of the secretion. T3 present in the brain is essentially produced by partial deiodination of T4. This reaction is catalyzed by the type II iodothyronine 5'-deiodinase (5'D-II). This enzyme belongs to a new family of eukariotic selenoproteins recently identified and cloned (1–3). 5'D-II is able to catalyze deiodination of T4 exclusively on the phenolic ring to yield T3 and is highly expressed in rat brain, anterior pituitary, brown adipose tissue and in placenta. Croteau and coworkers have also demonstrated similar results in human tissues (2). Northern blot analysis revealed the presence of 5'D-II transcripts in fetal and adult brain, in heart, in skeletal muscles and in placenta.

The finding of elevated 5'D-II activity in the rat and human CNS provides evidence of the essential role of this enzyme in the brain in supplying adequate amounts of the active thyroid hormone, not only during adult life but especially during the developmental period of mammals (4–6). Indeed, the expression of 5'D-II activity in rat brain increases at the end of gestation and is highest at 15–20 days after birth. This pattern of activity corresponds to the period when the developing brain is most dependent on thyroid hormone and correlates with increasing T3 concentrations, which peak at 2 weeks of age (6). Another interesting finding is represented by the fact that 5'D-II activity serves to maintain an adequate T3 production in the brain not only in basal conditions but also in the face of limiting amounts of T4, as often occurs in the case of iodine deficiency. Indeed, it has been demonstrated that 5'D-II activity is markedly elevated in the hypothyroid state, thus protecting brain T3 concentrations from the decrease in circulating T4 levels (5). Another important factor that contributes to maintaining adequate T3 levels in the hypothyroid brain is the reduction of the type III iodothyronine 5-deiodinase (5'D-III), which has been considered an inactivating enzyme as it converts T4 and T3 to inactive metabolites (reverse T3 and 3,3',di-iodothyronine respectively) by 5-deiodination (3). As a consequence, the coordinate regulation of 5'D-II and 5'D-III activity at the brain level seems to be crucial for thyroid hormone homeostasis in this tissue. There is some evidence that T3 sulfate (T3S) could serve as a minor source of cerebral T3 during fetal life as well as in the hypothalamic state. Even though sulfation of the iodothyronines is designed to accelerate their deiodination by the type I iodothyronine 5'-deiodinase (5'D-I), thus facilitating thyroid hormone inactivation and degradation, several studies have demonstrated the presence of enzymes capable of desulfating T3S to active T3 in some human and rat tissues, including the fetal cerebral cortex, and therefore this mechanism could be of some importance for local T3 production (7, 8).

New evidence of the essential role of 5'D-II activity in brain maturation and function mediated by local T3 production during the developmental period arises from recent expression studies performed by Guadano-Ferraz et al. in the neonatal rat brain (9). These authors found that 5'D-II is expressed in areas of the brain, such as cerebral cortex, hippocampus, caudate and...
hypothalamus, which are known to express nuclear T₃ receptors and to be targets of thyroid hormone action during fetal development. These results might explain some phenotypic alterations observed in the brain of congenital hypothyroid rats, such as alterations in the cytoarchitecture of the cerebral cortex, or alterations in the expression of the RC3/neurogranin gene, whose protein product seems to be important in long-term memory. Cerebral cortical and basal ganglia abnormalities are also observed in human cretinism, where mental retardation and alterations of posture and movement are observed. Moreover, another interesting finding that may be relevant to the deafness observed in congenital hypothyroidism is the expression of 5D-II activity in auditory relay nuclei (medial geniculate, olivary and ventral cochlear nuclei), suggesting that these regions are also thyroid hormone responsive (9). This observation is also supported by recent studies performed by Forrest et al. (10) who demonstrated that mutant mice without a functional thyroid receptor beta, obtained by the gene knock-out technique, display defective maturation of auditory function.

As mentioned before, previous immunohistochemical studies have demonstrated that T₃ receptors are expressed only in neurons and oligodendrocytes, but not in astrocytes (11). Additional evidence accounting for the view that astrocytes are not target cells of thyroid hormone action is represented by the fact that the expression of astrocytic marker genes is not affected during perinatal hypothyroidism. Surprisingly, Guadán-Ferraz and collaborators have reported that 5D-II is primarily expressed in specific subpopulations of glial cells, encompassing the protoplasmic astrocytes and ependymal cells of the hypothalamus, termed tanycytes (9).

Astrocytes are important cell types in neural biology as astrocyte processes, surrounding capillaries, are able to participate in the transfer of nutrients between blood and neurons. For example, glucose is taken up from the blood by astrocytes, processed to lactate and then released for neuronal use. A similar mechanism of cooperation between astrocytes and neurons may be postulated for T₃ production. Due to its large circulating concentrations, T₄ rather than T₃ would be taken up from the capillaries by astrocytes which would then deiodinate T₄ to T₃. This T₃ would be available to enter neurons and interact with its receptors to control expression and function of target neuronal genes.

Another interesting finding is represented by the expression of 5D-II activity in tanycytes. These cells are implicated in the uptake and transport of hormones and other substances from the cerebral fluid and the blood into the hypothalamus. As a consequence, tanycytes may not only take up T₄ but may also convert T₄ to T₃, which can be used in various regions of the hypothalamus. Moreover, T₃ transport to the median eminence and the portal system could also influence pituitary function.

Taken together, these findings show that 5D-II activity is highly expressed in those areas of the brain which are more thyroid hormone responsive, thus confirming the crucial role of 5D-II in the brain in supplying T₃ during the critical period of neuronal differentiation. Moreover, these data suggest a unique and important role for glial cells in controlling thyroid hormone homeostasis in the developing brain. These cell types may also modulate neuronal and oligodendrocyte function through the production and release of T₃. As a consequence, it is conceivable that all the substances able to stimulate 5D-II activity in the glial cells, as demonstrated in vitro for adrenergic agents, may be relevant for brain development and function.

References