Mini Review

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2018;90:73–81
DOI: 10.1159/000492129

Received: February 14, 2018
Accepted: July 15, 2018
Published online: August 29, 2018

Effect of Thyroid Hormones on Neurons and Neurodevelopment

Giovanni Prezioso Cosimo Giannini Francesco Chiarelli

Department of Pediatrics, "G. D'Annunzio" University of Chieti, Chieti, Italy

Keywords
Thyroid hormones · Neurodevelopment · Fetal brain · Congenital hypothyroidism · Iodine insufficiency

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.

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 experimental 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 thyrosin 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 thyroxin (fT4), a prohormone. 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 (TRα and TRβ) 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).

KARGER

E-Mail karger@karger.com
www.karger.com/hrp

Giovanni Prezioso
"G. D'Annunzio" University of Chieti
Via dei Vestini 5
IT–66100 Chieti (Italy)
E-Mail gprezioso@hotmail.it

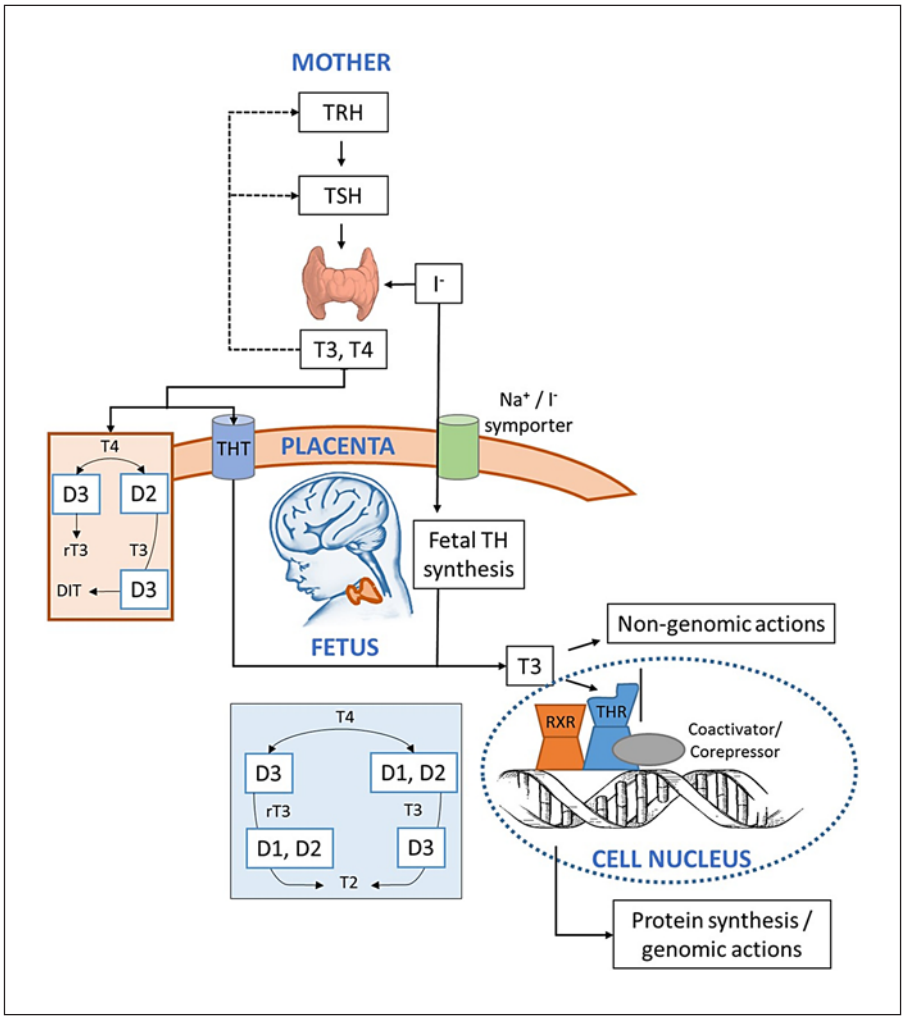

Fig. 1. Maternal and fetal thyroid hormone metabolism during pregnancy. TH synthetized by maternal thyroid cross the placenta by means of specific thyroid hormone transporters that appear to be more selective for fT4. Maternal fT4 is converted to T3 and rT3 by placental deiodinases. Afterwards, maternal 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

– 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

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 TRα and TRβ are synthesized earlier, at around stage 44, and TRβ 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 deyodinase activity and TR synthesis in CNS cells [16]. TRα1 has been localized in all CNS regions, while TRβ1 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 TRα mutant mice [21], while oligodendrocyte progenitor differentiation is influenced by T3-dependent neurotrophin secretion [18]. The inadequate

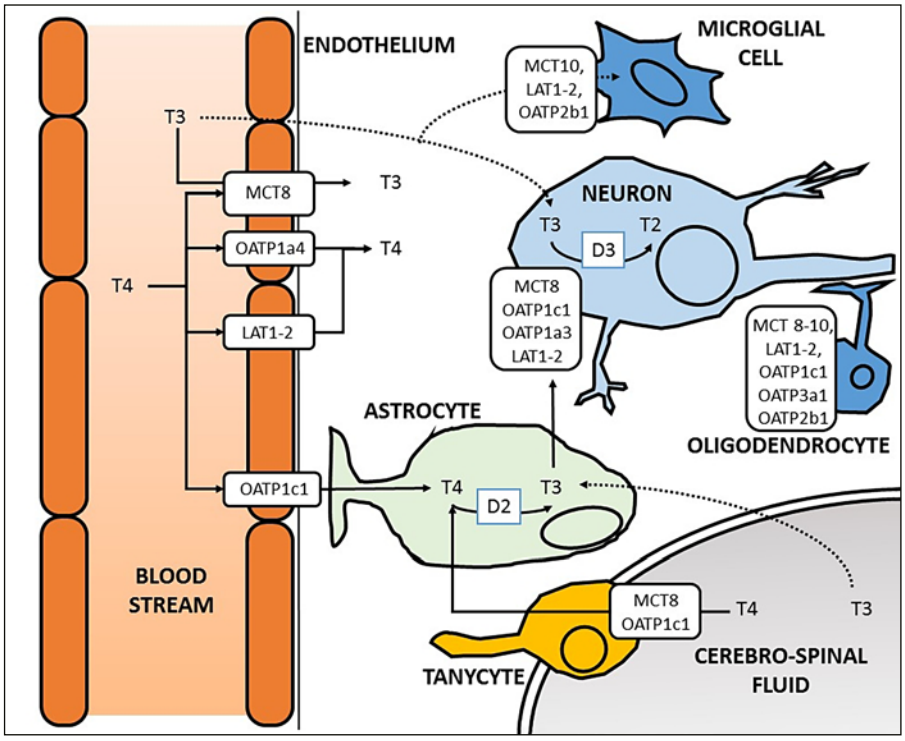

Fig. 2. T4 passes through the blood-brain barrier via different endothelial cells transporters (mainly OATP1c1), while tanycytes transporters allow T4 to cross the ventricle surface. The MCT8 transporter seems more selective for T3, although there are probably other unclear transport mechanisms (dashed 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, etriiodothyronine; 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 tanycytes, 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-Herndon-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 Pediatric 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 intellective 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-birthweight infants is another area of debate. Transient hypotyroxinemia 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 prophylaptic 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 metanalysis 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 metanalysis 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 hypotyroxinemic 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.

References

1 Kumar P, Mohan V, Sinha RA, Chagtoo M, Godbole MM. Histone deacetylase inhibition reduces hypothyroidism-induced neurodevelopmental defects in rats. J Endocrinol. 2015 Nov;227(2):83–92.
2 Préau L, Le Blay K, Saint Paul E, Morvan-Dubois G, Demeneix BA. Differential thyroid hormone sensitivity of fast cycling progenitors in the neurogenic niches of tadpoles and juvenile frogs. Mol Cell Endocrinol. 2016 Jan; 420:138–51.
3 Senese R, Cioffi F, de Lange P, Goglia F, Lanni A. Thyroid: biological actions of 'nonclassical' thyroid hormones. J Endocrinol. 2014 Apr;221(2):R1–12.
4 Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012 Mar;379(9821):1142–54.
5 Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience. 2017 Feb; 342:68–100.
6 Sachs LM, Buchholz DR. Frogs model man: in vivo thyroid hormone signaling during development. Genesis. 2017 Jan;55(1-2):e23000.
7 Kawahara A, Baker BS, Tata JR: Developmental and regional expression of thyroid hormone receptor genes during Xenopus metamorphosis. Development 1991 Aug;112:933–43.
8 Préau L, Fini JB, Morvan-Dubois G, Demeneix B. Thyroid hormone signaling during early neurogenesis and its significance as a vulnerable window for endocrine disruption. Biochim Biophys Acta. 2015 Feb;1849(2): 112–21.
9 Buchholz DR, Tomita A, Fu L, Paul BD, Shi YB. Transgenic analysis reveals that thyroid hormone receptor is sufficient to mediate the thyroid hormone signal in frog metamorphosis. Mol Cell Biol. 2004 Oct;24(20): 9026–37.
10 Havis E, Le Mevel S, Morvan Dubois G, Shi DL, Scanlan TS, Demeneix BA, et al. Unliganded thyroid hormone receptor is essential for Xenopus laevis eye development. EMBO J. 2006 Oct;25(20):4943–51.
11 Buchholz DR. More similar than you think: frog metamorphosis as a model of human perinatal endocrinology. Dev Biol. 2015 Dec; 408(2):188–95.
12 Morvan Dubois G, Sebillot A, Kuiper GG, Verhoelst CH, Darras VM, Visser TJ et al. Deiodinase activity is present in Xenopus laevis during early embryogenesis. Endocrinology. 2006 Oct;147(10):4941–9.
13 Hernandez A, Morte B, Belinchón MM, Ceballos A, Bernal J. Critical role of types 2 and 3 deiodinases in the negative regulation of gene expression by T_3in the mouse cerebral cortex. Endocrinology. 2012 Jun;153(6): 2919–28.
14 Thompson CK, Cline HT. Thyroid Hormone Acts Locally to Increase Neurogenesis, Neuronal Differentiation, and Dendritic Arbor Elaboration in the Tadpole Visual System. J Neurosci. 2016 Oct;36(40):10356–75.
15 Yost AT, Thornton LM, Venables BJ, Sellin Jeffries MK. Dietary exposure to polybrominated diphenyl ether 47 (BDE-47) inhibits development and alters thyroid hormone-related gene expression in the brain of Xenopus laevis tadpoles. Environ Toxicol Pharmacol. 2016 Dec;48:237–44.
16 Bernal J. Thyroid hormone regulated genes in cerebral cortex development. J Endocrinol. 2017 Feb;232(2):R83–97.
17 Bradley DJ, Towle HC, Young WS: Spatial and temporal expression of alpha- and beta-thyroid hormone receptor mRNAs, including the beta 2-subtype, in the developing mammalian nervous system. J Neurosci. 1992 Jun; 12(6)2288–2302.
18 Flamant F, Gauthier K, Richard S. Genetic investigation of thyroid hormone receptor function in the developing and adult brain. Curr Top Dev Biol. 2017;125(1)303–335.
19 Calvo R, Obregón MJ, Ruiz de Oña C, Escobar del Rey F, Morreale de Escobar G. Congenital hypothyroidism, as studied in rats. Crucial role of maternal thyroxine but not of 3,5,3′-triiodothyronine in the protection of the fetal brain. J Clin Invest. 1990 Sep;86(3):889–99.
20 Ausó E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology. 2004 Sep;145(9):4037–47.
21 Morte B, Manzano J, Scanlan TS, Vennström B, Bernal J. Aberrant maturation of astrocytes in thyroid hormone receptor alpha 1 knockout mice reveals an interplay between thyroid hormone receptor isoforms. Endocrinology. 2004 Mar;145(3):1386–91.
22 Powell MH, Nguyen HV, Gilbert M, Parekh M, Colon-Perez LM, Mareci TH et al. Magnetic resonance imaging and volumetric analysis: novel tools to study the effects of thyroid hormone disruption on white matter development. Neurotoxicology. 2012 Oct;33(5): 1322–9.

23 Wallis K, Sjögren M, van Hogerlinden M, Silberberg G, Fisahn A, Nordström K et al. Locomotor deficiencies and aberrant development of subtype-specific GABAergic interneurons caused by an unliganded thyroid hormone receptor alpha1. J Neurosci. 2008 Feb;28(8):1904–15.
24 Sawano E, Takahashi M, Negishi T, Tashiro T. Thyroid hormone-dependent development of the GABAergic pre- and post-synaptic components in the rat hippocampus. Int J Dev Neurosci. 2013 Dec;31(8):751–61.
25 Van Herck SL, Delbaere J, Bourgeois NM, McAllan BM, Richardson SJ, Darras VM. Expression of thyroid hormone transporters and deiodinases at the brain barriers in the embryonic chicken: insights into the regulation of thyroid hormone availability during neurodevelopment. Gen Comp Endocrinol. 2015 Apr;214:30–9.
26 Faustino LC, Ortiga-Carvalho TM. Thyroid hormone role on cerebellar development and maintenance: a perspective based on transgenic mouse models. Front Endocrinol (Lausanne). 2014 May;5:75.
27 Guadaño-Ferraz A, Escámez MJ, Rausell E, Bernal J: Expression of type 2 iodothyronine deiodinase in hypothyroid rat brain indicates an important role of thyroid hormone in the development of specific primary sensory systems. J Neurosci 1999;19:3430–9.
28 Mayerl S, Müller J, Bauer R, Richert S, Kassmann CM, Darras VM et al. Transporters MCT8 and OATP1C1 maintain murine brain thyroid hormone homeostasis. J Clin Invest. 2014 May;124(5):1987–99.
29 Kester MH, Martinez de Mena R, Obregon MJ, Marinkovic D, Howatson A, Visser TJ et al. Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas. J Clin Endocrinol Metab. 2004 Jul;89(7):3117–28.
30 Rovet JF. The role of thyroid hormones for brain development and cognitive function. Endocr Dev. 2014;26:26–43.
31 Lischinsky JE, Skocic J, Clairman H, Rovet J. Preliminary findings show maternal hypothyroidism may contribute to abnormal cortical morphology in offspring. Front Endocrinol (Lausanne). 2016 Feb;7:16.
32 Dimitropoulos A, Molinari L, Etter K, Torresani T, Lang-Muritano M, Jenni OG et al. Children with congenital hypothyroidism: long-term intellectual outcome after early high-dose treatment. Pediatr Res. 2009 Feb; 65(2):242–8.
33 Smith L. Updated AAP guidelines on newborn screening and therapy for congenital hypothyroidism. Am Fam Physician. 2007;76: 439.
34 Léger J, Olivieri A, Donaldson M, Torresani T, Krude H, van Vliet G et al.; ESPE-PES-SLEP-JSPE-APEG-APPES-ISPAE; Congenital Hypothyroidism Consensus Conference Group. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab. 2014 Feb;99(2):363–84.
35 Selva KA, Mandel SH, Rien L, Sesser D, Miyahira R, Skeels M et al. Initial treatment dose of L-thyroxine in congenital hypothyroidism. J Pediatr. 2002 Dec;141(6):786–92.
36 Albert BB, Heather N, Derraik JG, Cutfield WS, Wouldes T, Tregurtha S et al. Neurodevelopmental and body composition outcomes in children with congenital hypothyroidism treated with high-dose initial replacement and close monitoring. J Clin Endocrinol Metab. 2013 Sep;98(9):3663–70.
37 Buluş AD, Tiftik E. Evaluation of neurodevelopment of children with congenital hypothyroidism by the Denver Developmental Screening Test. J Pediatr Endocrinol Metab. 2017 Oct;30(10):1061–6.
38 Hauri-Hohl A, Meyer-Böni M, Lang-Muritano M, Hauri-Hohl M, Schoenle EJ, Biason-Lauber A. Aromatase deficiency owing to a functional variant in the placenta promoter and a novel missense mutation in the CYP19A1 gene. Clin Endocrinol (Oxf). 2011 Jul; 75(1):39–43.
39 Grüters A, Liesenkötter KP, Zapico M, Jenner A, Dütting C, Pfeiffer E et al. Results of the screening program for congenital hypothyroidism in Berlin (1978-1995). Exp Clin Endocrinol Diabetes. 1997;105(S 04 Suppl 4): 28–31.
40 Boileau P, Bain P, Rives S, Toublanc J-E: Earlier onset of treatment or increment in LT4 dose in screened congenital hypothyroidism: which as the more important factor for IQ at 7 years? Horm Res 2004;61:228–33.
41 van der Sluijs Veer L, Kempers MJ, Wiedijk BM, Last BF, Grootenhuis MA, Vulsma T. Evaluation of cognitive and motor development in toddlers with congenital hypothyroidism diagnosed by neonatal screening. J Dev Behav Pediatr. 2012 Oct;33(8):633–40.
42 Seo MK, Yoon JS, So CH, Lee HS, Hwang JS. Intellectual development in preschool children with early treated congenital hypothyroidism. Ann Pediatr Endocrinol Metab. 2017 Jun;22(2):102–7.
43 Huo K, Zhang Z, Zhao D, Li H, Wang J, Wang X, et al.: Risk factors for neurodevelopmental deficits in congenital hypothyroidism after early substitution treatment. Endocr J 2011; 58:355–61.
44 Tuhan H, Abaci A, Cicek G, Anik A, Catli G, Demir K et al. Levothyroxine replacement in primary congenital hypothyroidism: the higher the initial dose the higher the rate of overtreatment. J Pediatr Endocrinol Metab. 2016 Feb;29(2):133–8.
45 Corbetta C, Weber G, Cortinovis F, Calebiro D, Passoni A, Vigone MC et al. A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism (CH). Clin Endocrinol (Oxf). 2009 Nov;71(5): 739–45.
46 Alm J, Hagenfeldt L, Larsson A, Lundberg K. Incidence of congenital hypothyroidism: retrospective study of neonatal laboratory screening versus clinical symptoms as indicators leading to diagnosis. Br Med J (Clin Res Ed) 1984;289:1171–5.
47 Perez-Lobato R, Mustieles V, Calvente I, Jimenez-Diaz I, Ramos R, Caballero-Casero N et al. Exposure to bisphenol A and behavior in school-age children. Neurotoxicology. 2016 Mar;53:12–9.
48 Ergür AT, Taner Y, Ata E, Melek E, Bakar EE, Sancak T. Neurocognitive functions in children and adolescents with subclinical hypothyroidism. J Clin Res Pediatr Endocrinol. 2012 Mar;4(1):21–4.
49 Wu T, Flowers JW, Tudiver F, Wilson JL, Punyasavatsut N. Subclinical thyroid disorders and cognitive performance among adolescents in the United States. BMC Pediatr. 2006 Apr;6(1):12.
50 Cerbone M, Bravaccio C, Capalbo D, Polizzi M, Wasniewska M, Cioffi D et al. Linear growth and intellectual outcome in children with long-term idiopathic subclinical hypothyroidism. Eur J Endocrinol. 2011 Apr; 164(4):591–7.
51 Osborn DA, Hunt RW. Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2007 Jan;(1): CD005948.
52 Andersen SL, Laurberg P, Wu CS, Olsen J. Maternal thyroid dysfunction and risk of seizure in the child: a Danish nationwide cohort study. J Pregnancy. 2013;2013:636705.
53 Andersen SL, Olsen J, Wu CS, Laurberg P. Psychiatric disease in late adolescence and young adulthood. Foetal programming by maternal hypothyroidism? Clin Endocrinol (Oxf). 2014 Jul;81(1):126–33.
54 Dosiou C, Medici M. Management of endocrine disease: isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns. Eur J Endocrinol. 2017 Jan; 176(1):R21–38.
55 Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S et al.; Lancet Nutrition Interventions Review Group, the Maternal and Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013 Aug;382(9890): 452–77.

56 Ganaie MA, Charoo BA, Sofi RA, Ahmed A, Bhat JI: Maternal overt hypothyroidism and neurobehavioral outcome of neonates: a cohort study from an iodine-deficient area of Northern India. Indian Pediatr 2015;52:864–6.
57 Nazeri P, Mirmiran P, Shiva N, Mehrabi Y, Mojarrad M, Azizi F. Iodine nutrition status in lactating mothers residing in countries with mandatory and voluntary iodine fortification programs: an updated systematic review. Thyroid. 2015 Jun;25(6):611–20.
58 Watutantrige Fernando S, Cavedon E, Nacamulli D, Pozza D, Ermolao A, Zaccaria M et al. Iodine status from childhood to adulthood in females living in North-East Italy: iodine deficiency is still an issue. Eur J Nutr. 2016 Feb;55(1):335–40.
59 Min H, Dong J, Wang Y, Wang Y, Teng W, Xi Q et al. Maternal Hypothyroxinemia-Induced Neurodevelopmental Impairments in the Progeny. Mol Neurobiol. 2016 Apr;53(3):1613–24.
60 Harding KB, Peña-Rosas JP, Webster AC, Yap CM, Payne BA, Ota E et al. Iodine supplementation for women during the preconception, pregnancy and postpartum period. Cochrane Database Syst Rev. 2017 Mar;3:CD011761.
61 Ghassabian A, Bongers-Schokking JJ, de Rijke YB, van Mil N, Jaddoe VW, de Muinck Keizer-Schrama SM et al. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. Thyroid. 2012 Feb;22(2):178–86.
62 Velasco I, Taylor P. Identifying and treating subclinical thyroid dysfunction in pregnancy: emerging controversies. Eur J Endocrinol. 2018 Jan;178(1):D1–12.
63 Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med. 2017 Mar;376(9):815–25.
64 LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? Thyroid. 2005 Jan;15(1):60–71.