REVIEW ARTICLE

Action of thyroid hormone in brain

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ABSTRACT. Among the most critical actions of thyroid hormone in man and other mammals are those exerted on brain development. Severe hypothyroidism during the neonatal period leads to structural alterations, including hypomyelination and defects of cell migration and differentiation, with long-lasting, irreversible effects on behavior and performance. A complex regulatory mechanism operates in brain involving regulation of the concentration of the active hormone, T_3, and the control of gene expression. Most brain T_3 is formed locally from its precursor, T_4, by the action of type II deiodinase which is expressed in glial cells, tanycytes, and astrocytes. Type III deiodinase (DIII) is also involved in the regulation of T_3 concentrations, especially during the embryonic and early post-natal periods. DIII is expressed in neurons and degrades T_4 and T_3 to inactive metabolites. The action of T_3 is mediated through nuclear receptors, which are expressed mainly in neurons. The receptors are ligand-modulated transcription factors, and a number of genes have been identified as regulated by thyroid hormone in brain. The regulated genes encode proteins of myelin, mitochondria, neurotrophins and their receptors, cytoskeleton, transcription factors, splicing regulators, cell matrix proteins, adhesion molecules, and proteins involved in intracellular signaling pathways. The role of thyroid hormone is to accelerate changes of gene expression that take place during development. Surprisingly, null-mutant mice for the T_3 receptors show almost no signs of central nervous system involvement, in contrast with the severe effects of hypothyroidism. The resolution of this paradox is essential to understand the role of thyroid hormone and its receptors in brain development and function.

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INTRODUCTION

Thyroid hormones[1] are critically involved in development and function of the central nervous system. In the adult human individual thyroid hormone deficiency or excess may lead to an extensive array of clinical manifestations, including neurologic and psychiatric symptoms (1, 2), which are usually reversible with proper treatment. During development, however, the prolonged deficiency of thyroid hormones usually leads to irreversible damage, the consequences of which depend on the specific timing of onset and duration of thyroid hormone deficiency. The purpose of this review is to examine mechanisms of thyroid hormone regulation during mammalian brain development. A number of reviews are available on different aspects of this topic (3-11).

Most knowledge of thyroid hormone action has been derived from the study of the effects of hypothyroidism on the neonatal rat. Although the sequence of developmental events is similar among mammals, the timing of development in relation to birth presents substantial differences. Detailed comparisons between the patterns of development of several species (3) are out of the scope of this chapter. Suffice to say that most brain growth occurs after birth in the human. Also the rat is born with an immature central nervous system but, com-

[1]In this paper, thyroid hormones refer to the product of the thyroid gland, T_4 (thyroxine, 3,5,3',5'-tetraiodo-L-thyronine) and T_3 (3,5,3'-triodo-L-thyronine). When used in singular, thyroid hormone refers to the active hormone, T_3, that binds to the nuclear receptors and initiates genomic actions.

Key-words: Astrocytes, cretinism, deiodinases, gene expression, hypothyroidism, hypothyroxinemia, iodine deficiency, neurons, prematurity, receptors, thyroxine, triiodothyronine.

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paratively, with a less developed thyroid axis than the human. As a useful reference, and concerning neurodevelopment, it has been pointed out that "the newborn rat may be compared with a human fetus in the second trimester of pregnancy and the newborn human baby to a 6-10-day-old rat" (7).

STRUCTURAL EFFECTS OF THYROID HORMONE ON BRAIN DEVELOPMENT

Neonatal hypothyroidism in the rat leads to an extensive array of structural alterations, previously reviewed in detail by Legrand (7). Thyroid hormone is involved in relatively late processes of cell migration and differentiation. These effects are better observed in the rat cerebellum, where neonatal hypothyroidism delays granule cell migration and severely arrests Purkinje cell differentiation. Granule cell precursors proliferate in the external germinal layer (EGL) and migrate post-natally to the inside of the cerebellum to form the internal granular layer (IGL). When migration is completed by P20, the EGL disappears completely. In hypothyroid rats, however, the EGL persists beyond P20.

Neuronal cell migration is also affected by hypothyroidism in other locations, such as the cerebral cortex and the hippocampus, although the effects are more subtle. In the neocortex, six layers are formed by a process known as "inside-out migration": cells generated in the ventricular layer migrate along the radial glia to the inner edge of the most superficial layer, layer I. Newly generated cells migrate also to the edge of layer I, where they stop migrating, displacing older cells back, so that layer VI is formed first (around E13 in the rat) and layer II is formed last (around E17). Layer I contains a special type of cells, the Cajal-Retzius neurons (12), which are influenced by thyroid hormone (13, 14). These cells produce a large extracellular protein known as reelin (15). Reelin is essential for the orderly migration and the establishment of neocortical layers and is under thyroid hormone control (see below). Deficiency of thyroid hormone during the period of cortical development causes alterations in the final structure of the neocortex, which displays a blurred layering and altered distribution of callosal connections (16-18).

The hypothyroid brain presents many structural defects in addition to those described above (7). A reduction in the neuropil causes increments in cell density. In regions with significant post-natal cell acquisitions, such as the olfactory bulb and the granular layers of the hippocampus and cerebellum, neonatal hypothyroidism is associated with lower cell numbers. Some cell populations display stunted dendritic and axonal growth and maturation (19, 20). This is most evident in the Purkinje cells of the cerebellum which show markedly reduced dendritic arborization (21). In the cerebral cortex the pyramidal cells of layer V have decreased number and altered distribution of dendritic spines along the apical dendrite (22, 23). Changes of dendritic spine number are also observed after adult-onset hypothyroidism, and are reversible with T_4 treatment (24, 25).

In addition to altered migration and differentiation of neurons, the hypothyroid brain is characterized by delayed and poor deposition of myelin (26), whereas hyperthyroidism accelerates myelination (27). The amount of myelin deposited in white matter areas is reduced and the final number of myelinated axons is lower than in normal animals. Although lower in number, most of the myelinated axons present in hypothyroid animals appear to have a normal thickness of the myelin sheath. Since maturation of axons is impaired in the hypothyroid animal (28) the myelination deficit might in part be due to a lower diameter of axons in hypothyroid animals, with normal myelination of those axons that reach a critical size (29).

Thyroid hormone receptors in brain

Thyroid hormone receptors (TR) are encoded by two genes, TRα and TRβ, located in different chromosomes (17 and 3, respectively, in humans). The TRα gene encodes three proteins that differ in their carboxyterminal, the receptor protein TRα1, and two variants TRvα2 and TRvα3, which do not bind T_3 and whose physiological role is unknown (30-32). The TRα gene also produces an orphan receptor known as Rev-ErbAα. The Rev-ErbAα gene partially overlaps the TRα gene and is transcribed from the opposite strand (33, 34). It has a role in cerebellar development (35). In addition, there are truncated protein products of the α gene known as $\triangle\alpha$1 and $\triangle\alpha$2, of unknown function (36). The TRβ gene produces amino-terminal protein variants: the two classical receptors, TRβ1 and TRβ2, and two newly identified proteins, TRβ3 and $\triangle$TRβ3 (37). The receptors have T_3-dependent and T_3-independent actions. In the absence of T_3 they usually act as transcriptional repressors (38), but they can also activate gene expression, especially the TRβ2 isoform (39, 40).

Receptor ontogeny

In the rat fetus the T_3 receptor can be detected at low concentrations by E13.5-E14, several days before onset of thyroid gland function. It increases later on and reaches a maximum on post-natal day 6

(41-43). Total brain receptor occupancy by the hormone increased in parallel with plasma and cytosol total and free T_3 with a maximum of 50-60% on post-natal day 15 (44).
In the human brain, the T_3 receptor, measured by binding assays, is present at relatively low levels in the fetal brain around the 10th week post-conception (45). Receptor mRNAs are also detected during the first trimester (46). Receptor concentration in the brain increases 10-fold during the second trimester, in coincidence with a period of active neuroblast proliferation (47). The ligand, T_3, is measurable in brain from at least the 10th week of gestation, in contrast with other organs, such as liver and lung, where even at 18 weeks only T_4 is present (48). Thus a selective accumulation of T_3 in fetal brain occurs in presence of low fetal thyroid activity and low or undetectable T_3 concentrations in serum and other tissues (49). This is also observed in fetal lambs, where receptor occupancy in brain reaches 60% at a time when the occupancy of liver or lung receptors is only 10%. The early high occupancy of brain receptors may be due to early local expression of type II deiodinase or to active concentration of T_3 into the brain (50-52).
The presence of receptors in neural tissue at early stages of development suggests that the fetal brain is a target of thyroid hormone, even before onset of fetal thyroid gland function. Maternal hormone might influence gene expression in the fetus. Evidence that maternal hypothyroidism influences gene expression in the rat fetal brain has been recently provided (53).

Distribution of T_3 receptor mRNAs in brain

In the rat, TRα1 and the α2 variant, can be detected at low concentrations as early as E11.5 in the neural tube, with an increase at E12.5 (54). Also in the chicken, TRα can be detected as early as E5 but it is more evident at E9, mainly in the cerebellum (55). By E14, when the receptor protein is first detected, the predominant isoform is TRα1, which is present in neocortex, piriform cortex, hippocampus, and superior colliculus. In adult rats TRα1 is expressed in cerebral cortex, pyramidal and granular layers of the hippocampus, striatum, granular layer of the cerebellum and olfactory bulb (54, 56). TRβ1 expression is mainly post-natal. During fetal development low levels of this isoform are found in the neuroepithelium, the germinal trigone, which provides cells for the granular layers of the cerebellum, and the pyramidal cells of the hippocampal CA1 field. The first day after birth there is a rapid increase in the striatum and in the CA1 region. From P7 through adult age it is expressed in the cerebral cortex, and it is undetectable in the cerebellum. TRβ2 mRNA, originally thought to be pituitary specific is present at low levels in the rostral caudate, hippocampus, and hypothalamus, during the fetal period (54), although the protein can be detected by immunohistochemistry in the nuclei of neurons throughout the brain (57).
The distribution of T_3 receptor mRNAs *in vivo* by *in situ* hybridization or immunohistochemistry suggests a predominant neuronal expression. However, T_3 receptors have been detected also in cultured astrocytes and oligodendrocytes (58, 59). The number of binding sites in astrocytes was much lower than in neurons or oligodendrocytes. Studies *in vivo* have shown that TR isoforms colocalize with oligodendrocyte markers but not with astrocytic markers (60) and other studies have demonstrated that in primary culture, rat astrocytes do not express T_3 receptor, but only the TRα2 isoform (61, 62). The combined evidence therefore suggests that TRs are present predominantly in neurons and oligodendrocytes but it is difficult to completely discard the presence of significant amounts of receptor in astrocytes which could perhaps be involved in regulation of specific gene subsets.

THYROID HORMONES IN BRAIN

Origin of fetal thyroid hormones

In the rat, onset of fetal thyroid gland function takes place between days 17 and 18 post-conception (63). However thyroid hormones of maternal origin are present in the rat embryos as early as 3 days after implantation (64-68). During fetal development the proportion of hormone available to the fetus that originates in the fetal gland increases and that of maternal origin decreases, but before parturition maternal T_4 still accounts for about 17.5% of fetal extrathyroidal thyroxine pool (69). At the end of gestation, and despite low fetal serum levels, the concentrations of iodothyronines in the fetal brain reach about 50% of maternal brain concentrations.
In the human, despite early evidence for transplacental passage of thyroid hormone (70, 71), it was not widely accepted until the conclusive data from Vulsma *et al.* (72). These authors found T4 concentrations of the order of 50-70 nM, *i.e.*, 50-70% of normal values, in the cord blood of neonates unable to synthesize thyroid hormones because of an organification defect or thyroid dysgenesia. After parturition T_4 disappeared from the neonate's plasma with rate equal to its half-life, demonstrating that thyroid hormone was not formed in the fetus or newborn. T_4 is found in the coelomic fluid bathing

the yolk sack, as early as 6 gestational weeks (73) and its concentration is positively correlated to maternal circulating T_4.

Transport of thyroid hormone to the brain

The passage of substances from the blood to the brain is restricted by the blood-brain barrier and the blood-cerebrospinal fluid (CSF) barrier (74). The blood-brain barrier consists of three layers formed by the endothelial cells of brain capillaries, the basal lamina, and the astrocytic end feet which surround the capillaries. The blood-CSF barrier is formed by the epithelial cells lining the ventricular side of the choroid plexus. The bulk of hormone reaches the brain parenchima directly from the blood through the capillaries. The fraction of hormone transported through the choroid plexus and the CSF has been estimated to be around 20% (75). The passage from the CSF to the brain is limited, since T_4 injected directed into the CSF mainly reaches the median eminence (76, 77).

Concerning the mechanism of thyroid hormone passage through the choroid plexus it was suggested that transthyretin (TTR) plays an important role in T_4 transport (78, 79). TTR, a serum T_4 transport protein, is produced in the choroid plexus, in addition to the liver, and is the major protein of the CSF in many species. *In vitro* studies (80) suggested that TTR would either transfer T_4 from the epithelial cells, where the protein is synthesized, to the CSF, or facilitate its passage by binding T_4 once the protein is in the CSF. Against this hypothesis, the T_4 transfer rate from plasma to tissue compartments, including the brain, is normal in transthyretin null-mutant mice (81, 82).

EXPRESSION AND REGIONAL DISTRIBUTION OF DEIODINASES

Role of deiodinases

Deiodinases play an essential role in the local control of brain T_3, through mechanisms that operate under a variety of situations to keep T_3 concentrations under a narrow range. In contrast to the liver and kidney, where most T_3 derive from the plasma, more than 50% of brain T_3 derives from local deiodination of T_4 (83, 84). In the adult rat brain as much as 80% of nuclear bound T_3 is formed locally from T_4 (85).

Deiodinases (D) are seleno-proteins that catalyze the removal of iodine atoms from iodoaminoacids (86-89). There are three types, DI, DII, and DIII, which have been cloned (52, 90-92). DI and DII remove the iodine atom in the 5' position of the phenolic ring to give T_3 from T_4, thereby "activating" T_4. DIII produces rT_3 from T_4, and T_2 (3,3' diiodothyronine) from T_3, after removal of the iodine in position 5 of the tyrosil ring, thereby inactivating T_4 and T_3. Sulfation of iodothyronines also facilitates their degradation by DI (50). Deiodinase activity is regulated by nutritional factors and the thyroidal state such that DII increases in hypothyroidism whereas DI and DIII decrease in hypothyroidism and increase in hyperthyroidism (93-95). The predominant deiodinases expressed in brain are DII and DIII. The selenoprotein nature of DII has been recently questioned by Leonard *et al.* who have isolated a 29-kDa (p29) non-selenoprotein, highly homologous to Dickkopf proteins (96) claimed to be a T_4-binding subunit of DII (97). In spite of this, the selenoprotein nature of the enzyme cloned by Croteau *et al.* (52) is consistent with the finding of SECIS elements[2] in the human and mouse genes (89, 92). Null mutant mice lacking the DII selenoprotein have been recently generated (98).

Deiodinase type II expression

DII activity is detectable in the brain of the rat fetus and increases markedly by the end of pregnancy to reach adult levels (99, 100). This increased DII activity is apparently responsible for the 18-fold increase of brain T_3 during the same period (99). At the cellular level DII has the highest expression in the tanycytes, a specialized type of glial cells (101, 102). These cells line the walls of the lower third and the floor of the third ventricle and extend long processes to the adjacent hypothalamus and the median eminence (103). Within these locations, the tanycyte processes end in capillaries and axon terminals. The high expression of DII in tanycytes closely agree with studies on the regional distribution of DII activity in brain (104) which showed 3-4 times more activity in punches from the arquate nucleus-median eminence than in the neocortex. Expression of DII in the tanycytes suggests that these cells are involved in the uptake of T_4 from the capillaries of the median eminence and basal hypothalamus and/or from the CSF, and its subsequent conversion to T_3.

Throughout the brain DII is mainly expressed in glial cells, *i.e.* astrocytes (101), although in hypothyroid rats, DII can also be found in interneurons, especially in the cortical barrel fields (105). Astrocytes could be involved in the uptake of T_4 from the capillaries and the formation of T_3 for neuronal use, in a cooperation which is reminiscent of other forms of metabolic coupling between glia and neurons (106).

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[2]SECIS (selenocystein insertion sequence) elements are untraslated nucleotide sequences present in selenoprotein-encoding mRNAs that convert the termination codon UGA into a selenocystein codon.

A similar situation takes place in the cochlea, where DII is present in the connective tissue (107) whereas the T_3 receptor is expressed in the sensory epithelium and spiral ganglion (107-109).

Deiodinase type III expression

DIII activity is highest in placenta and in fetal tissues and its activity decreases after birth, in contrast to DI and DII (100, 110, 111). In the human placenta, the activity of DIII is 200 times higher than that of DII at all gestational ages (112, 113). In the adult rat, DIII expression is limited to the skin, brain and uterus. DIII activity may be induced in cultured astrocytes (114, 115) but *in vivo* the DIII mRNA is present in neurons (116, 117).

DIII plays an important role in the control of T_3 concentration in developing tissues. During metamorphosis there is a negative correlation between expression of DIII and responsiveness to thyroid hormone of different tadpole tissues (118-120). Overexpression of DIII in transgenic tadpoles strongly inhibits metamorphosis (121). In mammals high expression of DIII in the placenta controls the transfer of maternal thyroid hormone to the fetus (122) and recent studies have demonstrated very high levels of DIII expression in the uterus at the implantation site and in the epithelial cells of the uterine lumen surrounding the fetal cavity (123). In the newborn rat brain DIII expression selectively occurs in areas involved in sexual differentiation of the brain (117), suggesting that these areas need to be protected from a possible interfering action of T_3 during critical periods of sexual brain differentiation (124, 125).

CONTROL OF BRAIN GENE EXPRESSION BY THYROID HORMONE

According to the main action of thyroid hormone at the cellular level, *i.e.*, the regulation of gene expression, its physiological effects should be explained, in great part, by the control of specific genes and gene networks. Using the hypothyroid neonatal rat as a model, a number of genes have been found whose expression in the brain is modified by hypothyroidism, and thyroid hormone treatment *in vivo*. Some of these genes may be primary targets of thyroid hormone, since they are also regulated using cultured cells *in vitro*, or contain thyroid hormone responsive elements. The analysis of the role of thyroid hormone is in many cases complicated by the fact that some of the regulated genes are only expressed in fully differentiated cells. Thyroid hormone therefore may control gene expression secondarily as a consequence of effects on terminal differentiation (6, 126). How thyroid hormone influences terminal cell differentiation is not known with certainty, but actions on proteins controlling the cell cycle have been described (127).

Below follows a brief description of the genes that have been found as thyroid hormone-dependent *in vivo* in the rat brain. Most genes are dependent of thyroid hormone only during a critical period, which in the rat spans from about E18 to the third postnatal week. Only a few genes have been described to be regulated in adult animals: RC3/neurogranin (128), NGF, trkA and $p75^{NTR}$ (129), and a thyroid hormone-responsive protein homologous to the c-Abl interactor protein (130, 131).

Myelin genes

Thyroid hormone influences to similar extents, and with very similar patterns, the expression of practically all myelin genes analyzed, mainly those encoding the structural proteins myelin basic protein (MBP), myelin-associated glucoprotein (MAG), and proteolipid protein (PLP) (132-135). During development there is a myelination wave that starts in the more caudal regions and progresses rostrally. In hypothyroid animals the progression of the myelination wave is retarded (134, 135). If the concentrations of the myelin gene products, either mRNA or protein, are analyzed in different brain regions, the effect of hypothyroidism is found to be transient depending on the specific region and developmental time, in a pattern that follows the myelination wave. For example, lower expression of myelin genes is observed in the cerebellum of hypothyroid rats only until P10. After this age there is a spontaneous recovery even in the absence of thyroid hormone treatment, whereas in the cortex and hippocampus the differences persist until P25 or beyond. Eventually, shortly after the first month of life, expression of the myelin genes in hypothyroid animals reaches the same level as in normal animals in all regions, with the possible exception of the cerebral cortex. Therefore the role of thyroid hormone is to accelerate the rate of accumulation, but not the final concentrations, of specific oligodendrocyte mRNA and proteins (8, 136). Once the myelination wave is completed the myelin genes become refractory to thyroid hormone deficiency. However in spite of the recovery of myelin gene expression, rats made hypothyroid during the neonatal period show permanent deficits of myelination in the absence of treatment (137).

Mitochondrial genes

Manipulations of the thyroidal status induces biochemical and structural changes of brain mitochondria in a region-specific fashion (138-140) and

also leads to changes in the expression of nuclear-encoded, and mitochondrial-encoded, mitochondrial RNAs in the brain. Among the nuclear encoded RNAs are the cytochrome c oxidase subunits IV and VIc (141), and a homologue to the fungal Tom70, a mitochondrial protein import receptor (142). The thyroid hormone-dependent mitochondrial-encoded RNAs include subunit 3 of NADH dehydrogenase (143), subunit III of cytochrome c oxidase, and 12S and 16S rRNAs (141)

Neurotrophins and their receptors

One of the best examples of the cooperation between neurotrophic factors and thyroid hormones is in the growth and maintenance of cholinergic neurons of the basal forebrain (19, 144). This cooperation is also observed in other structures such as the hippocampus, olfactory bulb and cerebellum (145), and might be due in part to control of the levels of NGF receptors. Both in developing and in adult rats thyroid hormones affect mainly NGF, trkA, and $p75^{NTR}$ (129, 146, 147). In the cerebellum thyroid hormone controls expression of BDNF in Purkinje and granule cells and of NT-3 in granule cells (148, 149). BDNF and NT-3 increase granule cell survival whereas granule cell-derived NT-3 promotes Purkinje cell differentiation. A role of BDNF as mediator of the effects of thyroid hormone is supported by the delayed granule cell migration and decreased growth of Purkinje cell dendrites observed in BDNF knockout mice (150) and by the upregulation by thyroid hormone of specific BDNF transcripts *in vivo* (151).

Cytoskeletal components

Expression and cell distribution of cytoskeletal components have been for long time considered to be important effects of thyroid hormone during brain development, and responsible for the effects of the hormone on axonal growth, and dendritic architecture. In the cerebellum for example, Purkinje cell microtubules are scarcer, shorter, and the distribution throughout the dendritic tree is modified (152). Thyroid hormone controls the expression of specific tubulin isotypes and microtubule-associated proteins.

The tubulins are encoded by a multigene family which give rise to six α and five β isotypes with differential patterns of expression (153, 154). In the rat brain thyroid hormone promotes the downregulation of α1 and α2 tubulins and the upregulation of β4 tubulin, without influencing expression of β5 (155). The existence of several tubulin isotypes may lead to microtubules with unique properties depending on the composition of the tubulin polymers (156). In general, hypothyroidism appears to maintain an "immature" composition of microtubules.

Microtubule associated proteins (MAPs), which promote the polimerization and assembly of microtubules, are also under thyroid hormone control. The rate of tubulin polimerization in brain extracts from neonatal rats is markedly reduced by hypothyroidism and was corrected by addition of Tau, one of the MAPs (157). The major effect of thyroid hormone is not the control of Tau mRNA levels (158) but to promote the replacement of juvenile forms of Tau for the mature forms, a change that is accomplished at the level of RNA splicing (159).

Expression of other MAPs is regulated by thyroid hormone at a postranscriptional level. Concentrations of MAP-1 and MAP-2 proteins are affected by the thyroid status, but not the corresponding mRNAs (157, 158, 160). Hypothyroidism delays the accumulation of MAP-2 in the cerebellum during postnatal development. As with other targets of thyroid hormone the protein concentrations eventually attain normal levels spontaneously with age even in the absence of treatment. But despite this, the protein remains abnormally in the Purkinje cell bodies instead of being distributed along the length of the dendrites (160).

Transcription factors

Neonatal hypothyroidism is associated with a decreased NGFI-A (Krox-24, Egr-1 or Zif-268) (161) mRNA concentration in several areas of the brain, that normalize either spontaneously with time or after acute administration of thyroid hormone (162). T_3 stimulates the NGFI-A promoter *in vivo* through a TRE of the DR4 type (163).

The transcription factor BTEB is a member of the Sp1 family of transcription factors and binds to the basic transcription element (BTE) of cytochrome P-450IA1 (CYP1A1) promoter. As a T_3-regulated gene it was first identified in the tadpole diencephalon and subsequently in rat cerebrum (164). T_3 also regulates BTEB mRNA in cultured N2α cells expressing TRβ1, apparently at the level of transcription. In contrast, it was not induced in cells expressing TRα1 (164).

The orphan nuclear receptor RORα (165) is highly expressed in Purkinje cells (166). Disruption of the RORα gene is responsible for the staggerer phenotype in mice (167) with profound alterations in Purkinje cell growth and differentiation and granule cell migration, which resemble the abnormalities induced by hypothyroidism. The postnatal accumulation of RORα transcripts is delayed in hy-

pothyroid animals (168). RORα increases TR-mediated transcription when coexpressed in the same cells (169) and may play a role in the regulation of the pcp-2 gene (see below), since RORα binding sites have been described in the promoter region of this gene (170). Some actions of RORα, including those exerted on Purkinje cell differentiation and also on granule cell differentiation and migration may be exerted in cooperation with RevErbAα (35). It is not known whether RORα is regulated directly or indirectly by thyroid hormone.

Splicing regulators

It was mentioned above that thyroid hormone controls the splicing of primary transcripts of the Tau gene. Other splicing events influenced by thyroid hormone involve tenascin-C (171) and β-amyloid (172). The mechanism of these effects is not known, but thyroid hormone might control the expression of proteins involved in splicing (173). The expression of the mammalian homolog of the *Drosophila* splicing regulator Suppressor-of-white-apricot (SWAP) is altered in the hypothyroid rat cerebrum (174). Whether thyroid hormone controls the expression of other splicing regulators and the significance of this regulation in the physiological effects of thyroid hormones remains to be studied in detail.

Extracellular matrix proteins and adhesion molecules

Extracellular matrix proteins and cell adhesion molecules are important in brain development because they can act as guidance cues for cell migration and axonal growth. It is believed that extracellular matrix proteins secreted by astrocytes such as Laminin and Tenascin form "corridors" through which neurons migrate and axons reach their targets. Neurons interact with these extracellular proteins through membrane proteins such as integrins. On the other hand, cell adhesion molecules through homophilic or heterophilic interactions are involved in many developmental processes in the central nervous system (CNS), including promotion of neurite outgrowth, axon fasciculation and presynaptic differentiation.
Thyroid hormone controls the expression of the adhesion molecules NCAM and L1 (175, 176) and the extracellular proteins tenascin C, laminin, and Reelin (14, 171, 177). NCAM, L1 and tenascin C have high expression levels in the embryos and newborns and decrease postnatally. The postnatal decrease in the expression of these genes is slowed down in hypothyroid rats. The reelin protein, important in cell migration in cortex and other structures (178), is also under thyroid hormone control (14).

Genes encoding proteins involved in intracellular signalling

RC3/neurogranin is a neuron-specific, calmodulin-binding and PKC substrate peptide of dendritic localization, expressed in the cerebrum, and not in cerebellum (179). It is regulated by thyroid hormone in rats and goats (180, 181). There is well-delimited regional selectivity in the effects of hypothyroidism and T_3 administration on RC3 expression (182, 183). T_3 acts directly at the transcriptional level (184), and a TRE and additional regulatory sequences have been found in the first intron of the human gene (185, 186). RC3/neurogranin is important in the regulation of calcium and calmodulin-dependent functions that contribute to synaptic plasticity and spatial learning (187).
Calmodulin-dependent kinase IV (CaMKIV) is a monomeric enzyme, located in great part in the nucleus where it regulates gene expression through phosphorylation of CREB and Serum Response Factor (188). CaMKIV is expressed in the granule cells of the cerebellum (189). T_3 added to aggregating neuronal cultures of E15 rat embryos induced the expression of CaMKIV at the RNA and protein levels (190, 191). An interesting property of CaMKIV is that it increases transactivation by TRα (192). The significance that this cooperation might have in thyroid hormone-dependent cerebellar granule cell development is unknown.
Rhes (193) is a novel protein of the Ras family, greatly enriched in the striatum (hence its name, Ras homolog enriched in striatum). Unpublished results from our laboratory, show that the Rhes mRNA response to *in vivo* treatment with a single T_3 dose is very fast, making it likely that it is an early direct response to thyroid hormone. Nothing is known yet on the biochemical properties of Rhes or the nature of the specific signaling pathways involved in Rhes activity.
Prostaglandin D2 synthase (PGD2S) is the enzyme that produces prostaglandin D2 (PGD2) from prostaglandin H2 (194). The brain enzyme is identical to the human protein known as β-trace which is one of the major proteins present in CSF and a member of the lipocalin family of transporters. In the CNS PGD2 has multiple actions including regulation of body temperature, sleep induction and control of pain sensitivity. In addition, PGD2 is precursor of ligands for peroxisome proliferator-activated receptors regulating genes involved in lipid metabolism. Neonatal hypothyroidism is associated with changes in the expression of PGD2S mRNA and protein in several regions of the brain (13, 195). Intriguingly, Cajal-Retzius cells which abundantly express the PGD2S protein in control animals are devoid of PGD2S immunoreactivity in the brains of

hypothyroid rats. It is likely that thyroid hormone controls the expression of the PGD2S gene after direct interaction of the TR with genomic regulatory sequences, since TREs have been found in both the rat and human genes (196, 197).

Cerebellar genes

The pcp-2 gene encodes a Purkinje cell-specific protein of unknown function. Pcp-2 mRNA accumulates postnatally in the cerebellum reaching maximum levels around days 15-20. In hypothyroid animals the rate of accumulation is slower, so that euthyroid levels are reached after postnatal day 45 (136). This pattern is similar to the one described above for the myelin genes, and hypothyroid animals eventually reach the same levels as normal animals even in the absence of thyroid hormone replacement. As for the myelin genes, the mechanism for this pattern of control is unknown, and suggests that oligodendrocytes and Purkinje cells share a common feature related to thyroid hormone control. As already discussed for oligodendrocytes and myelin it may well be that the effects of thyroid hormone on gene expression in Purkinje cells are secondary to an effect on cell differentiation. In support of a direct effect of thyroid hormone is the finding of T_3 responsive elements in the promoter region and first intron of the pcp-2 gene (198). The gene contains, in addition, a silencing element that binds repressor proteins such as COUP-TF. It has been postulated that sensitivity to T_3 is determined by the balance between TRs and the repressor proteins, which change during development (8, 199, 200).

In the granular cells, expression of hairless and of a synaptotagmin homologue gene are upregulated by thyroid hormone (201). Both genes respond very fast to thyroid hormone administration *in vivo*, and hairless contains a TRE which might mediate a direct transcriptional response to T_3. Interestingly Hairless is a zinc-finger, nuclear repressor protein, which heterodimerizes with the TR, but the significance of this interaction is unknown. Other thyroid hormone-dependent genes in the cerebellum have been described above and include myelin genes, actin (202), cytochrome C oxidase subunit I (203), laminin (177), tubulin (146, 155), $p75^{NTR}$ (129, 146, 149), reelin (14), tenascin C (171) and RORα (168).

ROLE OF THYROID HORMONE RECEPTOR ISOFORMS IN BRAIN DEVELOPMENT: STUDIES IN NULL MUTANT MICE

The existence of T_3 receptor isoforms with different patterns of ontogeny and regional distribution suggests that there could be specific functions for each of the isoforms. The generation of mouse strains carrying targeted mutations in the T_3 receptor genes, generated hopes to find receptor isoform-specific effects [for a review see (204)]. Mice carrying a deletion of the TRβ gene are deaf due to a lesion in the cochela, but otherwise display no other obvious developmental abnormalities, and normal expression patterns of the PCP2 and MBP genes were found (205-207). Inactivation of the TRα gene results in developmental abnormalities of intestine, bone, and thyroid, but do not show signs of CNS involvement (208). One explanation for the lack of major developmental defects in single knock out mice is that in the absence of one type of receptor there are compensatory effects of the remaining receptor isoform. However, this seems to be not a satisfactory explanation, since mutant mice for all T_3 receptor isoforms display no obvious CNS abnormalities (209).

The fact that complete absence of thyroid hormone receptors results in a mild phenotype compared with the profound deficiencies induced by severe hypothyroidism is not clearly understood at present and several explanations have been suggested (204). Among these, the most appealing possibility is that the manifestations of severe hypothyroidism, at least those concerning CNS, are due to the repressor activity of unliganded receptors. For genes that are upregulated by thyroid hormone, in the absence of T_3, as occurs in hypothyroidism, the receptors would exert a strong repressive effect on the expression of target genes. This would counteract the inductive effect of other developmental factors that determine expression of the regulated genes. The changing balance between repression and induction, with a predominance of the latter as development proceeds would allow the spontaneous catch-up observed with most thyroid hormone regulated genes in untreated hypothyroid animals.

SYNDROMES ASSOCIATED WITH THYROID HORMONE DEFICIENCY DURING BRAIN DEVELOPMENT

The study of basic mechanisms concerning thyroid hormone regulation in the brain has greatly helped in the understanding of the pathogenesis of human syndromes which are consequence of deficits of thyroid hormone during development. A brief acount is given below.

Iodine deficiency disorders. Endemic cretinism

Daily adult needs of iodine are of the order of 150-200 µg, and even more during pregnancy (210). Iodine deficiency causes a wide spectrum of abnor-

malities collectively known as iodine deficiency disorders (211). Among these are a high incidence of abortions and stillbirths, increased perinatal and infant mortalities, neonatal goiter and neonatal hypothyroidism, and psychomotor and mental defects. The term cretin appeared in descriptions of affected inhabitants of alpine regions of Europe and the Himalayas (212), and should be restricted to the syndrome of mental deficiency arising as a consequence of severe iodine deficiency with a daily iodine intake below 25 µg. There are two forms of cretinism, known as neurological and mixedematous, respectively (213). Neurological cretinism is characterized by severe mental retardation, deaf mutism and spastic diplegia affecting the lower limbs (214). There are no differences in circulating thyroid hormone concentrations, usually low T_4 and normal T_3, between the cretin and the non-cretin population. The thyroid gland is normal and there are no physical signs of hypothyroidism. Mixedematous cretins (215) are also mentally retarded but not as severely as the neurological cretins, and signs of neurological involvement is observed only in a minority of cases. They have physical signs of hypothyroidism, such as short stature, craniofacial abnormalities and poor sexual development. Destruction of their thyroid glands is believed to be due to the combination of low iodine supply, high intake of goitrogens in the diet, and selenium deficiency (216, 217). An important difference between the two forms is the response to iodine. The only way to prevent neurological cretinism is by administration of iodine to women early in gestation or even before they become pregnant (218, 219). The pathogenesis of these two different clinical entities may be explained on the basis of what was said above on placental transfer of thyroid hormone, and the presence of T_3 receptors in the fetal brain during the second trimester. Maternal thyroid hormone may have an important role in fetal brain development before the fetal thyroid gland is fully active. Neurological cretinism would be the consequence of profound maternal hypothyroxinemia during the first half of pregnancy, whereas mixedematous cretinism is mostly due to failure of the thyroid gland of the fetus and newborn.

Congenital hypothyroidism

Congenital hypothyroidism is a relatively common disease, with an incidence of about 1 in 3000-4000 newborns (220). The most common causes of permanent congenital hypothyroidism are ectopic thyroid gland, thyroid agenesia and hypoplasia, and inborn errors of thyroid hormone biosynthesis. Besides the well known inborn errors, some genetic causes of the more prevalent thyroid agenesia and ectopia, have been identified recently, such as mutations in the genes encoding the TSH receptor, or the transcription factors Pax-8, TTF-1 and TTF-2 (221). Postnatal treatment with thyroid hormone of cases detected by neonatal screening is usually effective, but still some affected individuals remain with neuropsychological deficits such as learning disabilities and disturbance of fine motor coordination, indicative of minimal brain damage. Factors that influence the outcome include the severity and onset of thyroid failure, as well as an adequate supply of maternal hormone. In severe cases of early onset, maternal hormones may have a protective effect. It is very important to identify the children that may be at risk of having neurological sequelae even with early diagnosis and treatment because these children may require a substantially higher replacement dose of T_4 than the majority of cases (222).

Maternal hypothyroidism and hypothyroxinemia

The importance of maternal thyroid hormones for fetal development becomes evident in cases of combined severe fetal and maternal hypothyroidism, as occurs in Pit-1 deficiency (223) or in presence of high titers of thyroid stimulation blocking antibodies (224, 225). In these cases circulating thyroid hormones are undetectable in the mother and in the infant, who suffers from permanent sensorioneural deafness and irreversible neuromotor deficits despite early postnatal treatment with thyroid hormone.

In a recent study, Haddow *et al.* (226) assessed the performance of children born from mothers that had high TSH during the second trimester of pregnancy. They found that at 7-9 years of age, the children had an average reduction of 4 points in the IQ, compared with children born from normal mothers. They scored less in tests that measure intelligence, attention, language, and school and visual-motor performance. The study raised the convenience of screening all pregnant women for TSH during the first trimester of pregnancy. Still, high TSH is indicative of clinical or subclinical hypothyroidism, and maternal hypothyroxinemia is much more prevalent than hypothyroidism during pregnancy. Data from Glinoer in Brussels, showed that 30% of pregnant women had low serum free T_4 in the first trimester, whereas 2.3% had high TSH (210). Hypothyroxinemia, in the absence of hypothyroidism is mainly due to mild iodine deficiency (227). In this situation, euthyroidism is maintained by compensatory mechanisms, including increased DII activity, and preferential thyroidal secretion of T_3. Pop *et al.* (228) found that children from women with a free T_4 concentration in the first trimester of pregnancy below the 10^{th} percentile, even

with normal TSH, were more likely to have neurodevelopmental problems. Therefore, if maternal T_4 concentrations are important in fetal brain development, screening for high TSH would only detect a small percentage of the population at risk (11, 229). All these studies stress the need for ensuring an adequate supply of iodine to pregnant women.

Prematurity

Hypothyroxinemia lasting several weeks occurs in around 85% of preterm babies (230, 231). It is caused by several factors among which is the interruption of the maternal supply of T_4 to the fetus, at an stage of development when maternal T_4 contributes an important fraction of normal fetal plasma T_4. As said above, for the fetus at term this fraction has been estimated to be 30-50% (72), but in earlier periods it is likely to be much higher given the immaturity of the fetal thyroid gland (232). FT_4 concentrations are lower in pre-term neonates than in fetuses of comparable age still *in utero* (233-235). As pointed out above the fetal brain might be a target of thyroid hormone at least from the second trimester of pregnancy onwards. Therefore, the hypothyroxinemia of prematurity may have clinical consequences and several studies have shown that it may represent an independent risk of subsequent neurological and mental developmental problems (236), increased risk of cerebral palsy (237) and of white matter damage (238).

Should pre-term babies be treated with thyroid hormones? Treatment is clearly indicated in those cases with primary or secondary hypothyroidism, and there is an improvement of IQ at two years in the treated children (239). But whether hypothyroxinemic preterm babies in the absence of hypothyroidism should be treated is an unsettled issue, although some studies suggest that it may be beneficial (240). More studies are needed to establish whether the hypothyroxinemia of premature babies should be treated with T_4, and if so, what is the optimal dose, and whether some T_3 should also be administered.

CONCLUSIONS

Reflecting the importance of thyroid hormone in brain homeostasis, efficient regulatory mechanisms have developed to keep T_3 concentrations very tightly regulated. Central to these mechanisms are the activities of deiodinases II and III. Deiodinase II likely plays important roles in maintaining T_3 concentrations in selected brain areas in the face of decreased T_4 availability. Its location in glial cells suggest that these cells are main producers of brain T_3 and provide the hormone to nearby neurons. Deiodinase III is likely to be important in maintaining T_3 concentrations under strict limits during early development and, in newborn rats, in areas related to sexual differentiation of the brain, but the significance of the latter observations has to be worked out.

As in other tissues, thyroid hormone regulates gene expression in the brain. The regulated genes do not belong to a single category, but they encode proteins involved a great variety of processes, in agreement with the pleiotropic effects of thyroid hormone. Most of the regulated genes are sensitive to thyroid hormone only during a time window which in the rat extends from the last days of fetal development, to two-three weeks after birth. The role of thyroid hormone is to accelerate developmental changes in gene expression. In particular, thyroid hormone is involved in the rapid accumulation of some mRNAs and proteins that take place during the second week of life, for example the myelin proteins, and the down-regulation of many other genes (tubulin, matrix proteins). In the absence of thyroid hormone these changes take place but at a slower rate. Only a few genes have been found to be regulated by thyroid hormone in adult brain.

Clinical and epidemiological evidence suggests that thyroid hormones are needed for human brain maturation from mid-pregnancy. There is even the possibility that thyroid hormones may influence the proliferation and differentiation of specific cell populations even earlier. This is suggested by results of iodine replacement in endemic goiter and by the presence of T_3 receptors at least from the end of the first trimester. The spectrum of alterations of brain maturation due to thyroid hormone deficiency has widened and it is increasingly being recognized that maternal hypothyroxinemic states even in the absence of overt hypothyroidism may be detrimental to the fetus. This concept has followed the general acceptance that maternal thyroid hormones cross the placenta and reach the fetus in significant amounts.

Many questions remain for the immediate future. Important questions to examine include the molecular basis for the specific timing of action on gene expression, as well as the regional selectivity displayed by some regulated genes such as RC3. Also, the role of the thyroid hormone receptors needs to be studied in depth. If, as pointed out above the phenotype of severe hypothyroidism is a consequence of the repressor activity of the unliganded receptors, then one has to conclude that the main role of thyroid hormone is to derepress a repressor. This conclusion does not fit well with the meaning of the elaborate mechanisms that have evolved for the regulation of T_3 concentrations in brain, and inevitably leads one to pose questions as to the significance of the thyroid hormone receptor in evolution and ontogeny.

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