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Imprinting of maternal thyroid hormones in the offspring

María Cecilia Opazo[a], Henny Haensgen[b], Karen Bohmwald[c], Luis F. Venegas[a], Helene Boudin[f], Alvaro A. Elorza[g], Felipe Simon[a], Carlos Fardella[e], Susan M. Bueno[c,d], Alexis M. Kalergis[c,d], and Claudia A. Riedel[a]

[a]Departamento de Ciencias Biológicas, Millennium Institute on Immunology and Immunotherapy, Facultad de Ciencias Biológicas y Facultad de Medicina, Universidad Andres Bello, Santiago, Chile; [b]The Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; [c]Millennium Institute on Immunology and Immunotherapy, Departamento de Genética Molecular y Microbiología, Facultad de Ciencias Biológicas Pontificia Universidad Católica de Chile, Santiago, Chile; [d]INSERM UMR1064, Nantes, France; [e]Millenium Institute on Immunology and immunotherapy, Departamento de Endocrinología, Faculta de Medicina, Pontificia Universidad Católica de Chile; Santiago, Chile; [f]INSERM UMR913, Nantes, France; [g]Centro de Investigaciones Biomedicas, Millenium Institute on Immunology and Immunotherapy, Facultad de Ciencias Biológicas y Faculta de Medicina, Universidad Andres Bello

ABSTRACT

Thyroid hormones (THs) during pregnancy contribute significantly to cellular differentiation and development in several tissues of the offspring, principally the central nervous system (CNS). TH deficiencies, such as hypothyroidism or hypothyroxinemia, are highly frequent during pregnancy worldwide and known to be detrimental for the development of the fetus. The function of CNS in the offspring gestated under TH deficiency will be irreversible impaired, causing low intellectual quotient, attention deficit, and mental retardation. On the other hand, little is known about the effects of TH deficiency in the offspring immune system, being the prevalent notion that the effects are reversible and only for a while will affect the number of B and T cells. Recent studies have shown that maternal hypothyroidism can altered the function of immune system in the offspring, rendering the female offspring more susceptible to suffer autoimmune-inflammatory diseases, such as experimental autoimmune encephalomyelitis (EAE) and to be more resistant to a bacterial infection. In this article we discuss these recent findings, as well as the possible mechanisms underlying these effects and the potential implications for human health.

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Introduction

Thyroid hormones (THs) are essential for cell metabolism, differentiation and function [1,2]. TH deficiencies, like hypothyroidism and hypothyroxinemia, are highly frequent endocrine pathologies around the world population. The prevalence of hypothyroidism (TSH >10 mU/l) fluctuates around 0.3–0.4% [3,4] in the United States, according to the NHANES health survey hypothyroidism reaches the 3.7% of the population [5]. A recent report, indicates that the prevalence of the hypothyroidism in the UK is 1–2% [6]. The prevalence of this condition increases to 9.3% in women population [3–7] and 0.6–2.5% in pregnant women [8,9]. The first and leading cause of TH deficiency worldwide is the lack of iodide (I^-) in the diet, given that I^- plays a fundamental role in the structure and function of THs [10]. I^- is obtained exclusively from the diet and given that it is scarce element in nature it is highly recommend to introduce it in salt [11]. According to the analysis of Pearce et al. [12] based on the analysis of the urinary iodine concentration (UIC), there are 30 countries suffering from I^- deficiency (UIC: 20–49 μg/L) and twenty one countries have mild I^- intake (UIC: 59–99 μg/L); Ten countries affected by high iodide intake and 111 countries (UIC $\geq$ 300 μg/L), in Europe, Asia, Africa, Central and South America and Oceania regions to have an adequate intake of iodide (UIC: 100–299 μg/L) [12]. In spite of the adequate iodide intake, 12% of the population in these countries suffers hypothyroidism mainly to the development of autoimmune diseases against the thyroid gland, such as thyroiditis of Hashimoto, which shows a higher prevalence in women (27%) than in men (7%) [3]. In these countries, people using iodized salt by choice still can remain TH deficient [3] increasing the incidence of THs deficiency-related diseases. The latter point becomes especially relevant when women become pregnant. This situation is extremely risky due to it compromises pregnancy and because maternal TH during pregnancy are essential for development and differentiation of brain, bone, muscle, heart and liver [13–16]. However, the

CONTACT Claudia A. Riedel criedel99@yahoo.com Departamento de Ciencias Biológicas, Millennium Institute on Immunology and Immunotherapy, Facultad de Ciencias Biológicas y Facultad de Medicina, Universidad Andrés Bello, Santiago, 837960 Chile.
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importance of maternal TH for the offspring immune system it is not well known because it has not been profusely studied. The aim of this review is to discuss about what is known and the lately information that will break the notion that the offspring immune system is not altered by the status of TH during pregnancy.

Thyroid hormones

The main thyroid hormones (THs) in mammals are thyroxine (T_4) and 3,5,3′-triiodo-L-thyronine (T_3). THs are synthetized and secreted by the thyroid gland [13,14]. The secretion of THs is finely regulated by thyroid stimulating hormone (TSH), which in turn is secreted by the adenohypophysis and its secretion is negatively regulated by the THs. The most abundantly THs produced by the thyroid gland is T_4, which is considered to be a reservoir for the synthesis of T_3. In fact, T_4 is converted into T_3 by specific deiodinases that are located at the target tissues [17]. T_3 is considered to be the biological active form of THs [18]. At the molecular level, T_3 binds specifically to TH receptors (TRs), that are transcription factors bound to DNA consensus regions [19]. The binding of T_3 to TRs exerts a nuclear genomic effect by either inducing or repressing the expression of target genes [20]. There are reports showing that T_3 and T_4 can affect cell function through a non-genomic mechanism, which is independent of nuclear TRs [21]. This non-genomic mechanism starts at the plasma membrane by interacting with integrin αVß3 and then the generation of second messengers, such as calcium (Ca^{+2}) and cyclic AMP (cAMP) [20]. Thus, THs by different mechanisms genomic and non-genomic can regulate cell differentiation and function.

Maternal thyroid hormones in pregnancy

THs are essential for a healthy pregnancy and for the proper development of the fetus [13–16]. TRs in embryonic human tissue are detected as early as 4th week post-implantation [22]. In embryos, from animal models, TRs are found in the brain at embryonic day 14 (E14). However, the fetus thyroid gland begins late the synthesis of THs close to E17.5–18 [23]. A similar pattern is observed in humans, the expression of TRs occurs at the first trimester of gestation [24] and the fetus thyroid gland stars function after midpregnancy, even though it is not until the end of pregnancy when the synthesis of THs is finely regulated. The reason for this is that the hypothalamus-hypophysis-thyroid axis remains immature in the fetus until gestational week 38th [25], in spite of her/his thyroid gland can capture I^- from gestational week 17 [26]. Given that the fetus thyroid gland during gestation will not properly function, the maternal thyroid gland will be responsible for adequately supply of THs to the fetus [27]. In fact, the most important maternal TH for the fetus is T_4, because T_4 cross the placental barrier and achieve the fetus. The maternal thyroid gland of pregnant women must maintain T_4 levels between 30% and 100% higher than before pregnancy [28] causing a physiological stress to the gland [29–31]. Such a new physiological demand requires an adequate iodine intake by pregnant women that when not fulfilled can compromise the thyroid gland function, causing TH deficiencies including hypothyroidism or hypothyroxinemia [32].

Maternal hypothyroidism and hypothyroxinemia

The most common types of TH deficiencies during pregnancy are hypothyroidism and hypothyroxinemia [33]. Hypothyroidism is a pathological condition characterized by a reduction of T_3 and T_4 and an increase in TSH levels in the serum [34] [25]. Hypothyroidism has 4% of incidence worldwide among women at fertile age and this frequency increases during the pregnancy due to the physiological stress that this condition imposes to the thyroid gland [35]. The main causes of maternal hypothyroidism is a low I^- diet [31] and autoimmune disease against the thyroid gland [36]. Hypothyroidism has several symptoms such as fatigue, dry skin, weight gain, muscle weakness, depression and impaired memory, among others that aware the patient for medical consultation and treatment. However many of these symptoms can be confound with pregnancy symptoms, for that and for the threatened of maternal hypothyroidism to the fetus the American Thyroid Association (ATA) and the European Thyroid Association (ETA) recommend the diagnosis and treatment of hypothyroidism early in pregnancy [37]. Although maternal hypothyroidism is highly frequent condition in pregnant women, maternal hypothyroxinemia could be even more frequent, given that maternal hypothyroxinemia could be a condition that antecedes maternal hypothyroidism [33]. Maternal hypothyroxinemia is a TH deficiency characterized by low T_4 and normal T_3 and TSH levels [35–38]. The hypothyroxinemic pregnant women will not have detectable symptoms given that levels of T_3 are normal [38]. However, the lack of T_4 will impair irreversible the fetus development [39]. It has been reported that one of 20 women suffer hypothyroxinemia being this condition 200 times more frequent than congenital hypothyroidism [25–38]. Maternal hypothyroxinemia could be induced by several factors among them are the low I^- diet [40], some drugs like amiodarone [41], viral infection [42,43] and autoimmune diseases against thyroid gland [36]. Even though there, are many reports showing that maternal hypothyroxinemia causes irreversible fetus damage it is not considered yet for obligatory screening and

treatment [44–46]. The effects of maternal THs deficiencies have been associated with irreversible damage to the CNS [25]. Several reports indicate that THs can significantly modulate the function of immune cells [47]. Little is known about the impact of maternal TH deficiency during pregnancy over the offspring immune system.

Effects of maternal TH deficiency on the offspring CNS

Maternal THs regulate the development of several organs like brain, lungs, and skeletal muscles of the offspring [25–46]. At the cellular level THs control cell differentiation [19] and migration [48]. In humans it has been shown that the maternal T_4 levels correlates with cognitive function of the offspring [49–51]. Maternal TH deficiency at 12-weeks of gestation is associated with developmental delay and cognitive impairment. This fact was observed in children of 10 months of age [49] associated with cognitive and neuromotor delays at the age of 1 and 2 years [51]. Motor activity, language and information processing delay were observed in children [52–54]. Maternal hypothyroxinemia is also associated with attention deficit, a common disorder in children at school age with high prevalence worldwide (5.9–7.1%) [55]. Vermiglio et al. [56] observed that the 68% of the children gestated under hypothyroxinemia conditions present Attention Deficit Hyperactivity Disorder (ADHD), particularly girls gestated under low levels of thyroid hormones [57,58]. A decrease in the IQ scores, was observed in the offspring gestated in hypothyroxinemia. A low IQ score is indicative of intellectual disability (ID) and in more severe cases mental retardation [59]. Children gestated under maternal hypothyroxinemia presents 4.3 to 9 points lower IQ than normally gestated children [52–60]. More recently, increased risks for the offspring to develop autism have been associated to maternal hypothyroxinemia. Autism is a neurodevelopment disorder which is characterized by a deficit in social behavior and nonverbal interactions that develops during the first 3 years of age [61]. A prospective cohort study showed a 3.8 times increased probability of having a child with autism [62] and an evaluation of autistic symptoms at age 6 years showed higher scores for children gestated under maternal hypothyroxinemia [63]. Recently, maternal hypothyroxinemia has been directly related with schizophrenia showing that maternal hypothyroxinemia increases 2 times the odds of developing these mental disorder [64].

THs bind TRs expressed in neurons [65] oligodendrocytes [66] and astrocytes [67]. The main effects of THs over the offspring CNS are summarized in Table 1. The brain region affected during maternal TH deficiency depends on developmental stage [16], being affected at early stages of development the basal ganglia, cerebellum and hippocampus which can undergo cito-architectural and functional alterations [45]. Studies performed in animal models showed that maternal hypothyroxinemia alters the radial migration of projection neurons [22] and tangential migration of cortical neurons [68]. In the hippocampus it has been observed a decreased proportion of mature glial cell fibers showing an impaired maturation of these cells that are involved on hippocampal neural migration [69]. The hippocampus is a CNS structure that plays an important role in the consolidation of the information from short-term memory to long term memory and spatial navigation [70]. It has been demonstrated that the offspring gestated in hypothyroxinemia, has several alterations in the hippocampus region, such as an increase in neuronal death at the CA1 region [71], reduction in the number and size of neurites and axon size at the CA3 region, and impairment in sprouting dendrites at the dentate gyrus [72]. The offspring gestated under hypothyroxinemia conditions showed impairment in spatial learning capacity that correlates with alterations at the glutamatergic synapsis [71–73]. Gestation in hypothyroxinemia induces cerebellar dysfunction by a reduction of the parallel fiber–Purkinje cell (PF-PC) synapses trough a downregulation of the neurexin1/Cbln1/GluD2 complex involved in the formation and maintenance of these kind of synapsys [74]. The proliferation of cerebellar granule neuron precursors (CGNP) is dependent upon sonic hegdehog (Shh) signaling which directly induces the expression of N-Myc that activates proliferation of these cells [75]. Moreover, there are key enzymatic activities altered in the brain of offspring gestated in TH deficiency. In the offspring of partially thyroidectomized pregnant rats at day 16 of gestation the activity of monoamino oxidase (MAO) and choline acetyltransferase (ChAT) were

Table 1. Effects of maternal THs in the offspring CNS.

Effect	Reference
Alteration of cell migration, dendrite and axon outgrowth	[22,48,68–69]
Alteration of CNS maturation	[16–69]
Alteration of neurotransmitter system	[76–79]
Regulation of relevant genes for spatial learning and synaptic plasticity	[71–73]
Down regulation of MBP	[83–86]
Increase cell death into CA1 hippocampal region	[72]
Alteration in axon and neurite growth in CA3 hippocampal region	[71,72]
Alteration of spatial learning and LTP impairment	[71]
Up regulation of proteins important for synaptic function (PSD-95 and NR1)	[71]
Down regulation of spatial learning related genes (c-Fos and c-Jun)	[71]
Decreased number of myelinated axons and thickness of myelin sheets	[86]

LTP: Long term potentiation, MBP: Myelin Basic Protein, PSD-95: Postsynaptic density −95, NR1: NR1 subunit of the NMDA receptor.

significantly decrease meanwhile DOPA decarboxylase (DDC) activity was increased [76] at this stage of development the neurotransmitters have neurotropic roles indicating that the alteration of their levels could impair brain development. This is the case for offspring whose mothers were treated with propylthiouracil (PTU) during gestation. PTU is anti-thyroid drug used to inhibit thyroid function due to it blocks thyroid peroxidase (TPO) an important enzyme for THs synthesis. The offspring showed a decrease in acetylcholinesterase (AChE) activity in the brain of the offspring altering cognition [77–79]. Additionally, PTU treatment induces a decrease in brain Na^+K^+ ATPase activity [77] that is thought to be involved in neurotoxicity caused by hypothyroidism by modulating neuronal excitability, metabolic energy production and the uptake and release of neurotransmitters [80]. Additionally, it has been described that maternal hypothyroidism induces a decrease in total content and phosphorylation of the CREB transcription factor, as well as CREB activators, such as CaMK, Ras-ERK and PI3-AKT [81]. CREB plays a key role during hippocampal LTP and contributes to neuronal proliferation and synapse formation [82]. Thyroid hormones have a key role in to differentiation of oligodendrocyte precursor cells (OPCs) to oligodendrocytes [83]. Several reports indicate that T_3 and T_4 are necessary for OPC differentiation and for oligodendrocytes activity [83,84] in fact the timing of differentiation depend on T_3 and its receptors [85]. Animals models of THs deficiency showed a reduced number of oligodendrocytes together with a deficit in myelination [86], this due to the regulation by THs of the expression of myelin basic protein (MBP) which is an important component of myelin and the 2′,3-cyclic nucleotide 3′-phosphodiesterase-2 (CNP-2). The latter links myelin proteins to the cytoskeleton during myelin sheet formation [87,88]. Moreover, THs can induce the formation of more oligodendrocytes from multipotent stem cells this could be to the presence of a enhancer element region in the gene encondig nestin, a intermediate filament protein, which contains binding sites for TR [89]. In early development, THs triggers OPCs cell cycle exit in cooperation with the platelet-derived growth factor (PDGF) to undergo terminal differentiation [90]. Different TR isoforms participate during oligodendrocytes differentiation; TRß1 isoform increases during oligodendrocytes differentiation and its thought to be a molecular partner of p53 in cell cycle regulation [91]. TRα expression declines when OPCs progress to myelinating oligodendrocytes and TRß1 is associated to terminal maturation [92]. Oligondendrocytes present the same number of TR binding sites as neurons which twice the number present in astrocytes suggesting a key role for THs in oligodendrocyte differentiation and survival [93]. It has been shown that these alterations at the CNS, of the offspring gestated in TH deficiency, are irreversible and thus maintained for life.

Maternal hyperthyroidism

Maternal hyperthyroidism is defined as a low or suppressed TSH serum level in the presence of high levels of free T_4 (fT_4) [94] and it is not and isolated issue. The main cause of hyperthyroidism is Grave's disease, with an incidence equal to 35–50 cases per 100 000 per year in 20–29 year women. The incidence is higher in women over 30 years (55–80 cases per 100 000) [95]. According to the NHANES survey, the incidence of maternal hyperthyroidism is 65 cases per 100 000 per year with a higher incidence during the first trimester of pregnancy [5]. In addition to Grave's disease, several causes of maternal hyperthyroidism have been described, such as hCG-induced transient thyrothyrotoxicosis [96], a mutation present in the TSH receptor that increases its sensitivity to hCG [96] and TSH-producing pituitary adenoma [97], among others [94]. The diagnosis of maternal hyperthyroidism can be difficult due to the similarity with natural physiological changes that take place during pregnancy. However, maternal hyperthyroidism can be identified by the presence of severe tachycardia and thyromegaly, accompanied by exophthalmia and the lack of weight gain [98]. The consequences of maternal hyperthyroidism can be observed in both mother and fetus. Therefore, not only the mother suffers of hyperthyroidism but the fetus can also develop this pathology, increasing the associated risks, which in more severe cases can lead to fetal death [95–99]. During pregnancy, there is a transfer of thyroid-stimulating immunoglobulin from the mother to the fetus inducing the activation of the TSH receptor that promotes TH secretion and a thyrotoxicosis in utero that remains postnatally [100]. As for the mother, problems such as heart failure [101,102], preeclampsia [101–103] and premature delivery [101,102] have been observed.

Effects of maternal hyperthyroidism over the offspring

Due to their important role during the offspring development, an alteration in the levels of THs leads to physiological alterations that can last until adulthood. Millar et al. [103] reported that maternal hyperthyroidism increases almost 10 times the risk of low birth weight [103]. At the fetal level, development of goiter is one of the earliest characteristics of fetal hyperthyroidism and is associated to fetal tachycardia, which is a common feature that is used a diagnose parameter. Growth retardation

and craniosynostosis were also observed. In more severe cases, developmental alterations in the CNS can induce cognitive impairment and mental retardation [102–104]. Another important feature derived from maternal hyperthyroidism, is the presence of non-immune fetal hydrops, which are characterized by an increase of fluids in fetal compartments [104]. The presence of fetal hydrops increases the risk of mortality and leads to severe preeclampsia [105]. Advanced skeletal maturation is also observed in the fetus of hyperthyroid mothers, as a consequence of the action of thyroid hormones on fetal bone tissues [106]. Fetal prognosis depends on the control of the thyrotoxicosis and a direct association has been shown for treatment and the complexity of the observed alterations [107]. At the neonatal level, gestational hyperthyroidism has been associated to congenital malformations, such as malformation of the ear lobe, omphalocele and harelip [108]. These observations have also been linked to the effects of the use of antithyroid drugs [109] during pregnancy. The use of murine models has allowed us to assess the effects of maternal hyperthyroidism in a deeper level. Studies performed in mice have shown that an excess of TH results in an accelerated in utero development with behavioral deficit during adulthood [97]. The excess of T_4, can affect the maturation of neural circuits in the cortex and hippocampus [110,111]. In the cerebellum a delay in the growth of dendrites of Purkinje cells was observed, together with a decreased density of the dendritic network [112]. Similar data were obtained when basket cells were analyzed [112]. This phenotype was associated to an excess of oxidative stress due to an alteration of the antioxidant capacity [112]. The thyroid gland of offspring is also affected by maternal hyperthyroidism, as a severe atrophy of the thyroid gland with a reduction in the number of follicles together with edema has been reported for the offspring of hyperthyroid mothers [113]. In the same study, a significant increase of 5′-monodeiodinase (5′-DI) in the brain of the offspring of hyperthyroid mothers was observed suggesting a locally increased production of T_3 interpreted as a local mechanism to prevent the excess of T_4 [113]. Additionally, the offspring of hyperthyroid mothers show increased levels of catecholamine, serotonin, norepinephrine and dopamine, which are attributed to an altered amine metabolism due to the increased levels of thyroxin [113]. Two-photon imaging of the visual cortex showed a significantly increased retraction of the thalamo-cortical axonal branches in the offspring of hyperthyroid mothers along with a decrease of synapse stability and excessive synaptic loss, as compared to control and hypothyroid groups [114]. Even though THs are known to play a key role in brain development, little is known about the molecular mechanism involved in this process. Along these lines, the work of Chen at al. [115] showed that hyperthyroidism during pregnancy inhibits the proliferation and maintenance of embryonic neural progenitor cells by decreasing the phosphorylation of Janus kinases 1 and 2 (JAK1, JAK2). These signaling molecules activate the transcription factor STAT3 by inhibiting the STAT3-DNA binding activity. STAT3 activation defines the fate of neural progenitor cells [116] but the extracellular signals involved in STAT3 regulation are not completely identified. Together these effects of maternal hyperthyroidism can contribute to the altered cognitive phenotype described. Additionally, alterations of TH levels at neonatal period can induce a deficit of nerve cells myelination [117], a decreased number of oligodendrocytes due apoptosis [118] and an alteration in the number and function of the Leydig cells altering testosterone production [119]. A recent study, showed an effect in growth hormone (GH) expression. GH gene is directly regulated by T_3 [120–124]. The induction of a transitory hyperthyroidism during the neonatal period induces a decrease in the expression of GH in adult animals leading to a significantly decrease in body weight, length (head to tail), reduced lean body mass (LBM) and bone mineral density (BMD). These findings suggest that an increase of TH during this period, can induce tissue specific responses that result in a long term modification of GH secretion leading to physiological alterations that can be observed during the adult life [123]. Despite the evidence analyzed above, the complete effects of prenatal hyperthyroidism are still not understood.

The role of thyroid hormones and TSH in the immune system

The immune system compromises organs, cells and molecules involved in the surveillance of organs for keeping tolerance and for mounting a defense or inflammatory response in case of pathogens alert. The first mechanism of defense is accomplished by innate immune cells, such us macrophages, natural killer (NK) cells, monocytes and dendritic cells (DCs) [124]. The second is the adaptive immune response, principally mediated by DCs, which are the most efficient antigen-presenting cells (APC) and key cells like T and B cell. Furthermore, DCs are also involved in modulating tolerance and the maintenance of a regulated immune response [125]. While the adaptive cellular immune response is directed both by $CD4^+$ and $CD8^+$ T cells, B cells are responsible of humoral-antibody responses [126]. Several hormones like prolactin, growth hormone, insulin-like growth factor-I play important roles regulating the function of the immune system [77], in this review we will discuss what is known about THs and TSH over immune system.

Effect of TSH over immune system

TSH can modulate the expression of protein in cells of the immune system inside lymph nodes, thymus and spleen, especially during pathological conditions [127–129]. It has been demonstrated the presence of TSH receptors in DC, monocytes, NK [127] and mitogen activated B cells [130] but not resting B and T cells [131]. The effect of TSH in mitogen activated B cells is associated to an enhanced production of immunoglobulins, which could include autoantibodies [132]. The expression of TSHr in DC cells showed that TSH can enhance their immunogenic capacity of by strengthen their phagocytic activity and the secretion of pro-inflammatory cytokines, including IL-1β and IL-12 [133]. TSH can improve NK cell proliferation capacity and activity [134] (Figure 1). Monocytes have high levels of TSHr expression even more than lymphocytes and NK cells [135]. Upregulation of TSHr on blood monocytes during differentiation in to mature/activated DCs or macrophages could put them available for the use of TSH and or to maintain them in a basal state [129].

The role of THs in the immune system

Exposure of immature DCs to physiological levels of T_3 induces DC maturation, reflected as an increased expression of co-stimulatory molecules as CD80, CD86, MHCII and CD40, IL-12 secretion and an enhanced ability to induce naïve T cell proliferation [133]. T_3 can up-regulate the expression of the TRβ1 in DCs through a NF-κB which can promote DCs maturation and IL-12 secretion through an Akt phosphorylation-dependent signaling pathway [136]. Mature DCs, derived from mouse bone marrow express high levels of TRs in the cytoplasm [133]. Importantly, it was observed that mature DCs derived from murine bone marrow express high levels of TRs in the cytoplasm, both at mRNA and protein level [132]. L-thyroxine (L-T_4) treatment to DCs obtained from human peripheral blood of thyroidectomized patients showed an increased expression of CD86 and the MHC-class II receptor suggesting a modulatory effect of THs over DCs antigen presenting capacity and immunogenicity [133]. The same phenotype was observed *in vitro* for cultures of peripheral blood DCs stimulated with T_3 [137]. Furthermore, the presence of T_3 promotes the secretion of IL-12 and the proliferative response of PBMC cells when are incubated with DCs treated with T_3, supporting the effect of THs over the phenotype and function of DCs [125].

As explained above, T_3 can modulate DC function as it has been shown for macrophages [133]. Recent studies, have suggested an effect of T_3 over macrophage polarization. Macrophage can be polarized by environmental signals that activates specific functional programs [138]. Polarized macrophages can be classified in two main groups: classically activated or M1 and alternatively activated or M2 [138]. M1 macrophages distinguish because they promote inflammation meanwhile M2 macrophages stimulate tissue repair [139]. *In vitro* addition of T_3 can direct polarize macrophage towards a classically M1 with an increased phagocytic activity [138] (Figure 1) and *in vivo* studies using a murine model showing an up-regulation of bacterial phagocytosis when treated with T_4 [139]. Furthermore, addition of T_3 to cultures inhibits the migratory capacity of macrophages, which is consistent with previous observations in murine M1 macrophages [140]. Expression analysis of TH receptors TRα1 and TRβ1performed in macrophages primary

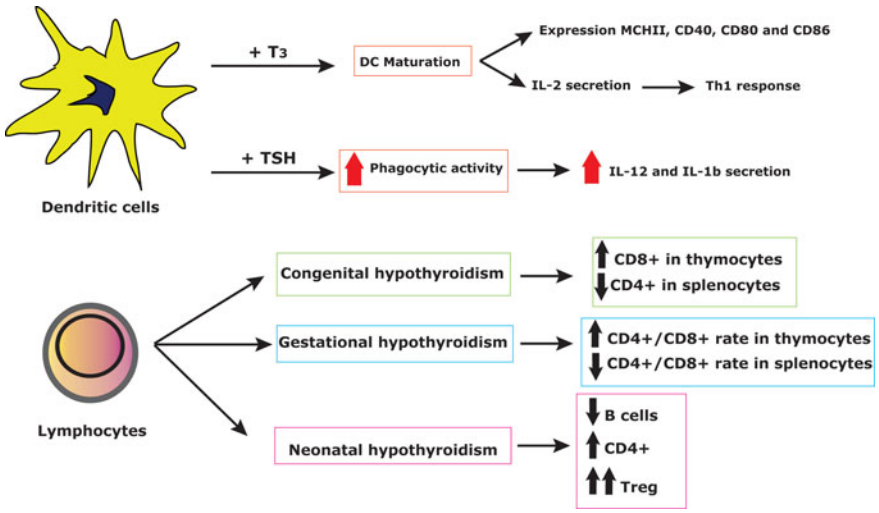

Figure 1. *Thyroid hormone effect(s) on the immune system.* Immature dendritic cells (DCs) isolated from adult mice respond to T_3 or TSH in vitro, which induce DC maturation and an increase in the phagocitic activity as seen by surface markers and interleukines (ILs) secretion. Changes in the proportion of immune cells in the progeny during different developmental stages induced by thyroid hormone deficiency.

cultures showed a differential expression of these receptors [138]. Even though, both activation phenotypes (M1 and M2) express TRα1 and TRβ1, an increased expression of TRβ1 is associated to M2 phenotype [138], this issue was observed in *in vitro* analysis of T_3 stimulated macrophages [138]. This data suggest an anti-inflammatory effect of T_3 trough the modulation of the phenotype and function of macrophages.

Murine models of hyperthyroidism have shown the relationship between NK activity and THs. Although treatment with T_4 did not alter the number of NK cells, NK activity was significantly decreased, suggesting an indirect regulatory role of T_4 through the modulation of IL-2 expression [141]. The lytic capacity of NK is also altered during hyperthyroidism due to an impaired release of lytic factors, such as NKCF (Natural killer cytotoxic factor) [141]. Hyperthyroidism can influence the immune system in various manners: alteration of the immune response [142], antibody production [143], increased chemotaxis [144–145], decrease of pro inflammatory markers [146], increase of lymphocyte proliferation and ROS with the consequent reduction of the antioxidant capacity [142]. Some of these studies report results that seem apparently at variance. Hyperthyroid rats stimulated with BCG showed a reduced migration of monocytes to the peritoneal cavity and decreased production of H_2O_2 by activated macrophages [142], suggesting a suppression of macrophage function by THs. In contrast, the work of Nishizawa et al. [147] showed that *in vitro* addition of T_4 to human macrophages induces ROS generation, an example of the contrasting results regarding hyperthyroidism. Across the literature, the obtained results depend on the duration of the T_4 treatment. Thus, while chronic treatment with T_4 leads to an increased pro-inflammatory response [148], short periods of T_4 treatment induce a decrease of the immune response [149]. In vitro experiments have shown that exogenous administration of T_4 decreases the expression of pro-inflammatory molecules, such as MIP-1α and IL-1β [146] and can stimulate macrophage chemotaxis [145] and phagocytosis [150], suggesting a regulatory role for TH over the immune system.

The effect of thyroid diseases over immune system

The effects of hypothyroidism in the adult immune system have been studied in a wide variety of animal models [131, 151–152]. In hypothyroidism the proportion of T helper cells respect to T suppressor cells was increased together with an increased number of activated T cells in both peripheral blood and spleen cells suggesting that the lack of TH leads to an increase of the inflammatory response [131–153]. The effect of antithyroid drugs treatment, methimazole (MMI) and PTU to induce hypothyroidism has also been widely used to analyze the intercommunication between TH and the immune system [154–156]. A rat hypothyroid model using PTU, showed an alteration of lipid content in polymorphonuclear cells, which are essential components on the innate immune response [157]. Hypothyroidism affects lipid metabolism in polymorphonuclear cells by reducing the expression of cholesterol synthetizing enzyme and the lipid content in these cells, although an increase of serum cholesterol in blood was observed, demonstrating that hypothyroidism alters lipid composition in polymorphonuclear cells which is essential for the cell membrane structure and function of immune cells [157]. To the other hand in a hyperthyroidism rat model by an intra peritoneal injection of large doses of T_4 suppress the effect of the immune response observed as an increased number of activated T cells in both peripheral and spleen cells [131], a similar phenotype was observed by Hassman et al. [158] in rats with a subcutaneous administration of T_4, where it was induced suppression of the immune response by lowering the number of T cells in the circulation [158].

Autoimmune diseases and its association to thyroid diseases

It seems to be that there is an association between several autoimmune diseases and thyroid diseases [159]. These association have been reported for systemic lupus erythematosus (SLE), Sjörgren's syndrome and giant cell arteritis [160]. SLE is an autoimmune disease with unknown etiology in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes directed mainly to DNA [161]. Regarding to SLE, there are several studies related to hypothyroidism [160,165,163]. There is an association between the demographical risk group for thyroid disease and SLE, which comprehends young and middle age women [164]. Weetman et al. (1987) described the clinical association of SLE and Hashimoto's thyroiditis by determination of antinuclear factor (ANF, antinuclear antibodies) in 13% of the Hashimoto's patients. High levels of ANF are characteristic in SLE patients and are used as part of the criteria for SLE diagnosis [163]. In the other hand, thyroglobulin (Tg) and microsomal (Mic) antibodies are twice more frequent in SLE patients, a condition associated to thyroid failure, demonstrating that SLE patients present a high frequency of hypothyroidism [163]. In 2002, a study of 300 SLE patients, showed a 5.7% of hypothyroidism prevalence compared to the 1% of the normal control group combined with a high prevalence of thyroid autoantibodies (68%) [160]. Following

this idea, it is described that SLE patients with an euthyroid condition present higher prevalence of positive anti-Tg and thyroid peroxidase (TPO) antibodies [166] indicating that patients with SLE can present thyroid autoantibodies but their presence in serum do not correlate with specific abnormalities of thyroid function [166]. MLR lpr/lpr mice are autosomal recessive for the lymphoproliferative gene (*lpr*) associated to B and T cell hyperplasia. These mice develop a lupus-like disease and they are used to study the progression of this disease [167]. Further analysis on these mice showed decreased levels of T_4 and increased levels of TSH accompanied with high levels of antibodies against Tg and TPO and extensive lymphocyte infiltration of the thyroid tissue, thus they are hypothyroid and present autoimmune thyroiditis suggesting a role of TH into autoimmune diseases [167]. At a molecular level is still unknown the role of TH in autoimmune diseases like SLE. In SLE, there is an increase of $CD27^+$ B cells, an impaired regulation of APC function due to a decreased of TGF-1β or IL-2, an increase in pro-inflammatory cytokines, a decrease of T_{reg} function due to the suppression of g-chain cytokines and a decrease of IL-10 and IL-35 secretion [161–167]. Higher levels of TSH during hypothyroidism can induce an increase of production of immunoglobulin due to TSH binding to activated B cells, which could include autoantibodies [132]. Regarding to T cell activation mediated by dendritic cells (DCs), the role of TSH is to enhance the immunogenic capacity of DCs activation since TSH can strengthen their phagocytic activity and activate the secretion of pro-inflammatory cytokines, including IL-1β and IL-12 [162–168]. IL-6, IL-17, IL-18 and TNFα are cytokines involved in inflammatory processes and tissue injury in lupus [167].

Autoimmune polyendocrine syndrome (APS) is defined as a multiple endocrine gland insufficiency associated to and autoimmune disease in a patient [166]. APSs are classified in to 2 major groups: APS I and APS II [103] but it has been described also two other APS III and APS IV [166]. In particular, APS-II present as major pathological conditions the presence of autoimmune adrenalitis (Addison's disease) together with a thyroid autoimmune disease (TAD), such as Graves´s disease and the presence of another autoimmune disease as type 1 diabetes [152]. APS-II prevalence is 5 per 100.000 inhabitants and it is three times more frequent in women than in males [169]. An alteration between effector and regulatory T cells balance is the main characteristic of APS, the recognition of peptides from target organs induces the production of autoantibodies that contribute to development of the syndrome [154]. Human leucocyte antigen (*HLA*) genes determinate target specificity and B cells are stimulated by T cells inducing antibody production generating tissue damage [167]. Grave's disease appears in genetically susceptible individuals that carry the *HLA* alleles *HLA-DR3* and DQA1∗0501 [170]. These two alleles confer the highest risk of development the disease [171]. These patients present diffuse lymphocytic infiltration of the thyroid gland accompanied with a loss of tolerance to thyroid antigens as TSH receptor, Tg, TPO and NIS generating autoantibodies that can stimulate or inhibit TH secretion [172]. An imbalance towards TSH receptor stimulation results in hyperthyroidism [172]. There is also a contribution of the cytotoxic T lymphocyte-associated (CTLA-4) gen, which is negative regulator of T cell activation in order to control T cell response. It has been proposed that a reduction of CTLA-4 repressive activity due to *CTLA-4* polymorphisms increases the number of overreacting T cells thus predisposing to autoimmunity [170]. *CTLA-4* gene is associated to several autoimmune conditions and to the production of anti-thyroid antibodies [173,174]. Besides the regulation of T cells, CTLA-4 can interact with APCs binding to the same ligands (CD80 and CD86) as CD28 but with higher affinity. So far, little is known about the CTLA-4 mediated signaling in the APC [175] but it has been shown that by suppressing the extracellular signal regulated kinase (ERK) and Jun kinase (JNK) activity interferes TCR proximal signaling [176]. Moreover, it can decrease the transcription factor activity of AP-1, NFAT and NF-κB in activated T Cells [177]. Another susceptibility gene is *CD40*, which is expressed on B cells, regulating B cell activation and antibody production [170]. A single nucleotide polymorphism (SNP) in *CD40* can alter its translation and expression [178]. CD40 is expressed also on thyroid follicular cells [179], which are involved in Grave's disease development. In fact, increased expression of CD40 on B cells enhance the production of TSH receptor antibodies [180] meanwhile increase expression of CD40 in thyrocytes triggers an autoimmune response to thyroid by the resident T cells [170]. Finally, the lymphoid tyrosine phosphatase (*PTPN22*) has been described as susceptibility gene [170]. PTPN22 is a negative regulator of T cell activation and it is associated with de development of autoimmune thyroid disease by a gain-of-function variant (R620W) which was observed in patients that suffers Grave's disease [181]. T regulatory cells genes such as *CD25* and *FOXP3* have been also related to autoimmune thyroid diseases, depletion of T regulatory cells in mice increases the susceptibility to Grave´s disease [182]. Together these findings can contribute to understand the molecular mechanism that underlie to the observed phenotypes in APSII.

Table 2. Effects of TSH and THs in the immune system.

Effect	Reference
Activation of B cells and antibodies production	[132]
Maturation of DC and activation of T cells	[152–168]
Increases of phagocytic activity and secretion of pro-inflammatory cytokines by DC	[133]
Maturation of DC	[125,133–137]
Polarization of macrophages to M1 phenotype	[138]
Increases of bacterial phagocytic by macrophages	[139]
Down-regulated of suppression of immune respond	[131,153–158]
Decreases of lipid content to innate immune respond	[157]
Increases the severity of autoimmune diseases	[160–164]

Taking together, there is an interconnection between thyroid hormones and immune system that can influence the onset of an autoimmune disease. The effects of TSH and THs on the immune system are summarized in Table 2.

The effect of thyroid hormone deficiency in the offspring immune response

The development of immune cells begins in the mesoderm and the extra embryonic mesenchymal tissue [169]. In humans, pluripotent progenitors cells of erythrocytes and macrophages are detected at gestational week 3rd–4th. Then these cells migrate to the liver at week 4th of gestation where they will differentiate. These cells are detected in the circulation as they migrate to the liver, the major site of blood cells formation. In consequence the liver increases its size due to cell proliferation until gestational week 10th [169]. At this point, there is higher proliferation but little differentiation so a small population of granulocytes and macrophages are observed. Finally, these cells arrive to the thymus and spleen at gestational week 12th and stem cells to the bone marrow [169]. From gestational week 12th to 19th it can be observed high levels of erythrocytes and granulocytes in fetal blood cultures. Hepatic blood cell formation declines in the third gestational trimester and concludes soon after birth [169]. The contribution of maternal THs to the offspring immune system was initially analyzed by inducing of neonatal hypothyroidism with PTU added to the drinking water of lactating rats from postnatal day 1 to 42 [154]. The authors demonstrated that postnatal hypothyroidism induces a temporary immunomodulation in the neonates [154]. The authors, observed a decrease in spleen and thymus weight together with an increased on the proportion of splenic TCD4$^+$ cells, NK cells decreasing their lytic ability consistent with previous report indicating that THs can affects NK function [134] and a decrease of the proportion of B cells [154]. In another experiment PTU was also used to induce prenatal and postnatal (PN) hypothyroidism from gestational day 10 until postnatal week 3, observing that the amount of both CD4$^+$ and CD8$^+$ T cells increased after PTU treatment. They also found that within CD4$^+$ T cells, there was an increase of CD4$^+$CD25$^+$ regulatory T cells population in spleen and CD3$^+$CD71$^+$ (active T cell) population in peripheral blood at PNW11 [156]. There is some controversy over the results reported by Rooney et al., given Nakamura et al., opposite results. This can be due to differences in their experimental protocol, such as the PTU exposure period and doses. The effects of the PTU treatment were reverted to normal levels at PNW6 and PNW11, suggesting that anti-thyroid drugs administered at postnatal stages have a temporary and reversible modulatory effect on the immune system [156].

The effect of congenital hypothyroidism in the immune system development was studied in homozygotes mice for the *hyt* mutation. This mutation change in the TSH receptor Pro556 by Leu inactivating the TSH receptor in the thyroid gland which is no longer responsive to TSH, causing hypothyroidism [170]. The effect of this condition on immune system development was determined in adult *hyt/hyt* mice. It was observed a decrease in both thymus and spleen weight, a lower expression of CD8$^+$ T cells in thymocytes and a higher number of CD4$^+$ T cells in splenocytes compared to euthyroid mice [170]. In the same study, maternal hypothyroidism was studied in the euthyroid young-adult (12 weeks old) progeny from *hyt/hyt* dams. These mice showed an increased thymus weight with a higher ratio between CD4$^+$ and CD8$^+$ thymocytes and a lower percentage of CD4$^+$ T cells in splenocytes when compared to mice gestated in euthyroid mothers [170]. The latter is the only data reported for the effects in the progeny of hypothyroid mothers in relation to the immune system. The long term effects in the progeny of hypothyroid or hypothyroxinemic mothers were not reversible, is an issue that should be further addressed as it could open a new field to the deleterious effects reported for this condition (Figure 2).

Multiple sclerosis (MS) is an autoimmune disease characterized by an axonal injury, demyelination of neurons and inflammation of the CNS [171]. The etiology of MS is unknown [172], but it is thought that autorreactive T cells might play a central role in the pathogenesis of the disease [173]. The pathological changes result from a combined action of T cells specific for CNS antigens, activated macrophages, and antibodies directed against CNS antigens [174,175].

Many studies have demonstrated that experimental autoimmune encephalomyelitis (EAE) is a good animal model to understand mechanisms of innate as well as adaptive immunity. It is therefore used as the animal model for MS, in order to understand the pathology and

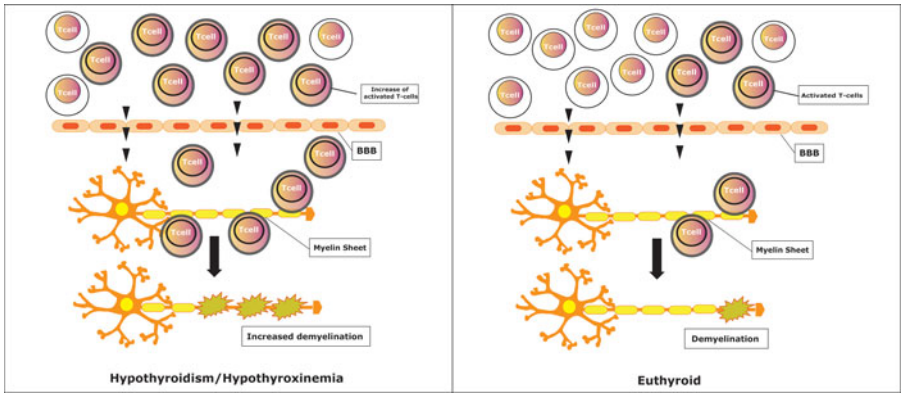

Figure 2. Key targets of maternal thyroid hormone deficiency in the offspring. Gestational hypothyroidism induces higher EAE score in the offspring. The higher EAE in these animals is due to an imprinting in several biological targets: the immune system, the BBB and the oligodendrocytes. When maternal thyroid hormones are decreased during pregnancy and the adult offspring suffers, they present an increase of activated T cells that cross the BBB to enter the brain. Activated T cells invade the brain and encounter antigens that are then presented by microglial cells, leading a direct attack to the myelin sheet. This induces an increase in demyelination in the adult offspring of thyroid hormones deficient mothers, and is reflected in the increased EAE scores.

clinical course. Our research group analyzed the immune system response of the offspring gestated under hypothyroidism challenged to EAE a model to study multiple sclerosis [176,177]. Maternal thyroid hormones deficiency during pregnancy increases the clinical EAE scores in the female offspring gestated in hypothyroidism offspring compared to control or offspring, when the disease is induced in their adulthood [178] suggesting an increased susceptibility of the progeny. Subsequent analysis performed in females Hypo offspring show a decrease in myelination and an increase in oligodendrocyte apoptosis in the spinal cord [178] which is consistent with the idea of the idea of the influence of TH in myelination process through the control of oligodendrocyte differentiation. Increased levels of T cell infiltration in the spinal cord in the female offspring gestated in hypothyrodism with EAE as a higher number of $CD4^+$ and $CD8^+$ cells compared to control [178]. This last observation could be due to an increase brain blood barrier (BBB) permeability possibly due to the effects of TH deficiency during pregnancy. To explain this phenotype in the offspring gestated under hypothyroidism, some models are proposed in Figure 2. One of them is the idea that gestational hypothyroidism could affect the precursor cells that form the BBB. A damaged BBB might facilitate the entrance of autorreactive immune cells into the CNS, thus favoring the inflammation observed in the pathology. The immune system is also an interesting target for THs during gestation, resulting in the progression of the disease. Additionally, maternal hypothyroidism can affect the response of the offspring to infections. Recently published data indicate that female mice gestated under hypothyroid conditions present an increased survival rate to pneumonia, presenting higher amounts of inflammatory cells in the lungs and a reduced production of sepsis cytokines after infection together with an increase vascular permeability in the lungs [179], suggesting an alteration of innate cells functionality or in the compositions of endothelial barriers in the offspring gestated under hypothyroid conditions. The effects of maternal THs in the offspring immune system are summarized in Table 3.

Table 3. Effects of maternal THs in the offspring immune system.

Effect	Reference
Reduction of leukocytes in spleen and thymus	[154]
Decreases number of T cells and B cells in thymus and spleen	[154]
Decreases of weight of spleen and thymus	[170]
Change of ratio $CD4^+$ and $CD8^+$ T cells	[170]
Increases of lymphocytes in spinal cord during autoimmune diseases	[178]
Increases of inflammatory cells in lung during pneumonia infection	[179]

Concluding remarks

Several works that support that TH are important for the immune system function however little is known about the mechanisms triggered in immune cells and the physiological implications in patients. Importantly, the role of THs during gestation has been sub-estimated due to the number of immune cells was re-established postnatal. However, the function of the immune system in the offspring gestated in TH deficiency was not analyzed until recently. From these two works it is possible to suggest that TH deficiency during gestation will increase the immune response in their offspring. Nevertheless, the mechanisms behind this phenotype remain still unknown. This aspect and the evaluation of the physiological impact of TH deficiency in gestation over the

offspring and in the adulthood should be deeply investigated aiming to improve the quality of life of many people affected by TH deficiency.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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