THYROID HORMONES IN BRAIN DEVELOPMENT AND FUNCTION

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ABSTRACT

Thyroid hormones are essential for normal brain development. They influence neurogenesis, neuronal and glial cell differentiation and migration, synaptogenesis, and myelination. Thyroid hormone deficiency may severely affect the brain during fetal and postnatal development, causing retarded maturation, intellectual deficits, and neurological impairment. Neural cells express the thyroid hormone nuclear receptors THRA and THRB, which mediate most actions of T3, the active hormone. Brain T3 derives in part from the circulation, and part from type-2 deiodinase-mediated 5'-deiodination of T4 in glial cells. Type 3 deiodinase inactivates T4 and T3 by 5-deiodination in neurons. Membrane transporters facilitate the passage of T4 and T3 across the brain barriers. The main transporters are the monocarboxylate transporter 8 (MCT8) and the organic anion transporter polypeptide 1C1 (OATP1C1). MCT8 facilitates T4 and T3 transport whereas OATP1C1 transports T4 but not T3. T3 regulates the expression of a large number of genes in the brain, mostly during developmental stages, but also in the adult. Rodent models of disease have provided most of our knowledge on thyroid hormone action in the brain. However, species-specific differences in brain maturation and organization make it difficult sometimes to extrapolate the data obtained in rodent models to the human. This review will present a summary of the main concepts developed from rodent studies, with a focus on the human brain.

INTRODUCTION

Thyroid hormones are crucial for brain development, and influence brain function throughout life. In adults, hypothyroidism causes lethargy, hyporeflexia, and poor motor coordination (1,2), is associated with bipolar affective disorders, depression, or loss of cognitive functions (3,4). Subclinical hypothyroidism is often associated with memory impairment. Conversely, hyperthyroidism causes hyperreflexia, irritability, and anxiety among other symptoms (5). Hypo- or hyperthyroidism can lead to mood disorders, dementia, confusion, and personality changes. Most of these disorders are usually reversible with proper treatment, indicating that adult-onset thyroid hormone alterations affect neural function but do not leave permanent structural defects.

The actions of thyroid hormones during mammalian brain maturation are qualitatively different. They influence many developmental processes, usually during limited time windows. They are required for the timely synchronization of independent events and facilitate the transition between fetal and postnatal stages (6,7), similarly to promoting amphibian metamorphosis (8,9). Thyroid hormone deficiency during critical transition periods may lead to irreversible brain damage, the consequences of

which depend on the severity and duration of the deficiency, and most importantly its time of onset (10-14).

Until recently, the rat was the most widely used animal model in the study of thyroid physiology and the actions of thyroid hormones in the brain. However, for more than 20 years, the mouse is the preferred animal model, and the use of knockout and knockin mice has facilitated our understanding. However, it is important to be aware of species specificities which make it difficult to extrapolate the results to the human situation. The timing of development in relation to birth among mammals presents substantial differences, even if the sequence of events might be similar (15-17). The web resource www.translatingtime.org (18) provides tools to compare neurodevelopmental time across species. As an approximation, the newborn rat may be compared with a second-trimester human fetus, and the maturation of a newborn human cerebral cortex to that of a 12-13-day old rat pup (19). For integrative reviews on molecular and evolutionary aspects of the cerebral cortex and cerebellar development and the effects of thyroid hormones see (20-23).

Whenever possible, this chapter focuses on observations in humans. Gene and protein notations follow the HUGO nomenclature (http://www.genenames.org): for human genes, names are in italics and in capital letters, protein names are written in non-italic capital letters irrespective of species.

STRUCTURAL DEFECTS CAUSED BY THYROID HORMONE DEFICIENCY

As an approach to understanding how thyroid hormones influence brain development, the changes caused by thyroid hormone deprivation are informative. In rats, perinatal hypothyroidism causes reduced myelination and diverse structural defects (for a classical review on this topic see (24). A reduction of the neuropil causes increased cell density in the cerebral cortex (25,26). Reduction in total cell numbers of regions with significant neurogenesis during the postnatal period, such as the olfactory bulb and the granular layers of the hippocampus and cerebellum (26-28). Transient structures show retarded disappearance. An important example is the subplate, a transient structure of the cortex involved in the organization of thalamic afferents to the cortex (29). In the cerebellum, regression of the external granular, or germinal layer, is retarded by a few days (30). The Cajal-Retzius cells, formed early during cortical development and involved in the regulation of the inside-out migration of neurons have delayed appearance (Fig. 1 left panel) (31). The GABAergic interneurons have altered distribution and connectivity, and the parvalbumin subclass is reduced in number (32-35). The maturation of several types of neurons is compromised, with stunted dendritic and/or axonal growth and maturation, for example cholinergic cells (36), cerebellar Purkinje cells (Fig. 1 central panel) (37,38), and cortex layer V pyramidal cells (39,40). Changes in dendritic spine number are also observed in the cortex and hippocampus after adult-onset hypothyroidism and are reversible with thyroxine treatment (41,42). Hypothyroidism also causes delayed and poor deposition of myelin (43-46) whereas hyperthyroidism accelerates myelination (47). After prolonged neonatal hypothyroidism, the number of myelinated axons in adult rats is abnormally low in hypothyroid animals although most of the myelinated axons appear to have a normal thickness of the myelin sheath (Fig. 1 right panel).

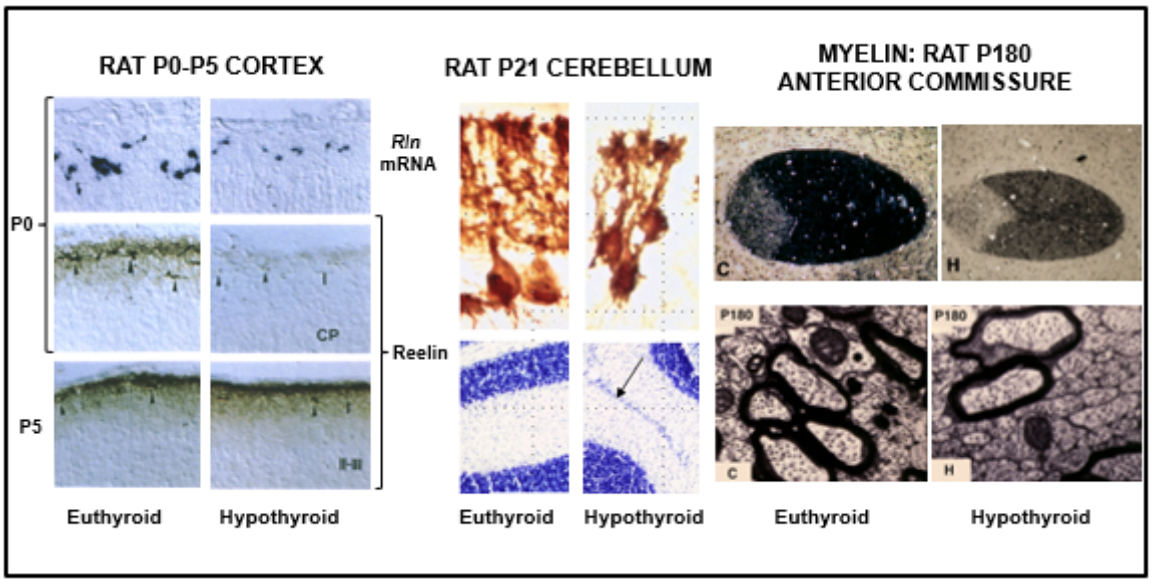

Fig. 1. Examples of the effects of hypothyroidism on developmental timing, cell differentiation, and cell migration. Left panel: In the cortical plate, hypothyroidism of fetal onset reduced the number of Cajal-Retzius cells, *Rln* mRNA (reelin), and reelin protein at P0. Normal amounts of reelin were present in the cortex at P5, indicating that thyroid hormones control the timing of *Rln* expression (from (31)). Central panel: Neonatal hypothyroidism causes arrested Purkinje cell differentiation (upper panels), and delayed disappearance of the external (germinal) granular layer due to delayed migration of granular cells. The right panel shows a permanent myelin deficit in hypothyroidism. Myelin staining of the anterior commissure of adult rats with fetal/neonatal-onset hypothyroidism and their respective euthyroid controls shows a thinner and paler commissure in the hypothyroid rats. Electron microscope imaging reveals that a higher proportion of axons of hypothyroid rats were of lower diameter and unmyelinated (from (48)).

Less information is available on *how* hypothyroidism affects the structure of the human brain. Post mortem examination in two cases of deficient thyroid hormone transport to the brain caused by MCT8 mutations revealed anatomical changes compatible with thyroid hormone deficiency (49) (Fig. 2): delayed maturation of the neocortex and cerebellum, delayed myelination, altered neuronal differentiation with lower expression of neurofilaments, and reduced synaptogenesis with reduced synaptophysin expression. Specific cellular changes included a reduced number of Cajal-Retzius cells and parvalbumin interneurons in the cortex. Cerebellar Purkinje cells had a normal morphology in contrast to the usual finding in hypothyroid rodents. These findings indicate that it is possible to extrapolate, but with caution, the brain lesions observed in hypothyroid rodents to humans.

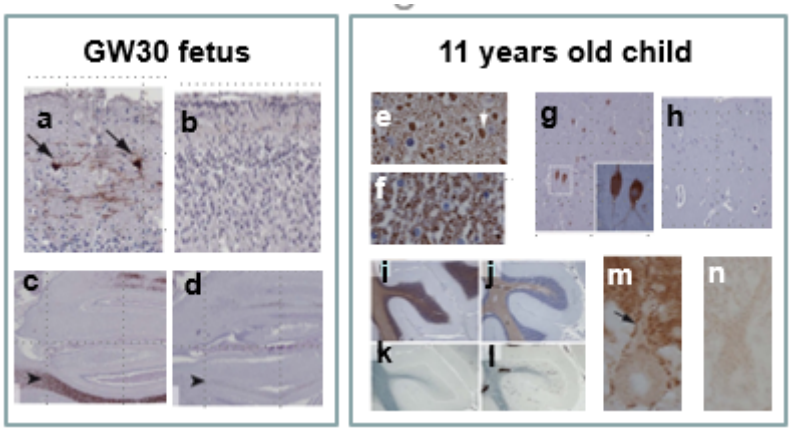

Fig. 2. MCT8 mutations cause anatomical changes compatible with cerebral hypothyroidism already during fetal stages. The left upper panels show staining of the cortex with neurofilament (brown color) in a control fetus (a) and a fetus with a MCT8 mutation (b). The normal cortex shows staining of Cajal-Retzius cells, which were absent in the MCT8 fetus. The left lower panels show staining of the cerebellum with anti-myelin basic protein. The normal fetus (c) shows immunoreactivity, which is not present in the MCT8 fetus (d). The right panels correspond to an 11-years old boy with MCT8 mutation (panels f, h, k l, n) and control of the same age (panels e, g, i, j, m). Panels e, f: cross-section of the pyramidal track stained with neurofilament; in the MCT8-mutated patient the axonal diameter is smaller than in the control. Panels g, h: staining of the cortex with anti-parvalbumin antibody shows that parvalbumin interneurons are present in the normal cortex but not in the MCT8 cortex. Panels i-l: cerebellar staining for myelin basic protein (i, j) and myelin (k, l). Panels m. n: cerebellar staining for synaptophysin showing the presence of synaptic boutons around the body of a Purkinje cell in the control (m) but not in the patient (n). Data from (49).

THYROID HORMONES IN THE DEVELOPING BRAIN

Maternal and Fetal Thyroid Hormones

The relative roles of the maternal and fetal thyroid hormones on brain development is a most important question. Fetal brain thyroid hormones depend on the transplacental passage of the maternal hormones and the onset of fetal thyroid function. In rodents, the onset of active fetal thyroid secretion occurs at E17.5, but thyroid hormones are present earlier in the embryos, a few days after implantation. This hormone is of maternal origin, as T4 and T3 cross the placenta (50-55). In normal rats at term, the maternal T4 accounts for about 17.5% of the total extra-thyroidal fetal thyroxine pool (56). However, in the fetal brain the concentrations of T4 and T3 are low before the onset of fetal thyroid function, and rapidly increase several-fold from E18 to E21 (57).

In humans, Vulsma et al. (58) demonstrated the transplacental passage of T4 by showing that in neonates with thyroid agenesis or a total organification defect, T4 was present in cord serum at 30-50% of the normal concentration. The only possible origin of this T4 was maternal. Transfer of T4 from the mother to the fetus protects the fetal brain in congenital hypothyroidism, preventing neurological damage before birth, and making it possible that early postnatal treatment is effective (59). The importance of maternal hormones becomes apparent in situations where protection does not take place. This occurs in the combined maternal and fetal

thyroid failure, as in feto-maternal PIT-1 deficiency (60), or presence of high titers of thyroid stimulation blocking antibodies (61). In these cases, mothers and neonates had extremely low thyroid hormones. The infants suffered profound developmental delays, permanent sensorineural deafness, and irreversible neuromotor impairment.

STUDIES IN RODENTS

If thyroid hormones from the mother offer protection to the brain in cases of fetal thyroid failure, one could then ask about the relevance of maternal thyroid hormones for brain development in the presence of a normal fetal thyroid gland, or before the gland becomes functional. If maternal thyroid hormones contribute to fetal brain development, then alterations of maternal thyroid physiology might have consequences on the fetal brain. A relevant question is whether the isolated failure of the mother's thyroid gland causes thyroid hormone deficiency in the fetal brain. Thyroidectomy in pregnant rats, a situation of maternal hypothyroidism with intact fetal thyroid, causes a reduction in the total extra-thyroidal T4 and T3 of the fetuses and developmental delays, but at E21 there was no reduction of T4 and T3 in the brain compared to fetuses from control dams (62). In these experiments, fetal thyroid activity compensated for any possible reduction of brain thyroid hormones caused by maternal thyroidectomy. More recent studies (63), confirmed that thyroidectomy of the dams did not alter the concentrations of T4 and T3 in the fetal cerebral cortex at E21, whereas dams treated with methyl-mercapto-imidazole (methimazole), which causes maternal and fetal hypothyroidism, had greatly reduced brain T4 and T3 concentrations. Microarray analysis of the fetal cerebral cortex successfully identified many genes with altered expression in the combined maternal and fetal hypothyroidism methimazole-induced model but with unchanged fetal expression in the offspring of thyroidectomized mothers. The conclusion emanating from the comparison of these two models is that fetal brain gene expression in the rat at term is under predominant control of the fetal thyroid gland.

In contrast to these studies, the offspring from rat dams thyroidectomized at day 16 of pregnancy showed altered cortical lamination and other structural defects when analyzed at P40 (29). The bulk microarray studies of the cortex might have failed to identify subtle, layer-specific changes of gene expression requiring time to transduce into structural alterations. Other studies support the effect of maternal thyroid hormones before the onset of fetal thyroid function. Transient maternal hypothyroidism of pregnant rats, from E12 to E15, caused the displacement of cells in the neocortex and hippocampus of the offspring, associated with audiogenic seizures when analyzed at 40 days of age, (64). Moderate thyroid hormone deficiency during pregnancy caused neuronal ectopias in the corpus callosum of the progeny (65). Thus, although the fetal thyroid gland exerts the main control on fetal brain development, there is experimental support for subtle actions of maternal thyroid hormone before the onset of fetal thyroid function. These actions do not have yet a correlate in terms of defined molecular events, and the possibility remains that they reflect indirect effects of systemic hypothyroidism rather than direct actions of the hormones on neural targets (66).

STUDIES IN HUMANS

Early studies on the human fetal thyroid gland development showed that colloid formation, iodide concentration, and synthesis of thyroglobulin and T4 could be demonstrated by the 11th week of gestation (67,68). Recent gene expression studies showed that the genes encoding thyroid transcription factors, thyroglobulin, thyroid peroxidase, and the TSH receptor are expressed already by week 7, and that the sodium-iodide symporter is strongly upregulated

by the 10th week (69). From the 11th week, serum total and free T4 and T3 increase with time (Fig 3) (70,71), and T4 reaches maternal concentrations by the 36th week (72). The increased T4 and T3 observed in Fig. 3 are clearly due to fetal thyroid gland activity, and it is uncertain to what extent the maternal hormones contribute to the fetal hormone pool in the presence of a normally active fetal thyroid gland. Supporting the contribution of maternal hormones in a situation of normality, its interruption might explain the relative hypothyroxinemia of premature babies (73). Early in gestation, T4 is present in low amounts in the coelomic fluid from the 5th-6th gestational weeks, and the amniotic fluid contains T4 and T3 from the 10th-12th week (74,75).

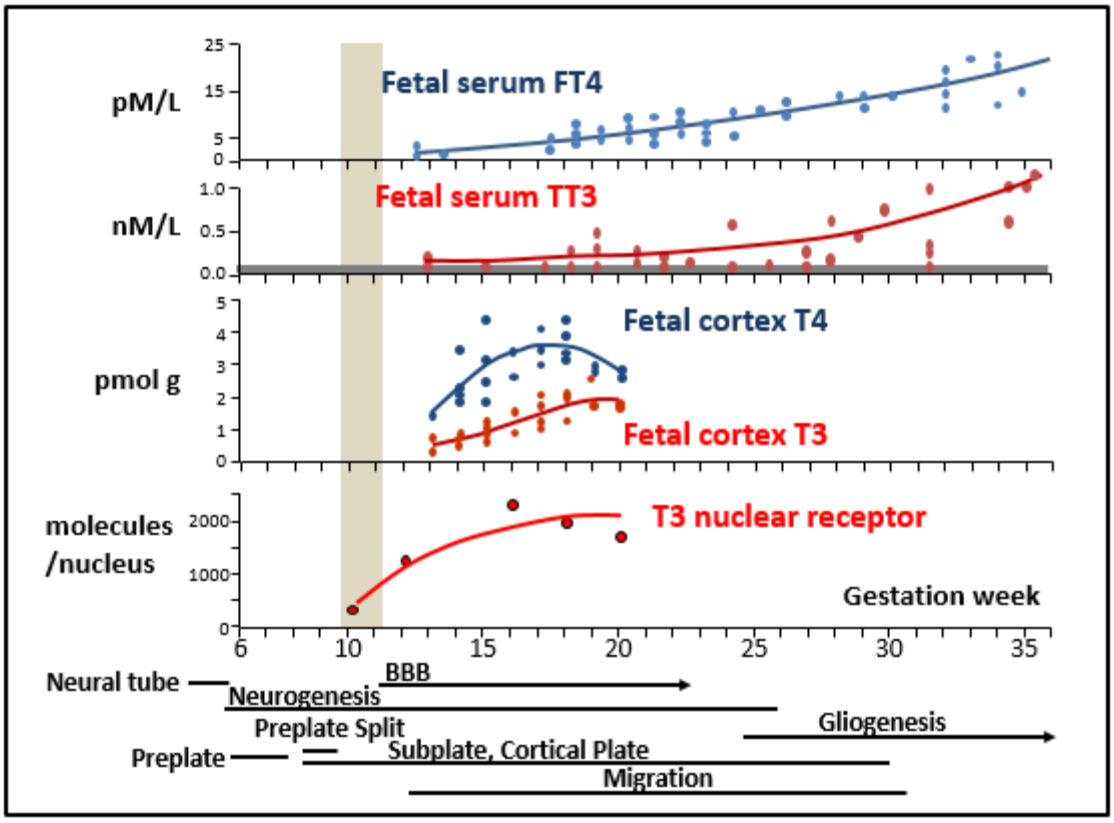

Fig. 3. Developmental events in the human fetal cortex and changes of thyroid hormone concentrations and nuclear receptor. The lower part of the figure shows the approximate timing of developmental events, the formation of the neural tube; the start of neurogenesis on GW5-5; the formation of the preplate, i.e. the formation of the first neurons, the Cajal-Retzius cells in the marginal zone, and the subplate cells; the preplate split, when the first projection neurons migrate and start filling the space between the Cajal-Retzius and the subplate cells, leading to the formation of the cortical plate; the appearance of tight junctions between vascular endothelial cells, and the blood-brain barrier (BBB), neuronal migration, and gliogenesis with the appearance of astroglial cells and oligodendrocytes. The vertical gray band marks the onset of thyroid gland function. Data on thyroid hormone concentrations in serum are from (71). Data on thyroid hormone concentrations in the cortex are from (76). Data on T3 nuclear receptor are from (77).

The recognition of the transplacental passage of thyroid hormones, described above, raised the question of the role of maternal T4 on fetal brain development (78). The implication is that maternal T4 exerts actions on the fetal brain before onset of the fetal thyroid gland, and even complements the fetal hormones after midgestation (79). Reports are indicating adverse effects of hypothyroxinemia on cognition and behavior of the progeny (80-82), or no effects (83). The issue is unsettled, mainly due to disparities in methodological approaches and the presence of compounding factors. Among these, the definition of hypothyroxinemia, the presence or not of hypothyroidism, iodine deficiency as the main cause of hypothyroxinemia (84), environmental pollutants, and indirect effects of hypothyroxinemia through complications of pregnancy (85-88). Clinical trials involving treatment of hypothyroxinemic pregnant women with T4 gave no clear answers yet (89-91).

Transport of Thyroid Hormones into the Brain

Other chapters of this book describe in detail the issue of thyroid hormone transport (92). This section contains only a few specificities concerning transport in the brain. The crucial role of transporters in the brain is to facilitate that T4 and T3 from the circulation cross the brain barriers (93-97). There are two main barriers in the mature brain: the blood-brain barrier (BBB) and the blood-cerebrospinal-spinal fluid barrier (98,99). The presence of tight junctions between endothelial vascular cells, or choroid plexus epithelial cells form barriers that hamper paracellular transport. Crossing these barriers requires transporters at the opposite sides of the plasma membrane facilitating the influx and efflux of the transported solutes. The gradient concentration of the free solutes determines the flux direction. The BBB surface is 5000-fold larger than that of the blood-CSF barrier (100). The larger exchange surface and the short distance of individual neurons from microvessels (8-20 μm (98)), makes the BBB the most relevant site of transport from the blood to the brain parenchyma.

Tight junctions between vascular endothelial cells, i.e., the BBB proper, are present in rodents by E15-E16 (101,102), and in humans by GW12 (99) (Fig. 3).

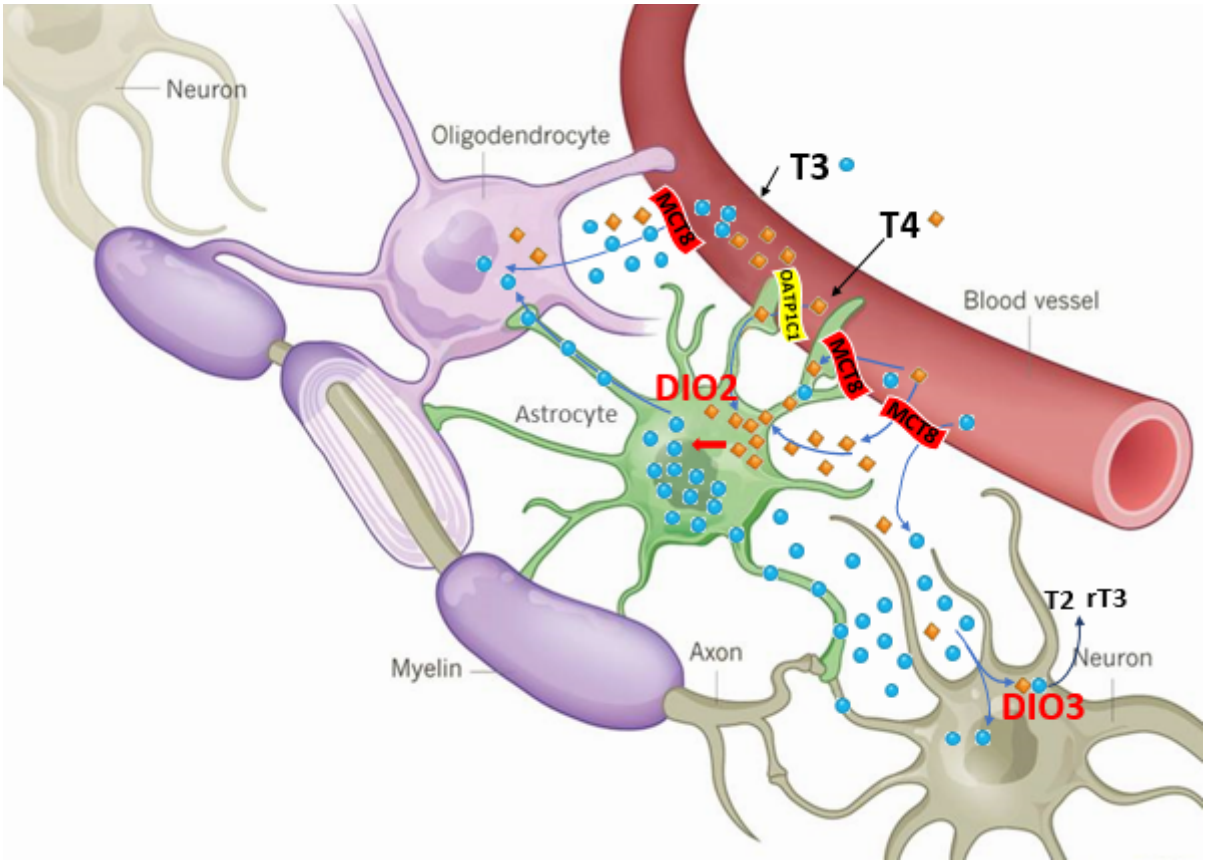

Fig. 4. Thyroid hormone transport and metabolism in the rodent brain. MCT8 in the blood-brain barrier facilitates the transport of circulating T4 and T3 to the brain parenchyma and OATP1C1 the transfer of T4. T4 in the astrocytes is converted to T3 by DIO2, providing additional T3 to nearby neural cells. DIO3 in neurons degrades T3 to T2 and T4 to rT3. Modified with permission from (103).

Further maturation and consolidation require the presence of pericytes and astrocytes in the vascular unit (104). Lopez-Espindola et al. (96) found immunoreactive MCT8 at GW12 in the human fetal brain endothelial cells, possibly highlighting the importance of MCT8-mediated transport at a time when the BBB starts limiting the entry of solutes to the brain. MCT8 was also present in other barriers such as the blood-cerebrospinal fluid barrier, the transient outer cerebrospinal fluid-brain barrier, and the ependymocytes. These findings suggest the presence of alternative routes by which T4 and T3 could reach the brain parenchyma in the fetus.

There is a fundamental difference between rodents and humans in the transport of thyroid hormones through the BBB. The rodent BBB contains MCT8 and OATP1C1 (Fig. 4). MCT8 transports T4 and T3 whereas OATP1C1 transports T4, reverse T3 (rT3), and T4 sulfate. In humans, as in other primates, the BBB contains MCT8 but lacks OATP1C1 (93,105). One explanation why MCT8 mutations cause profound neurological impairment in patients but not in mice is that T4 transport through OATP1C1 compensates similar mutations in mice by making T4 available as a DIO2 substrate. There is experimental

support for this mechanism as follows: *i*. MCT8-deficient mice lack neurological impairment (106), with only slight alterations of brain gene expression (107), contrary to what would be expected; *ii*. DIO2 activity and T3 generation increase in the brain of MCT8-deficient mice (108,109); and *iii*. To achieve cerebral hypothyroidism in mice, a compound deficiency of MCT8 and DIO2, or MCT8 and OATP1C1 is needed, i.e., a knockout of *Slc16a2* and *Dio2* or *Slc16a2* and *Slco1c1* (66,107,110,111).

Role of Deiodinases

The deiodinases present in the cerebrum are DIO2 and DIO3 (112). The adult mouse cerebellum also contains significant DIO1 activity (113). Different cells express *DIO2* and *DIO3* in the brain. Glial cells and some interneurons express *DIO2*, and excitatory neurons express *DIO3* (114-118). The glial cells expressing *DIO2* include radial glial cells, astrocytes, and tanycytes (Fig. 5) (114,116,118). *Dio2* expression occurs in most brain areas, and increase in hypothyroidism (Fig. 5). *Dio3* shows a restricted high expression at P0 in discrete nuclei, related to sexual differentiation of the brain, but the physiological relevance of this expression has not been studied (Fig. 5 (119)).

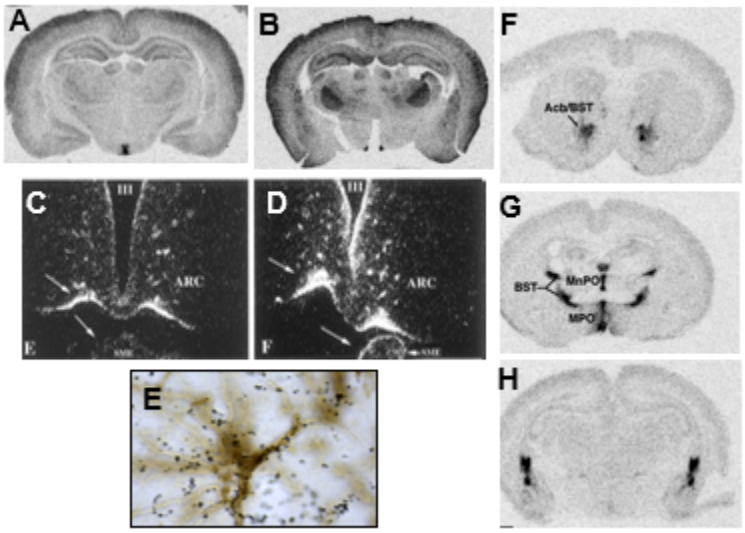

Fig. 5. *Dio2* and *Dio3* expression by *in situ* hybridization. Panels A, E, *Dio2*: in euthyroid rats (panel A) *Dio2* is distributed all over the brain especially in the upper layers of the cortex, the hippocampus, the thalamic ventromedial nucleus, with increased expression in hypothyroid rats (panel B). The median eminence, infundibulum, and walls of the 3rd ventricle show high expression in tanycytes, a specialized type of glial cells (panel C). *Dio2* increases in hypothyroidism also in this region (panel D). In the rest of the brain, *Dio2* is expressed in the astrocytes as shown in panel E after GFAP counterstaining of the *in situ* hybridization. Panels F-H; *Dio3* expression in the mouse at P0: Selective expression in the accumbens nucleus and the anterior pole of the bed nucleus of *stria terminalis* (Acb/BST, panel F), BST, median and medial preoptic nuclei (MnPO and MPO, panel G) and amygdala (panel H). Panels A, B, and E (114,115). Panels C and D are adapted from (116). Panels F,G,H are from (119).

Astrocytes, which exceed by ten-fold the number of neurons supply T3 to other neural cells by DIO2 deiodination of T4 (Fig. 3) (114,115,120). In rodents, the majority of astrocytes arise during the first postnatal week, and DIO2 expression and activity increase accordingly. Tanycytes are specialized glial cells lining the walls of the 3rd ventricle and the cause for the high hypothalamic DIO2 activity (121). Tanycytes in the median eminence form a blood-hypothalamus barrier, modulated in response to metabolic factors, which control the access of blood-borne substances to the arcuate nucleus (122). These cells are linked to the central control of feeding, body weight, and energy balance, and may act as stem cells to produce hypothalamic neurons (123). The hypothalamic paraventricular nucleus does not express *DIO2*, and T3 generated in astrocytes or tanycytes might control TRH production in this nucleus (114).

It is estimated that in *DIO2*-expressing tissues, such as the brain, brown adipose tissue, and pituitary, 50% or more of T3 derives from local T4 deiodination (124-127). In the adult rat brain, as much as 80% of nuclear-bound T3 is formed locally from T4 (128). Through *DIO2* and *DIO3* expression, the concentrations of T3 meet the local requirements of the particular developmental stage independently of fluctuations of circulating T3. Some discrete examples are the roles of *Dio3* (129) and *Dio2* (130) in the mouse cochlea with a peak of DIO2 activity on P7 before the onset of hearing, and the sequential expression of *Dio3* and *Dio2* in the control of retinal cone specification (131).

The balance between DIO2 and DIO3 activity during development is critical to ensure adequate amounts of T3 in neural tissue. Extremely high levels of *Dio3* expression and activity are present in the uterine implantation site, and later on in the uterine epithelium, preventing that inadequate amounts of T4 and T3 reach the embryos at early stages (132). By the end of pregnancy in the rat, DIO2 activity increases markedly in the fetal brain, in parallel with a 10-fold increase of T4 and 28-fold increase of T3 (133,134). The increase in DIO2 activity occurs after the start of gliogenesis and generation of astrocytes by E17 (135).

The fetal brain produces most T3 locally from circulating T4. Circulating T3 has poor access to the fetal brain. In a classical experiment, Morreale de Escobar and coworkers (136) showed that generation of T3 from T4 provides a means to regulate the concentrations of T3 within narrow limits (Fig. 6).

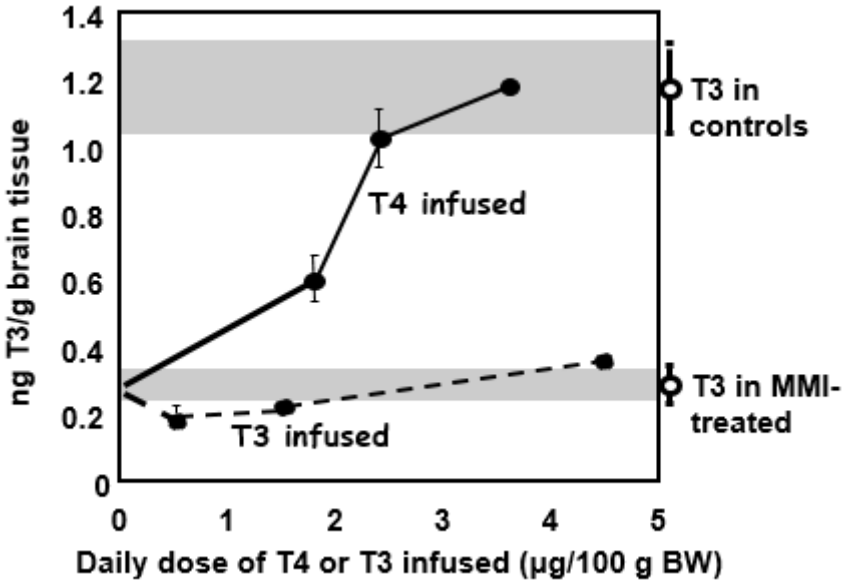

Fig. 6. T3 concentrations in the fetal brain after infusion of pregnant rats with increasing doses of T4 or T3. MMI-treated pregnant rats were infused with T4 or T3 using osmotic pumps from gestational day 15 through 21. The doses shown correspond to the starting dose on E15 and remained constant during the infusion period. Infusion of T4, but not T3, increased T3 in the brain. Data from (136).

In this experiment, they infused increasing doses of T4 or T3 to hypothyroid pregnant rats and then measured the resulting concentrations of T3 in the hypothyroid fetal brain. After T4 infusion to the mother, the fetal brain T3 concentration increased, reaching a normal concentration with a relatively low dose of T4. In contrast, it was difficult to increase T3 in the fetal brain after T3 infusion only over a wide dose range. DIO2-dependent generation of T3 in the fetal brain from maternal T4 also occurs in euthyroid pregnant mice. Administration of T3 to the mothers increased T3 in the fetal brain, not by direct transfer, but by stimulating *Dio2* gene expression and DIO2 activity (137).

The reason why the fetal rodent brain is not permeable to T3 is unknown. One possibility would be lack of expression of the T4 and T3 transporter MCT8, but the fetal brain expresses high concentrations of MCT8, even larger than in the postnatal period (138). One possible mechanism would be selective T3 degradation by DIO3 after crossing the brain barriers. Different cellular transport routes for T4 and T3 could be involved in the selectivity of this mechanism. Knocking out *Dio3* increases the sensitivity of the fetal and postnatal mouse brain to thyroid hormones (139-141).

STUDIES IN HUMANS

In the developing human cerebral cortex, DIO2 mRNA and activity are present already by GW7-GW8 (142). The relative expression of *DIO2* and *DIO3* is an important determinant of the T3 concentrations as development proceeds and has a strong regional component, as shown by Kester et al. (76) (Fig. 7).

Fig. 7. T3 concentrations in the fetal cortex and cerebellum respectively at different gestation weeks. Data extracted from (76).

These authors measured T4 and T3 concentrations and deiodinase activities in several brain regions from GW12-GW20 fetuses. The cerebral cortex had a progressive increase in T3 concentrations (Fig. 3), which correlated with an increased concentration of T4 and DIO2 activity. The parallel increase of T4 and DIO2 activity indicated an increased *DIO2* transcription since T4 inhibits DIO2 activity. DIO3 activity was very low, near the limit of detection. The cerebellum showed a completely different picture: T3 was very low, and D3 activity was the highest among all regions. The difference between the cortex and the cerebellum (Fig. 7) supports the notion that the relative expression of *DIO2* and *DIO3* regulate the tissue response to thyroid hormones during development.

These changes occur in parallel to the accumulation of the nuclear receptor (77), indicating an increased sensitivity of the cortex to thyroid hormones from GW12 onwards (Fig. 3). This occurs after the preplate split, i.e., when the first migrating neurons start the formation of the cortical plate overlapping the period of neurogenesis and cell migration. Gliogenesis and the generation of astrocytes, the main cells expressing DIO2, occur around GW25 in the cortex (143).

The cells expressing *DIO2* before astrocytes are formed are the radial glial cells (96,118), especially the outer radial glial cells (Fig. 8). This is most surprising because the outer radial glial cells, the universal stem cells of the cortex, are especially abundant in the cortex of primates, including humans. They are responsible for the enlargement of the subventricular zone and cortex expansion in these species (144). Furthermore, there is tightly correlated coexpression of *DIO2* and the T4 transporter *SLCO1C1* (OATP1C1) (Fig. 9) (118), indicating that the outer radial glia is the origin of the T3 formed locally in the human cortex at midgestation.

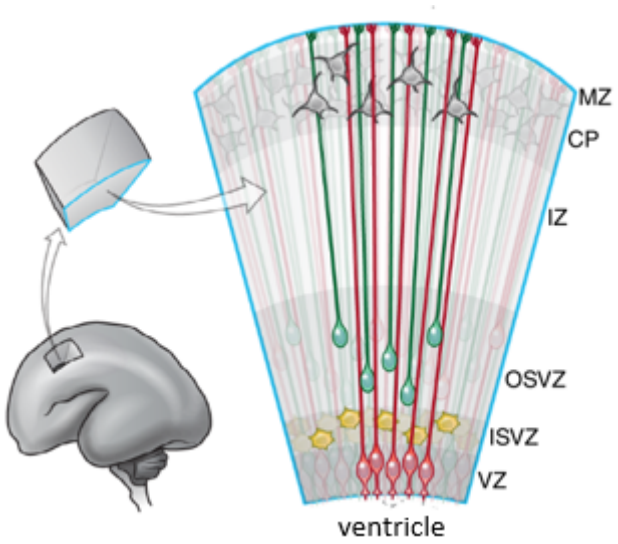

Fig. 8. A scheme representing a cross-section of the human fetal cerebral cortex at 18 -19 weeks of gestation. MZ, marginal zone; CP, cortical plate; IZ, intermediate zone; OSVZ, outer subventricular zone; ISVZ, inner subventricular zone; VZ, ventricular zone. In red, the ventricular or apical radial glia, with their bodies located in the ventricular zone, extending an apical process to the ventricular Surface and a basal process to the Surface of the brain. In green, the outer radial glia, lacking the apical process. Migrating neurons arriving at the cortical plate along the radial glial processes. In yellow, intermediate progenitors in the internal subventricular zone. Drawing reproduced with permission from (144).

The locally produced T3 could be involved in neurogenesis or could act on the newly formed neurons, which express *THRA* (145), or interneurons expressing *THRB* (118) to regulate their migration or terminal differentiation. T4 could reach the radial glia from the circulation. Alternatively, T4 could reach the apical processes of the ventricular radial glia by crossing the neuroepithelium from the inner CSF, or their basal processes from the outer CSF in the subarachnoid space (146). After the onset of gliogenesis, astrocytes express DIO2 (96,118). In contrast to the specific expression of *SLCO1C1*/OATP1C1, *SLC16A2*/MCT8 is widely expressed in most cell types (Fig. 9).

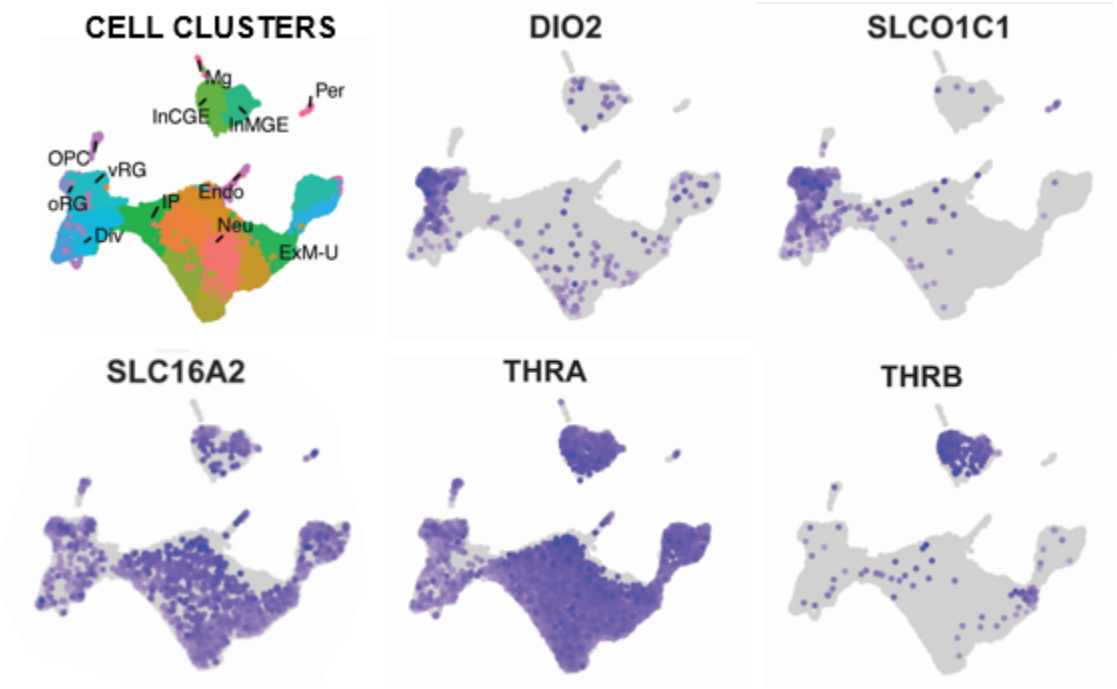

Fig. 9. Single-cell transcriptome profiling of *DIO2*, *SLCO1C1*, *SLC16A2*, *THRA*, and *THRB* expression (data from reference 118). In color are bulk cell clusters obtained using Uniform Manifold Approximation and Projection plots from the single-cell RNA sequencing datasets of human fetuses at gestational weeks 17–18 by Polioudakis et al. (147). Endo: endothelial cells, DIV: proliferating cells, ExM-U: excitatory neurons upper cortex enriched, InCGE: interneurons from the caudal ganglionic eminence, InMGE: interneurons from the medial ganglionic eminence, IP: intermediate progenitors, Mg: microglia, Neu: excitatory projection neurons, OPC: oligodendrocyte precursor cells, oRG: outer radial glial cells, Per: pericytes, vRG: ventricular radial glial cells. Blue dots represent single cells. DIO2 and SLCO1C1 coexpress in the outer radial glial cells. DIO2 is also expressed in some interneurons.

THYROID HORMONE RECEPTORS IN THE BRAIN

Flamant and coworkers have reviewed the relative roles of the receptor isoforms on developing and adult brain, using mouse genetic models (148,149). Two different genes *THRA* and *THRB* encode two receptor types, alpha (THRA1) and beta (THRB1 and THRB2), respectively. *THRA* also encodes THRA2, which does not bind T3 and is not a T3 receptor.

The cellular and regional complexity of the brain and its asynchronous maturation requires a previous understanding of the ontogeny and patterns of expression of the receptors to understand their physiological role. The low number of receptor molecules per nucleus, and the relative lack of specificity of receptor antibodies have precluded their use to analyze receptor expression by conventional immunohistochemistry. Analysis of the regional and cellular expression requires *in situ* hybridization histochemistry. This technique provides data on receptor mRNA expression that may not reflect accurately the concentration of the receptor protein (150,151).

Studies on receptor protein concentration used T3 binding assays in nuclei isolated from whole brain or brain regions, with a sensitivity of about 100-200 molecules/nucleus. Binding assays detect indistinctly the THRA1 and THRB subtypes, but discrimination between THRA1 and THRB may be possible to some extent using a combination of T3 binding and immunoprecipitation, or by competitive binding assays using the acetic acid derivative triac. THRA1 has the same affinity for triac as for T3, and THRB up to ten-fold higher affinity for triac than for T3 (152). Receptor expression studies have also used knock-in mice in which the receptor protein was tagged with green fluorescent protein (GFP) (145), or with hemagglutinin epitopes (151).

There are discrepancies between the cellular abundance of receptor-encoded mRNAs and the corresponding receptor proteins (150). At the mRNA level, all receptor isoforms are present in the brain. Apart from the highly abundant, non-receptor encoding, *Thra2* transcript, the predominant receptor isoform is *Thra1*, widely distributed in the CNS from E14 to adulthood (151,153-155). From E19 to P0, *Thra1* is present in the outer part of the cerebral cortex and hippocampal CA1 field. During the late fetal stage, *Thra1* is present in the piriform cortex, superior colliculus, pyramidal cell layer of the hippocampus, and the granular layer of the dentate gyrus. In adult rodents, *Thra1* expression is prominent in the cerebral cortex, cerebellum, hippocampus, striatum, and olfactory bulb. Knock-in mice studies with green fluorescent protein-tagged THRA1 (145) showed that most neurons express the THRA1-GFP as they become postmitotic in tanycytes of the third ventricle and very low expression in astrocytes. In the cerebellum, the conjugated protein was present in migrating granule cells of the molecular layer and mature granule cells of the internal granule cell layer but not in the proliferating cells of the external germinal layer (also known as the external granular layer). Juvenile, but not adult Purkinje cells expressed THRA1-GFP. In the study by Minakhina et al. (151) the hemagglutinin-tagged THRA1 protein was the predominant receptor subtype in the mouse brain, and THRA2 concentration was 5-10-fold higher.

In cultured cells T3 receptors are present in neurons, astrocytes, oligodendrocytes, sensory neurons, Schwann cells, and microglia (156-160). Primary cultures of mouse astrocytes, which respond transcriptionally to T3, express *Thra* and *Thrb* (7). Receptor-specific actions can be demonstrated on some genes such as *Dio3*, which is specific for *THRA1* (161-164). Some cells express specific receptor isoforms, for example, the mouse retina expresses *Thra1* widely whereas immature photoreceptor cells selectively express *Thrb1* (165,166).

Thrb1 expression during rodent development is low during the fetal period and increases during the postnatal period and through adulthood. Between E17 and E20, only low levels are present in the brain, especially in the hippocampal pyramidal layer. On P0, an increase occurs in the accumbens, striatum, and hippocampus. From around P7 *Thrb1* appears in the cerebral cortex. The patterns of expression of *Thra1* and *Thrb1* overlap (Fig. 10), but in some cells, one of the isoforms is predominant.

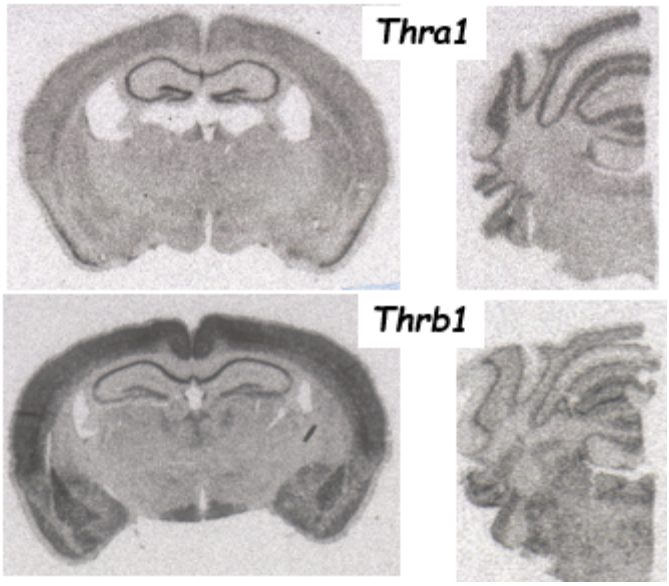

Fig. 10. T3 receptor mRNA expression in the mouse brain, by *in situ* hybridization with *Thra1* and *Thrb1*-specific probes. In the cerebrum (left panels) there is an overlapping distribution of both receptor subtypes, with some differences in the hippocampus, amygdala, and hypothalamus. In the cerebellum (right panels) *Thra1* is expressed in the granular layer (left upper panel), whereas *Thrb1* is expressed in the Purkinje cell layer.

As an example, in the cerebellum, differentiated granular cells express *Thra1* while Purkinje cells express *Thrb1*. *Thrb2*, which is abundant in the pituitary, is also expressed in the retina and the hypothalamus (166,167). During fetal stages, low levels of *Thrb2* are present in the striatum (153). The web resource of the Allan Brain Institute (https://celltypes.brain-map.org/rnaseq/mouse_ctx-hip_smart-seq) provides a tool to explore the specific distribution of *Thra1* and *Thrb* during mouse development.

Ontogeny of Thyroid Hormone Receptors in the Developing Brain

T3 binding assays detect the T3 receptor for the first time in the rat brain at E13.5-E14.5 and then increase, reaching stable concentrations from E17 to P0 (168). In close agreement, studies in knock-in mice expressing a conjugated TRα1-green fluorescent protein detect the receptor for the first time at E13.5 in the cortical plate (145). This date marks the onset of brain responsiveness to thyroid hormones (141). The receptor increases at birth and the highest concentrations are reached at P6 (169,170), but receptor occupancy is maximal at P15 (171).

In the human brain, the receptor protein quantified by nuclear binding assays, and receptor mRNAs by PCR, are detected during the first trimester (77,142,172). The receptor protein, with a binding profile typical of THRB, is present at low levels in the fetus around GW10 and increases in concentration 10-fold up to GW18-GW18 (77) (Fig. 3), during neurogenesis and neuron migration. At these stages, subsets of *CALB2* (calretinin) and *SST* (somatostatin) interneurons selectively express *THRB* (Fig. 9) (118), but its contribution to the total

receptor protein measured by binding assays is unknown.

Occupancy of receptors with the ligand in the brain antecedes the occupancy in other tissues. In the human brain, the T3 ligand is present from GW10, at concentrations enough to result in about 25% occupancy of receptor (77,173), and when no T3 is detected in other organs. As stated above, this is due to the early presence of DIO2 activity (76). A similar situation occurs in fetal lambs at gestational day 100. The brain had a 74% receptor occupancy compared with 10% in the liver and lung (174). In rats total receptor occupancy by the hormone increases in parallel with the postnatal increase in plasma and cytosol total and free T3, and reach a maximum of 50-60% at postnatal day 15 (171).

THYROID HORMONE ACTION ON BRAIN GENE EXPRESSION

Aporeceptor and Holoreceptor

Thyroid hormones regulate the expression of many genes in the rodent brain, mainly during the postnatal period, but the brain is also sensitive in the fetus and in adult animals (6,7,107,175-182). T3 interacting with the nuclear receptors, i.e., the holoreceptor, has a modulatory role on the receptor transcriptional activity, upregulating or downregulating gene expression. In the absence of the hormone, the aporeceptor has intrinsic transcriptional activity, relevant in events such as amphibian metamorphosis (183), PC12 cell differentiation (184) or development of the inner ear in mice (185). To some extent, the hypothyroid phenotype is the consequence of aporeceptor activity (30,186). Similarly, mutations of receptors that abolish T3 binding cause developmental abnormalities (166,187,188) (see the chapter on the syndromes of resistance to thyroid hormones).

Non-genomic Actions

It is unclear to what extent non-genomic actions might also mediate effects of T4 and T3 in the brain (189-191). Interaction of T4 with integrin $\alpha_v\beta_3$ might have a role in the expansion of progenitors in the neocortex (192). Proposed non-genomic actions of T3 include the maturation and plasticity of hippocampal pyramidal neurons (193), and the regulation of the onset and duration of the sensitive period of imprinting in chicks (194).

For many genes, the role of thyroid hormones during development is to regulate the timing of gene expression with a strong regional specificity, for example on the myelin genes (46) (see also Fig. 1). In the absence of DIO3, developmental expression of some T3 target genes is accelerated (141). The response of many target genes is region-dependent and shows partial overlap in different brain areas (9). Even within the same area, the same gene may be responsive only in a fraction of cells, as shown by *Nrgn* (RC3/neurogranin (175)). Transcription of thyroid hormone target genes is likely the result of the combinatorial activity of transcription factors, which include the T3 receptor whose relative weight may depend on the specific region and developmental period. It also reflects the diversity existing within apparently homogeneous cell classes.

Thyroid Hormone-Responsive Elements

Early studies showed the presence of thyroid hormone-responsive elements in the promoter or intronic regions of thyroid hormone-dependent brain genes. To name a few, the myelin basic protein (195); the Purkinje cell-specific gene PCP2 (196); the calmodulin-binding and PKC substrate RC3 (197); the prostaglandin D2 synthetase (198,199); the transcription factor Hairless (200); the neuronal cell adhesion molecule NCAM (201); and the early response gene NGFI-A (202). More recently,

Chromatin immunoprecipitation assays identified receptor binding sites in the developing mouse cerebellum (203) or cerebellar cell lines expressing THRA1 or THRB1 (162). Other targets are regulated at the levels of mRNA stability (acetylcholinesterase), protein translation (MAP2 (204)) or mRNA splicing (TAU (205)). Regulation of splicing might be due to a primary action on the transcription of splicing regulators (206).

Genes Responsive to Thyroid Hormones in the Fetal and Postnatal Rodent Brain

Thyroid hormone regulation of several genes occurs in the rodent fetal brain *in vivo* (207-209). In the fetal cerebral cortex at the end of gestation, thyroid hormone controls the expression of genes involved in the biogenesis of the cytoskeleton, cell migration, and branching of neurites. In some studies, a large percentage of the thyroid hormone-dependent genes were related to Camk4 signaling pathways (63,210). *Camk4* is regulated by T3 in cultured primary neurons (211,212), but is not in the postnatal rat brain *in vivo* (213). Results of extensive analysis by RNA-Seq of primary embryonal cerebrocortical cultures disclosed many thyroid hormone targets with roles during cortical development (6,20). The responsiveness of the fetal brain to thyroid hormones increases in *Dio3* knockout mice (139,141).

Many of the thyroid hormone-regulated genes identified during the postnatal period in the rodent brain are sensitive to the hormone only during a time window that spans the first 2-3 weeks after birth. Many of these genes are not dependent on thyroid hormone in the fetal or in the adult brain, possibly due to a DIO3-related mechanism (141). Chatonnet et al. (9), performed an analysis of the published data on thyroid hormone action on gene expression in the brain and cultured cells and arrived at a list of at least 37 genes consistently found in different studies as targets of the T3 receptors. Some of them are candidates for transcriptional regulation because they contain a thyroid hormone-responsive element. These genes include *Adamtsl4*, *Dbp*, *Fos*, *Hr*, *Kcna1*, *Klf9*, *Scd1*, *Stat5a*, and *Txnip*. Additional genes found regulated transcriptionally by T3 in several independent studies are *Shh*, *Hr*, *Dbp*, *Gbp3*, and *Nrgn*.

In our studies, employing RNA-Seq of primary cerebrocortical cells (6) we found that T3 up-or down-regulated up to 7.7% of expressed genes 24 hours after treatment. T3 was active in the presence of cycloheximide on about 30% of these genes indicating an effect on transcription. No response to T3 occurred in similar cells from *Thra* and *Thrb* knockout mice, as expected for receptor-mediated actions. Additionally, a large proportion of the T3-responsive genes in the presence of cycloheximide contained T3-responsive elements (162). The estimation is that T3 regulates around 2.5% of all expressed cellular genes and at least 1% at the transcriptional level through a T3 responsive element.

Brain deprivation of thyroid hormones caused by systemic hypothyroidism causes larger changes of gene expression than compound inactivation of the MCT8 and OATP1C1 transporters, or inactivation of MCT8 and DIO2. In the MCT8 plus OATP1C1 deficiency, the transport of T4 and T3 is severely compromised, resulting in isolated brain hypothyroidism with low tissue T4 and T3 (66). In the MCT8 plus DIO2 deficiency, the transport of T3 and the generation of local T3 from T4 are blocked, leading also to brain hypothyroidism buy with normal T4 and low T3. Contrary to what would be expected, the changes in gene expression are not equivalent in these two models of brain hypothyroidism, which are also different from systemic hypothyroidism. The latter causes altered expression of about the double number of genes in the cerebral cortex and the striatum than the cerebral hypothyroidism of the

double knockouts. One reason is that systemic hypothyroidism causes many effects on gene expression that are secondary to other actions of T3 elsewhere in the body. When transcriptionally-regulated genes were compared, similar profiles were found in the three conditions. In systemic hypothyroidism, among the transcriptional targets of T3, the most affected downregulated genes in the cortex were *Kcnj10*, *Hr*, *Ky*, *Cyp11a1*, *Nefm*, *Npt*, *Stac2*, *Hcrtr1*, *Shh*, *Prlr*, *Sema7a*, and upregulated, *Aldh1a3*, *Adamts18*, *Ntf3*, *Mc4r*, *Dio2*, *Trhr*. In the striatum, the most affected downregulated genes were *Prlr*, *Cyp11a1*, *Cnr1*, *Sema7a*, *Gls2*, *Shh*, *Igsf9*, *Enpp2*, *Gdf10*, *Arg2*, *Nefm*, and upregulated, *Cyp26b1*, *Syt10*, *Trhr*, *Mc4r*, *Dio2*, *Gabra5*.

Interactions with Glucocorticoids and Retinoids

The interactions of thyroid hormones with other hormonal systems (214) might be relevant to their actions on neural cells. In primary cerebrocortical cultures, one of the most significant processes regulated by T3 was the control of G-protein-coupled receptor activity (164), estimated to be important in the transition from fetal type to adult-type gene expression. A detailed analysis of these interactions is beyond the scope of this chapter, and only one example is mentioned related to the crosstalk with glucocorticoids and retinoid signaling pathways. T3 controls the expression of several enzymes involved in retinoic acid (RA) metabolism: the RA synthesizing enzymes ALDH1A1 and ALDH1A3, and the degrading enzyme CYP26B1 (9,163). The final effect on RA concentrations depends on the relative expression of each of the enzymes, which have developmental and regional variations, and on glucocorticoid signaling. *Aldh1a1* is upregulated by T3, preferentially through TRα1, and glucocorticoids potentiated the effect of T3. Additionally, T3 controls the expression of *Nr3c1*, the glucocorticoid receptor. *Aldh1a3* is downregulated by T3 in primary cells and increases in expression in hypothyroidism as indicated in the previous paragraph. On the other hand, *Cyp26b1* is upregulated by T3 in primary cells and is downregulated in the hypothyroid cortex but upregulated in the hypothyroid striatum. By increasing ALDH1A1, especially in the presence of glucocorticoids, T3 will increment RA concentrations, whereas acting on ALDH1A3 and CYP26B1, T3 will reduce RA concentrations. A recent study on *Dio3* knockout mice has found evidence for these interactions (141).

Actions on Gene Expression in the Adult Brain

In adult subjects, thyroid hormones influence mood and behavior, and thyroid dysfunction affects neurotransmitter systems (215) often leading to psychiatric disorders (216). High doses of T4 improve mood in bipolar depression (217,218). In the adult rat striatum, administration of a large single T3 dose leads to up-regulation of 149 genes and down-regulation of 88 genes (177). Physiological doses of T3 given for several days to hypothyroid animals led to up-regulation of 18 genes, and down-regulation of just one gene. Therefore, acute large doses of thyroid hormone cause large changes in gene expression, with more modest changes with lower doses. Some of the regulated genes are related to circadian rhythms and wakefulness, with one of them (*Dbp* or D-site binding protein) proposed as a candidate gene in bipolar disorders (219), and likely to be regulated directly by TRα1 (176). Many other genes were involved in striatal physiology as components of several signaling pathways. Fig. 11 shows a putative model of T3 action on the adult striatum.

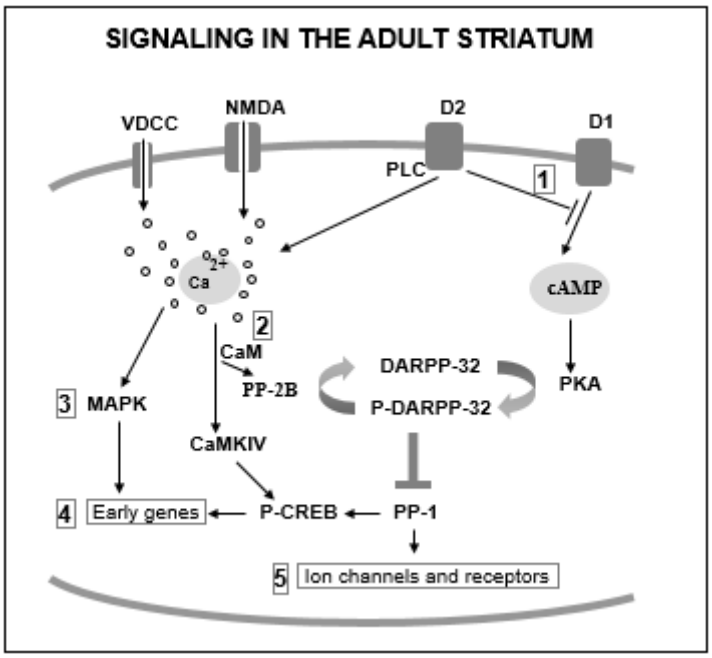

Fig. 11. Regulation of gene expression by thyroid hormones in the adult striatum. Signaling pathways are schematically represented and the main groups of regulated genes are shown in numerals. 1: G-protein coupled receptor signaling (*Cnr1*, *Rgs9*, *Rasd2, Rasgrp1*). 2: Ca2+/calmodulin pathway (*Nrgn*); MAPK pathways (*Map2k3*, *Fos*). 4: Early genes (*Nr4a1, Arc, Dusp1, Egr1, Homer*). 5: Ion channels (*Scn4b*). Abbreviations: VDCC, voltage-dependent sodium channels, NMDA, N-methyl-D-aspartate, D1 and D2, dopamine receptors 1 and 2. From (177).

ACTIONS OF THYROID HORMONES ON SPECIFIC DEVELOPMENTAL EVENTS

There are several possible approaches for studying the role of thyroid hormones on brain development. One way would be to analyze the effects of hypothyroidism and thyroid hormone treatment on the development of the cerebral cortex, the striatum, the cerebellum, the hippocampus, and other regions. Another way is to analyze common events occurring in the different brain regions, such as neurogenesis, cell migration, and differentiation, among others. In this review, we have opted for this second approach, with a focus on the T3 regulation of genes involved in these processes. Reviews on the cerebral cortex, and the cerebellum are available (20,21,23).

Neurogenesis

Generation of neurons, or neurogenesis, starts in humans around the fifth gestational week (GW5, Fig. 3), and in mice around embryonic day 10 (E10). The bulk of neurogenesis takes place until GW25 or E16/17 respectively, partially overlapping gliogenesis. The granular cell layers of the hippocampus, olfactory bulb, and cerebellum continue accumulating neurons postnatally, a reason why they are especially sensitive to thyroid function. At the onset of neurogenesis, the neuroepithelial cells sequentially express *Pax6*, *Neurog1/2*, and *NeuroD*, undergoing glutamatergic identity, and under the influence of FGF10 undergo a fast transition to radial glia (20,220). These cells remain attached by an apical process to the ventricular

surface and elongate as the embryonic brain epithelium thickens, adopting a bipolar morphology (Fig. 8). In the cortex, the elongated basal process reaches the pia providing a scaffold for cell migration (221,222). In addition to this structural and supportive function, the radial glia is the universal cortical stem cell that generates all neurons and glia, directly or through intermediate precursors. (220). In primates, enlargement of the cortex is due to the accumulation of a population of radial glial cells that lose the apical process and accumulate in the outer part of an enlarged subventricular zone (Fig. 8). Human-specific changes occur with further enlargement of the cortex over the great apes (223).

The role of thyroid hormones on proliferation and differentiation of neural precursors in the embryonic neurogenic areas has been shown during tadpole premetamorphosis (224) and concerning the effects of maternal thyroid hormones (192,225,226). *NeuroD*, mentioned above, is sensitive to thyroid hormones in the cerebellum (227), and *THRA1* mutations cause abnormal proliferation and adhesion of human cortical progenitors (228). Iodine deficiency in rats affects hippocampal radial glial cells (229). The first neurons originating in the cortex, the Cajal-Retzius cells, and the subplate cells, are sensitive to thyroid hormones in rodents and in humans (31,49,210).

Limited neurogenesis also occurs in the adult brain, related in humans to neuropsychiatric conditions, cognitive deficits, and depression. Adult neurogenesis takes place in two structures: the subventricular zone, located underneath the surface of the lateral ventricles, and the subgranular zone, adjacent to the granular layer of the hippocampal dentate gyrus. The subventricular zone generates olfactory bulb interneurons in adult rodents, and in humans provides new interneurons to the adjacent striatum (230). The subgranular zone generates dentate gyrus granular neurons in adult rodents and humans (231). Hypothyroidism and thyroid hormones influence neurogenesis in the rodent subventricular zone and subgranular zone (224,225,232-241).

Neural Cell Differentiation

Thyroid hormone controls the expression of many genes with roles on terminal cell differentiation, such as cell cycle regulators, cytoskeletal proteins, neurotrophins, and neurotrophin receptors, and extracellular matrix proteins. Among the cell cycle regulators, E2F1, p53, cyclins, and cyclin-dependent kinase inhibitors are regulated by thyroid hormone in cell culture (242-244).

Neural cell shape is determined by the cytoskeleton, which consists of microtubules (tubulin), microfilaments (actin), and intermediate filaments, specific for neurons (neurofilaments), glia (glial fibrillary acidic protein), or maturing cells (vimentin, nestin). Tubulins α1 and α2 are downregulated by thyroid hormone, and tubulin β4 is upregulated (245,246). Microtubule-associated proteins (MAPs) are also under thyroid hormone control at a posttranscriptional level. For example, thyroid hormone regulates Map2 protein distribution in the Purkinje cell dendritic tree (204), and conversion of immature forms of the microtubule-associated protein TAU (MAPT) to mature forms by alternative splicing of the *MAPT* mRNA (205). The neurofilament genes *Nefh*, and *Nefm* are also under thyroid hormone control in the fetal and postnatal cerebral cortex (63,107).

Astrocytes (247,248) cerebellar Golgi epithelial cells (249), and microglia (160) are thyroid hormone targets. Thyroid hormones influence the *in vivo* expression of astroglial genes encoding tenascin C, laminin, and L1 adhesion molecule, with effects on neuronal migration and differentiation, and axonal fasciculation (250-252) . *In vitro,* β-adrenergic receptor antagonists block the effect of T3 on

astrocyte differentiation (253). In another studies T3 upregulates *Arrb1* (arrestin beta1), facilitating endocytosis of β2 adrenergic receptor (ADRB2) and ERK activation (254).

The control of neurotrophin expression might mediate some of the effects of thyroid hormone on differentiation and survival. Interactions between thyroid hormone and NGF are important for the growth and maintenance of cholinergic neurons in the basal forebrain (36). Unliganded THRA1 in PC12 cells expressing *Thra1* blocks NGF-induced differentiation and the blockade is released by T3 (184), suggesting a possible mechanism for the control of differentiation timing. Changes in NGF, NTRK, P75NTR, BDNF, and NTF3 after hypothyroidism have been described (255-257).

Thyroid hormones influence myelination directly through effects on oligodendrocyte differentiation (258,259), and may also have indirect effects by stimulating axonal maturation, which is impaired in hypothyroidism (Fig. 1 right panel (260,261)). A lower axon diameter prevents reaching the critical size to become myelinated (262). Low axon diameter also occurred in a patient with MCT8 mutation (Fig. 3 (49)), which might contribute to the hypomyelination of these patients.

As thyroid hormones are required for terminal differentiation of oligodendroglial cells, they influence the expression of practically all myelin protein genes, but only during the myelination period. In the rat, this period extends from about the end of the first postnatal week up to the end of the first month, with a strong regional component in parallel with the wave of myelination (46,263). The control of myelin gene expression is transient, and in hypothyroidism, there is a developmental delay, but the effect on the myelin content is permanent (Fig. 1).

Early studies showed that T3 inhibits proliferation and promotes differentiation of oligodendrocyte precursor cells (OPC) (264,265) through repression of the E2F1 transcription factor (266). Transcriptomic analysis identified the universal T3-target gene *Klf9* (Krüppel-like factor 9) as a mediator of the effect of T3 on OPC differentiation (267). The transcriptional repressors NCoR and HDAC repress the oligodendrocyte differentiation pathway. T3 relieves this repression and induces *Sox10*, needed for the maintenance of the differentiated state (268). Oligodendrocyte precursor cells express *Thra1* and *Thrb* (269-271), but *Thra1* is the predominant receptor gene expressed in the newly formed and myelinating oligodendrocytes.

Neural Cell Migration

Thyroid hormone also influences neuronal migration in the cerebral cortex, hippocampus, and cerebellum. Thyroid hormone deficiency during cortical development leads to less than the normal definition of cortical layers (260,272,273). Thyroid hormone influences the maturation of the radial glia, the path along which radial migration occurs in the cerebral cortex and the hippocampus (229).

An important cellular target of thyroid hormone is the Cajal-Retzius cell. These cells are located in the marginal zone, the future cortex layer 1, and are required for proper migration of neurons in the cerebral cortex and the hippocampus, cortical lamination, and establishment of synaptic connections (274-276). These cells secrete reelin (RLN), an extracellular matrix protein under thyroid hormone control (31). RLN function is essential for the inside-out pattern of cerebral cortex development. The protein disabled (DAB), a component of the RLN signaling pathway is also under thyroid hormone control. The *Rln* and *Dab1* genes are not regulated by T3 at the transcriptional level, but other genes expressed in Cajal-Retzius cells are transcriptional

targets of T3 in primary neurons: these include *Rgs4*, *Npnt*, *Ephb6*, *Clstn2*, and *Dnmt3a* (6,20). Cajal-Retzius cells, therefore, appear to be important and selective cellular targets of thyroid hormones during development. Their number is low in perinatal hypothyroidism in rat pups (277), and in a human embryo with mutated MCT8 (49).

There are many extracellular matrix proteins regulated by thyroid hormones, with actions on cell migration and neuronal differentiation, synaptic plasticity, etc. The extracellular matrix proteins are heterogeneous, comprising laminin, fibronectin, collagen, neurotrophic factors, adhesion molecules, hyaluronan proteins, proteoglycans, and other components. As already mentioned, thyroid hormones regulate negatively tenascin C, laminin, and L1 (250-252), and the adhesion molecule NCAM (201,278). In addition to these proteins, regulated by T3 *in vivo*, T3 regulates many other genes of this heterogeneous group in cultured primary cerebrocortical cells (6) twenty-five of them at the transcriptional level. Among these, seven have thyroid hormone receptor responsive elements: *Adamts2*, *Lingo3*, *Mfap3l*, *Bmp1*, *Megf10*, *Nav2,* and *Crim1*. The function of these genes and the significance of their regulation has been discussed (20).

In the rodent cerebellum (279,280) thyroid hormones are involved in the late phase of granular cell migration from the external germinal layer (EGL) to the internal granular layer (IGL). This process takes place postnatally in rodents ending by P20 with the complete disappearance of the EGL. A characteristic feature of the hypothyroid cerebellum is a delay in the migration of granule cells and the persistence of the EGL beyond P20 (Fig. 1) (281). It is unclear how the absence of thyroid hormone interferes with granule cell migration. Cell migration in *Thra1* knock-out mice proceeds normally, and there is no effect of hypothyroidism (30). This suggests that the migration defect in hypothyroid mice represents a non-physiological action of the unliganded receptor. On the other hand, these cells express *Thra1* during the migration period (P7-P19) and not before (145), which might indicate an action of the receptor on granule cell maturation during migration. Several groups have described T3-regulated genes involved in different processes (9,163,282).

CONCLUSIONS

Thyroid hormone actions in the brain are extremely complex with a continuously changing landscape as development proceeds. Brain maturation involves continuous changes in cell composition, i.e., the target organ of thyroid hormone is under constant change. This is reflected in the changing regulated gene network. Genes that are transcriptional targets of T3 at a certain developmental time may be refractory at another time. The importance of thyroid hormone for the brain requires tightly controlled mechanisms of thyroid hormone delivery to the brain and cellular interactions in the metabolism of thyroid hormones, with crucial roles of DIO2 and DIO3 regulating the cellular concentration of T3.

Disruption of these mechanisms results in syndromes of profound neurological impairment. The challenge is to understand in detail the mechanisms of action of thyroid hormones at different stages of development in the human brain, and not merely extrapolating from rodent models, for a better understanding of thyroid hormone action defects.

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