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Review

Thyroid hormone signaling during early neurogenesis and its significance as a vulnerable window for endocrine disruption ☆

Laetitia Préau, Jean Baptiste Fini, Ghislaine Morvan-Dubois, Barbara Demeneix *

UMR CNRS 7221, Evolution des Régulations Endocriniennes, Département Régulations, Développement et Diversité Moléculaire, Muséum National d'Histoire Naturelle, 75231 Paris, France

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ABSTRACT

The essential roles of thyroid hormone (TH) in perinatal brain development have been known for decades. More recently, many of the molecular mechanisms underlying the multiple effects of TH on proliferation, differentiation, migration, synaptogenesis and myelination in the developing nervous system have been elucidated. At the same time data from both epidemiological studies and animal models have revealed that the influence of thyroid signaling on development of the nervous system, extends to all periods of life, from early embryogenesis to neurogenesis in the adult brain. This review focuses on recent insights into the actions of TH during early neurogenesis. A key concept is that, in contrast to the previous ideas that only the unliganded receptor was implicated in these early phases, a critical role of the ligand, T_3, is increasingly recognized. These findings are considered in the light of increasing knowledge of cell specific control of T_3 availability as a function of deiodinase activity and transporter expression. These requirements for TH in the early stages of neurogenesis take on new relevance given the increasing epidemiological data on adverse effects of TH lack in early pregnancy on children's neurodevelopmental outcome. These ideas lead logically into a discussion on how the actions of TH during the first phases of neurogenesis can be potentially disrupted by gestational iodine lack and/or chemical pollution. This article is part of a Special Issue entitled: Nuclear receptors in animal development.

1. Introduction

The thyroid gland synthesizes and secretes thyroid hormones (TH), principally in the form of thyroxin (T_4), a pro-hormone. In target tissues, T_4 is converted locally by the deiodinases 1 (D1) and 2 (D2) into biologically active triiodothyronine (T_3) [67]. Deiodinase 3 (D3) (and to a lesser extent, D1) can inactivate both T_4 and T_3, producing rT_3 and T_2 respectively. The principal role of T_3 is to regulate target gene transcription via its nuclear receptors, TRs. Other, less well characterized, non-genomic effects have been described for both T_4 and T_3, but they are not discussed here as they have been the subject of a recent review [112]. In vertebrates, two genes encode two TRs isotypes: TRα and TRβ. Each gene encodes several isoforms. However, the specific functions of all isoforms, particularly those of TRα, have yet to be fully elucidated (recently reviewed in Ref. [41]).

It has often been proposed that an unliganded receptor, acting principally as a repressor, had a predominant role during early development [9,37,77,114]. One line of strong experimental evidence supporting this idea came from the demonstration of the crucial role played by unliganded receptors during eye embryogenesis in the pre-metamorphic tadpole [53]. Another line of evidence supporting the general repressor hypothesis was the high level of inactivating deiodinases (D3) in the mammalian placenta [45,59,64]. However despite these reports, several studies show that the concept of generalized unliganded receptor repression during early development is an over simplification and this for at least two major reasons. First, we now know that T_3 is found in significant, physiologically relevant amounts, in eggs and early embryos of all vertebrates studied to date [42,102,113,117] and that in mammals including humans, maternal T_4 reaches the embryo from very early developmental stages onwards [29]. Second, even if circulating T_4 levels in the human fetus (FT_4) are low compared to those of the mother, FT_4 levels are in the same order of magnitude [21] and that T_3 increases significantly between 13 and 20 weeks in the frontal cortex of the fetal brain [69]. This increase is of particular interest given that the fetal gland does not become functional before 18 weeks of development [92]. Moreover, TR occupation by T_3 at 10 weeks gestational age reaches 25% [38] and in embryonic brains, a liganded receptor can modulate the transcription of numerous TH regulated genes [39,58].

Two other factors that can be usefully brought into the discussion are first, the tissue and cell-specific nature of T_3 signaling during embryogenesis and second, that liganded TR can also repress gene transcription, and not only activate it (e.g. *Sox2*, *Trh* etc.) [24,75]. Cell specific deiodinases and transporters control TH availability, the expressions of which are also spatially and temporally controlled during early development [39]. The plasticity of these controls opens up multiple

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* Corresponding author.
E-mail address: bdem@mnhn.fr (B. Demeneix).

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possibilities for both liganded and unliganded TR action during early development. In this review we focus more on the role of TH signaling during early neurogenesis and the importance of precise TH availability control during brain development. Given that most studies on TH signaling and brain development concentrate on the perinatal period, we think it is opportune to review the data on the early stages of embryogenesis. Also, we place the data in the context of potential iodine lack and the consequences of broad exposure to thyroid disruptors during embryo-fetal development.

2. Fetal neurogenesis requires thyroid hormone signaling

Historically, neurodevelopmental diseases have long been linked with TH lack (for review see Ref. [132]). Furthermore, the roles of TH signaling in brain development have been reviewed many times, see for instance, Howdeshell [62]. However, the focus on early embryonic development is more recent. Observations from animal models on the presence of components of TH signaling (TRs, T_3/T_4 and deiodinases) in embryos have led to the hypothesis that TH and TRs have numerous roles during early development, particularly during neurogenesis [39,48,86,119,128]. These observations have resonance with epidemiological data. In humans, maternal TH status during early pregnancy is better correlated with the child's later development, notably cognitive and behavior skills, than the maternal levels in the later stages of pregnancy [52,56,66,101,107]. This idea has been reviewed by Donaldson and Jones [34].

2.1. Epidemiological data on TH requirement during fetal neurogenesis

Untreated, congenital hypothyroidism (CH) causes the severe mental retardation characteristic of cretinism, but also dwarfism, bone ossification defects and deafness. However, these effects can be partially reversed after birth by early post-natal treatment with T_4. Owing to the introduction of post-natal testing in the second part of the 20th century and governmental iodine supplementation [22] CH, and consequently cretinism, is no longer the public health problem it once was. However, many countries still have insufficient iodine intake and iodine-deficiency in women of child bearing age is more frequent than previously suspected [6,50]. The resulting slight hypothyroid states can lead to subtle, but deleterious, effects during embryogenesis or fetal development with repercussions on later brain development and cognitive performance [5].

Numerous epidemiological studies have shown that during pregnancy the importance of maternal TH levels for the child's later neurodevelopment and behavior is particularly marked in early pregnancy, i.e. before the fetal thyroid gland becomes functional [72]. Some of the first data came from a Dutch group [100,101] who showed that lower maternal TH levels in the first trimester of pregnancy increased risk of delayed psycho-motor development. These results actually confirmed previous data obtained on smaller samples [98,99,124]. Similarly, Haddow et al. [52] showed correlations between maternal hypothyroidism during pregnancy and decreased IQ scores in 7 to 9 years old children (all born euthyroid). Many other studies have confirmed the critical role of TH during the earliest stages of brain development, i.e. the first 3 months [55,72,76,107,136]. At this developmental stage TRs and especially TRα, are expressed in the brain [10]. A common idea arising was that effects of hypothyroidism observed in neurodevelopmental defects are mostly due to unliganded TR [9,40,85]. Moreover, recent studies underline the importance of the presence of the ligand. Indeed, maternal T_4 and T_3 pass the placental (despite the high levels of placental D3) and fetal barrier [21,76,108,109]. However, maternal T_4 levels appear to be the more important source of ligand in embryonic rat brain prior to thyroid gland function as T_4 is more efficiently transported through the fetal blood–brain barrier [51].

Zoeller and Rovet [136] distinguished maternal hypothyroidism (MH), affecting the fetus before thyroid gland formation, and congenital hypothyroidism (CH) with deficient fetal TH production. Children that experienced MH (i.e., TH lack during the first trimester but with normal levels at birth) have smaller hippocampal regions and lower memory skills compared to controls [62,133]. This body of work underlines how this first trimester in human is a crucial period for TH signaling, with a clear window of susceptibility during early neurogenesis. In parallel to progress in understanding the importance of TH for early development, there has also been an accumulation of data revealing a worldwide increase in incidence of neurodevelopmental syndromes such as autism spectrum disorders (ASD). Recent studies have linked this increase in ASD with perturbation of thyroid signaling due to endocrine disruption during fetal development [3]. Effectively, attention is increasingly turning to "gene × environment" interactions [130], with environmental chemical exposure during embryonic development being a major window of concern. TH disruption is potentially a direct entry point for "gene × environment" interactions, due to the fact that TH signaling has an essential role in normal brain development. This possibility is strengthened by the observation that many potential thyroid disrupting contaminants are present in human fluids, crossing the placental barrier and thereby having the potential to directly impact embryo and fetal development [135] (see also Demeneix [152]).

2.2. Turning to the evidence from animal models

Studies on TH action during development have often focused on brain development in mammals, notably the perinatal period. This focus could be partially due to the ease of studying this developmental period in mammals, but also the marked influence of TH on brain growth during this period in both experimental animals and humans. However the epidemiological findings that early pregnancy, and thus early embryogenesis could also be important windows of TH action have led to the use of alternative models to study the process. Two main reasons underlie the usefulness of non-mammalian models in this context: first the limited accessibility of early mammalian embryos, given their *in utero* development and second, the difficultly of controlling their thyroid status independent of that of the mother. In contrast, non-mammalian models such as amphibians or teleosts, develop externally, and allow easier accessibility and control of total TH availability during early development. It is worth emphasizing that THs are exactly the same in mammalian and non-mammalian models, as is the mode of synthesis. There are also high homologies in the sequences of TRs, their ligand binding specificities, with high conservation in the mode of action and sequences of the deiodinases and membrane TH transporters (THT). The presence and active conversion of T_4 into T_3 in egg laying species prior to fetal thyroid onset suggests a potential role for TH in early development [58,86,105]. Furthermore, all the elements of TH signaling, receptors, transporters and deiodinases have been shown to be present during early embryogenesis in many classes of vertebrate embryos including in neurogenic area [35,39,120]. Presence of both T_4 and T_3 during early embryogenesis has been shown in most vertebrates examined to date and THs have been demonstrated in significant amounts in the developing brains of numerous species of fish, amphibians, birds and mammals including humans. Notably, Kester et al. [69] showed that between 13th and 20th weeks gestation, when the fetus is very much dependent on maternal TH levels, T_3 levels in the human developing cortex are actually higher than in maternal serum. In contrast, in the cerebellum, high activity of D3 appears to protect this brain area from precocious stimulation by TH. These differences strongly suggest that local control of TH availability in brain by deiodinases is essential for normal brain development. Modification of brain TH content is able to perturb brain development in newborn mice [60].

Morreale de Escobar's group in the early 1990s carried out a number of elegant experiments to address the question of active roles for thyroid signaling during early development. These authors made rat embryos hypothyroid (between embryonic days E12 and E15) by exposing the dams

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