Effect of Thyroid Hormones on Neurons and Neurodevelopment

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Abstract

This review focuses on the current knowledge of the effects of thyroid hormones on central nervous system differentiation and development in animals and the human fetal brain. The outcomes of children with congenital hypothyroidism and of newborns with hypothyroid pregnant mothers are emphasized, focusing on how therapies could affect and especially improve the outcomes.

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Introduction

Thyroid hormones (TH) play an essential role in growth and metabolic homeostasis in humans as well as in animals. In the last decades, growing attention has been focused on the effects of TH during fetal life in terms of tissue differentiation and development. By studying the severe neurocognitive impairment of patients with congenital hypothyroidism (CH) first, and through ex-

perimental animal studies thereafter, it has been proved that already since the early weeks of embryonic development the nervous system is highly TH sensitive in prenatal life.

TH synthesis takes place inside of thyroid follicular cells via iodination of thyroglobulin tyrosin residues, stored in the follicle lumen. The thyroid iodine uptake is regulated by the pituitary thyroid-stimulating hormone (TSH). When required, thyroglobulin is endocytosed and broken down by lysosomal enzymes into triiodothyronine (T₃), the active hormone, and thyroxine (fT₄), a pro-hormone. Then, TH are released into the bloodstream, mostly linked to thyroid-binding globulins. Once they reach the target cells, TH cross the membrane through specific membrane TH transporters isoforms. T₃ acts on its nuclear receptor (TR α and TR β) heterodimers and binds specific sites of the promoter regions of target genes, i.e., TH response elements (TRE). TRE do not modulate only gene transcription when linked to its ligand; indeed, they can also have influence on TRE through a complex interaction with coactivators [1]. Within the cells, fT₃ and fT₄ availability is regulated by the iodothyronine deiodinase enzymes, existing as 3 isoforms (D1, D2, and D3), by removing specific iodine atoms from TH [2] (Fig. 1).

Fig. 1. Maternal and fetal thyroid hormone metabolism during pregnancy. TH synthesized by maternal thyroid cross the placenta by means of specific thyroid hormone transporters that appear to be more selective for fT4. Maternal fT4 is converted to T3 and rT3 by placental deiodinases. Afterwards, maternal T3 can reach the fetal tissues before fetal thyroid maturation. A tissue-specific distribution of deiodinases, as can be detected in the CNS, may be essential for tissue development and differentiation. D2-3, type 2/type 3 iodothyronine deiodinase; I⁻, iodide; rT3, reverse triiodothyronine; RXR, retinoic X receptor; THR, thyroid hormone receptor; T2, 3,5-diiodo-L-thyronine; T3, triiodothyronine; T4, thyroxine; THT, thyroid hormone transporter.

In addition to its genomic action, TH have “nongenomic” effects as they interact with cell membrane receptors and cytosolic proteins in order to activate different signal pathways involving serine-threonine kinase, PI3K, Akt/protein kinase B, AMP-activated protein kinase, and calcium [3].

More recently, the products of TH metabolism have found to be involved in metabolic regulation, cardiac and skeletal muscle function, and brain activity [3].

Among all of the systems influenced by thyroid action, the central nervous system (CNS) appears to be highly sensitive during the developmental stages. A clear example is well described by the neurological impairment in overt CH. The clinical spectrum goes from developmental delay to hearing and speech impairments, squint, and involvement of voluntary motor activity (lower limb spasticity up to diplegia, ataxia), with the most severe

condition being historically known as cretinism. Even milder forms (subclinical hypothyroidism, SH, and normal fT3 and fT4 values associated with TSH levels from 5 to 10 mU/L) often show mental deficiency and psychomotor impairment in those countries where a screening program is undertaken [4]. Beyond fetal thyroid, the mother’s TH also have a considerable influence on the CNS and other systems [5].

Animal Studies

The preserved TH synthesis pathway throughout phylogenesis, the absence of a maternal hormonal influence on embryos, the ease in culture techniques, and their accessibility for experimental studies make amphibians a simplified but compelling model for investigation of the

Table 1. Main effects of TH deficiency on CNS development

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- Reduced progenitor expansion
 - Deficit in neuronal migration
 - Delay in neuron proliferation
 - Decreased expression of neuronal differentiation factors
 - Impaired generation of primitive patterns of network activity
 - Reduced cortical thickness
 - Cortical dysplasia
 - Abnormal layering and foliation of the cerebellar cortex
 - Impairment in dendrites and axons development
 - Decreased expression of proteins involved in synaptic plasticity
 - Delayed myelination and reduced axonal guidance and fasciculation
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List of the most relevant CNS alterations secondary to TH deficiency. The events are showed in chronological order (i.e., from the first trimester to postnatal life).

effects of TH on prenatal stages of neurodevelopment [6]. Frogs and humans share similar molecules in THs signaling; previous studies have demonstrated the similarity between TR isoforms (α and β), their heterodimer partners, co-receptors, and co-activators, as well as TRE in DNA [6]. Likewise, TH membrane transporters and deiodinases D1, D2, and D3 have been highly conserved up to human beings [6].

Amphibian metamorphosis is induced by TH; in *Xenopus laevis*, the most studied specimen, TH are first secreted during stage 54 [7], although an early TH sensitivity before this stage has been documented [8]. Kawahara et al. [7], using an in situ hybridization technique, found that TR α and TR β are synthesized earlier, at around stage 44, and TR β reaches a high concentration in the brain and spinal cord of tadpoles. TR has been only recently demonstrated to have a role in early *Xenopus* development, probably by repressing the gene expression [9]. Amphibians have also helped to determine the TR corepressor and coactivator roles. Havis et al. [10] reported that eye development in *Xenopus* is dependent on corepressor binding to unliganded TR. Furthermore, a dual function model has been proposed assuming TR and corepressors as early negative regulators of metamorphosis initiation until TH synthesis when liganded TR and coactivators induce TRE transcription [11]. However, there is not a unanimous consensus on this model [2].

Relevant findings come also from frog studies concerning deiodinase intervention on TH activity. D2 and D3 expression begins in selected tissues before thyroid gland activation. The retina, brain, and spinal cord are the

first regions where deiodinases can be found, suggesting a potential role in early CNS development [12]. D2 is involved in the negative feedback loop between the pituitary gland and TH in frogs, while D3 is a negative regulator of THs signaling in early tadpole stages and it has been shown to be essential for retinal maturation [13].

Specifically in CNS, the experimental manipulation of TH availability has shown a direct effect on cell proliferation, neuronal differentiation, and dendritic arbor elaboration [14] (Table 1).

Moreover, increasing interest has been directed towards those exogenous chemicals interfering with thyroid signaling, especially during early embryo development. Also on this topic, amphibian studies are contributing to a better understanding. Some studies have highlighted that CNS may be one of the most affected tissue, as TRE are downregulated in the brains of tadpoles after disruptor exposure [15].

In mammalian studies, also fT4 and fT3 have been detected before the initial thyroid activity, as well as early deiodinase activity and TR synthesis in CNS cells [16]. TR α 1 has been localized in all CNS regions, while TR β 1 has been found selectively in the hypothalamus, the pituitary, the retina, and the cochlea, but only in later stages [17, 18].

These findings may underline the importance of maternal TH levels during early fetal development. Experiments on rat embryos have revealed that in early prenatal exposition to hypothyroid agents maternal fT4 is crucial for early brain development [19]. On the other hand, maternal induced hypothyroidism or hypothyroxinemia has led to critical damages in the rat brain architecture, such as aberrant neuronal migration and structural gray matter organization in the somatosensory cortex and the hippocampus [20].

The earlier stages of progenitor migration, differentiation, and maturation seem particularly impaired in TR-mutant or TH-deprived rats. For instance, Cajal-Retzius and subplate cells, involved in cerebral cortex stratification, cell migration, and axon routing, are regulated by T3 [16]. The synthesis of extracellular matrix proteins is also under direct TH control and has been linked to basal progenitor cell proliferation and reduced cortical thickness [16]. The impaired neuronal migration can result in white matter and subcortical band heterotopia, as shown in models of moderate maternal hypothyroidism [5]. Low TH levels affect glial cells as well; astrocyte maturation is impaired in TR α mutant mice [21], while oligodendrocyte progenitor differentiation is influenced by T3-dependent neurotrophin secretion [18]. The inadequate

Fig. 2. T4 passes through the blood-brain barrier via different endothelial cells transporters (mainly OATP1c1), while tanyocytes transporters allow T4 to cross the ventricle surface. The MCT8 transporter seems more selective for T3, although there are probably other unclear transport mechanisms (dashed arrows). Astrocytes transform T4 into the activated hormone via the D2 enzyme; T3 is then delivered to neurons provided with different transporters. T3 metabolites result from the D3-mediated deiodination. Other transporter proteins have been detected in microglial cells and oligodendrocytes. D2-3, type 2/type 3 iodothyronine deiodinase; LAT1-2, L-type amino acid transporter 1-2; MCT8-10, monocarboxylate transporter 8-10; OATP1a4/1c1/2b1/3a1, organic anion-transporting polypeptide; T2, 3,5-diiodo-L-thyronine; T3, triiodothyronine; T4, thyroxine.

axon myelination leads to a reduction in interhemispheric connections and in white matter volume [5], which is irreversible after hormone supplementation [22].

Studies on TRα1 knockin and knockout rats have reported impairment of dendrites and axonal development of GABA-ergic interneurons, pivotal for early neuronal circuit organization [23, 24].

Interesting findings derive from studies on cerebellar cells. A complex interaction between Purkinje cells and granule cells, that secrete growth factors, generates a positive loop initially enhanced by T3 ligation to TRα1 and TRβ1. Though it is still unclear, this mechanism is important for adequate maturation and layering of the cerebellar cortex. Indeed, impaired foliation and laminar organization of the cerebellum, delayed Purkinje cells and granule cell differentiation, abnormal dendritogenesis, and reduced cerebellar gene expression have been described in TRα and TRβ mutant mice [18].

Another field of interest is the blood brain barrier control on TH uptake (Fig. 2). In the embryonic chicken brain, the presence of D3 and L-type amino acid transporter 1 (LAT1) on brain capillary surface controls the main doorway of T3 to CNS [25]. Notably, T3 levels and T3/T4 ratio are higher in the brain than in the systemic circulation as previously reported in mammalian brain

studies [26]. D2 has also been found in tanyocytes, interneurons, and astrocytes [27]; the latter are able to provide T3 to neurons by fT4 conversion. A second regulatory level is localized in the choroid plexus, where a system of transporters and receptors (OATP1C1, LAT1, LAT2, MCT8, and MCT10) needs to be better elucidated [26]. When some of these are lacking, in mice cerebellar development delay, impaired myelination, and poor locomotor outcomes are developed [28], while even worse neurological symptoms are present in humans (Allan-Herdon-Dudley syndrome). Such differences in human and mouse TH brain uptakes may be explained by the synergic cooperation of other transporters [26].

Human Studies: Effects on Psychomotor Development in Children

The experimental animal models appear to be strongly representative of what occurs in humans with fetal TH deficiency. Whether the fetus carries a genetic mutation in the TH signaling pathway, or maternal hypothyroidism occurs, or endocrine disruptors alter the TH availability, CH affects the child's psychomotor milestones and his neurological outcomes.

These outcomes are differently affected by the duration of fetal TH deficiency exposure. The early brain development of fetuses with CH is protected by the maternal TH supply, mainly through a D2-mediated conversion of maternal fT4 [29]. Therefore, the cerebral areas hit in CH are those developed lately, i.e., spatial and associative memory, language, and auditory processing, but also attention and executive processing. Gross motor skills, visual processing, visual attention, and event memory seem to be affected when TH are lacking in the first trimester, as for maternal deficiency [30]. MRI human studies have also found differences in cortical abnormalities (thinning and thickening) between CH and maternal hypothyroidism, though this requires further confirmation [31].

In the following sections, we will separately discuss the most recent findings on these 2 conditions.

Congenital Hypothyroidism

Since the diffusion and careful revisions of newborn screening in the 20th century, excellent neurodevelopmental outcomes have been reached with optimized hormonal therapies, preventing the risk of intellectual disability typical of cretinism. Nonetheless, a small number of patients with mild cognitive delay or poorer school performance persists after the screening era [30]. The subgroup of patients with athyreosis, syndromic CH, and additional CNS malformations partially explains the previous findings. Indeed, among 63 CH children who were prospectively followed-up, the patients affected by athyreosis presented with a lower IQ, especially on the performance scale [32]. Low- and very-low-birth-weight infants represent an additional population at high risk, and they often have a delayed elevation in TSH levels that some screening program may miss [33].

An interesting research field is the optimization therapy. Recent guidelines from the European Society for Paediatric Endocrinology (ESPE) state that “treatment with L-T4 should be started as soon as possible, and no later than the first 2 weeks of life or immediately after confirmatory serum test results in infants identified in a second routine screening test,” with an “initial L-T4 dose of 10 to 15 µg/kg per day” [34]. The evidence that this approach is effective for adequate cognitive development is conflicting. A randomized controlled trial showed that a higher dose results in a quicker normalization of THs levels and improvement of the global but not verbal or performance IQ [35]. Positive motor skills results were recorded in a longitudinal study on early and high dose

therapy [36]. Furthermore, a difference in neurodevelopment between patients treated before or after the 15th day of birth was detected in a recent study [37], though it was not significant in comparison to controls. A Swiss study demonstrated lower points of adaptive fine motor performance in subjects who started therapy later [38], whereas, data from the German screening program displayed no correlation between cognitive outcome and age at onset of treatment, starting dose, and CH severity, in contrast to the family’s socioeconomic status [39]. Moreover, an evaluation of 131 French CH children showed no significant difference between patients treated before or after day 21, although the early recall guaranteed an optimal global IQ [40]. More recent studies are in line with previous findings [41, 42]. Other studies have revealed that a better outcome can be achieved by shortening the time of thyroid function normalization [43]. A lower IQ was associated with a lower starting dose and a diagnosis of athyreosis, but the overall outcome could not be fully normalized with early high doses [32]. On the other hand, higher LT4 doses have been found more frequently to be associated with overtreatment that, in turn, may result in worse outcomes [44]. In the case of a TSH concentration between 6 and 20 mU/L beyond 21 days in an otherwise well baby, the ESPE suggests better investigating the patient and discussing with parents whether to start treatment or wait and retest [34]. The current trend is to treat these patients for up to 3 years to avoid mental retardation and other morbidities like growth failure. On the contrary, in the case of severe CH due to athyreosis, even an early therapeutic approach does not seem to reverse the intrauterine brain damage.

The TSH cut-off value for neonatal screening is another important issue. The cut-off reduction to 7–10 mU/L has doubled the incidence of CH and unveiled a relevant group of patients with SH [45]. The neurodevelopmental outcome in SH is not yet clear, and treatment for these patients in the early stages of life is questionable. A retrospective study showed that patients with transient SH did not develop an intellectual disability at 5 years of age [46]. A cohort study on healthy children from 9 to 11 years of age found subtle deficits in verbal comprehension and memory among those with a TSH level in the upper tertile of the reference range [47]. In other studies lower attention scores were underlined [48]. A wide survey, by contrast, did not show cognitive impairment but did report better scores in block design and reading among SH children [49]. No significant differences in IQ, behavioral problems or depression were found in another study [50]. Nonetheless, a recent cohort study has newly

expressed concern about the risk of long-term educational and developmental delays in newborns presenting with TSH levels at the upper normal limit [34].

Supplementation in preterm and low/very-low-birth-weight infants is another area of debate. Transient hypothyroxinemia due to hypothalamic immaturity is very common in preterm/low birth weight infants and an association with abnormal cognitive outcomes has been reported [33]. In these cases, a second screening is recommended at about 2 weeks of age, or 2 weeks after the first test, adapting the results for gestational age, birth weight, and age at sampling. If the fT4 level is persistently low, a serum test for fT4 and TSH should be performed. ESPE guidelines suggest starting therapy when hyperthyrotropinemia persists at 6 weeks of age. After 3 years of age, the patients should be retested after therapy suspension [34].

Although some studies have attempted to assess improvement after prophylactic hormonal therapy, present data are conflicting and well-designed and powered trials are still required [51].

Maternal Hypothyroidism

As demonstrated by animal studies, the lack of maternal TH often leads to irreversible deficits in brain cytoarchitecture and development. Furthermore, data from a Danish prospective study revealed an increased risk of seizure disorders, autism spectrum disorder, attention deficit hyperactivity disorder, and other psychiatric conditions among patients born to mothers with thyroid dysfunction [52, 53].

The causes of maternal thyroid dysfunction range from milder hypothyroxinemia and iodine deficiency to SH or overt thyroid diseases.

Maternal hypothyroxinemia occurs when normal TSH levels are found but fT4 is abnormally low. It has been mainly associated with iodine deficiency but novel studies are focusing on environmental disruptors, obesity, iron deficiency, and angiogenic factor impairment [54]. It is essential to recall that the TH metabolism remarkably changes in pregnant women, with up to a 50% raise in TH levels. This means that the iodine intake, which is already often below the indicated values at baseline, needs to be increased at least to 50% [55]. However, several surveys have demonstrated how frequent iodine deficiency is in pregnant women, both in developed and in developing countries [56–58]. Recent studies investigating the effects of hypothyroxinemia on fetal neurodevelopment, in general terms, have reported a negative

correlation, especially when it occurs during the first trimester [30]. However, data on the later phases of pregnancy are less concordant [54]. A recent metaanalysis concluded that there is a 3-fold increased risk of child cognitive impairment when hypothyroxinemia is detected in mothers during gestation, although the big heterogeneity among the definitions of cognitive delay, the tests performed, and the assessment periods limits these findings [59]. In terms of iodine supplementation, another metaanalysis concluded that, at present, the literature data are undermined by low evidence and several limitations, and no clear benefits or risks of iodine supplementation on children's outcomes can be summarized [60].

There are conflicting data on the risk of coexistence of maternal autoantibodies and maternal iodine deficiency treated with oral supplementation. Particularly, when SH coexists with thyroid autoantibodies, this may result in a significant reduction in the maternal TH supply to the offspring in early pregnancy. Clinical studies on maternal prenatal autoimmunity have revealed an association between high titers of autoantibodies and attention problems [61]. Interestingly, after adjusting for maternal thyroid function, this association resulted milder. The possible transient effect of maternal thyroiditis on the offspring or the autoimmunity involvement of different pathways in fetal neurodevelopment might explain the contrasting results in the literature. Further studies on thyroid and nonthyroid autoimmunity might clarify whether maternal thyroiditis is an independent risk factor for cognitive outcomes in offspring.

Contrasting results and nonunivocal guideline recommendations complicate medical decision-making even in the case of SH. Whereas LT4 treatment is suggested in specific medical conditions when SH coexists with autoimmunity, there is no definite evidence of its efficacy in autoantibodies-negative patients in terms of positive effects on offspring neurodevelopment [62]. In fact, a randomized controlled trial comparing treated and untreated SH and hypothyroxinemic pregnant women did not reveal better cognitive outcomes in children belonging to either of the 2 groups [63].

The risks for fetal neurodevelopment are even higher when the mother shows overt hypothyroidism (TSH >95th percentile with fT4 <5th percentile). Several studies have reported a rise in severe pregnancy complications, including fetal death, when hypothyroid women are left untreated, especially during the first trimester [64].

In addition to intrinsic causes of dysthyroidism in pregnancy, a large amount of data is coming from studies evaluating the effects of external endocrine disruptors on

maternal and fetal thyroid metabolism as well as on child brain development [8]. The chemicals belonging to polychlorinated biphenyls and polybrominated diphenyl ethers, widely spread in the environment, are only 2 examples of all of those substances showing an evident impact on fetus and child growth. Institutions have already begun to take safety measures and the industrial use of some of these chemicals is now banned, but much still needs to be regulated.

Conclusion

CH, even in its milder forms, and maternal thyroid insufficiency are definitely proven to be associated with child neurodevelopment retardation. However, even

though the diffusion of hormonal therapy prevented the severe neurological sequelae of CH, there are still many issues to be clarified. Even though the effectiveness of early treatment for newborns with CH and pregnant women with hypothyroidism is largely recognized, SH and maternal hypothyroxinemia continue to be subjects of debate. More clinical trials and standardization of tests and classifications are needed in order to properly clarify these relevant components of thyroid function in children.

Disclosure Statement

The authors declare no conflict of interests.

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