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Review

Thyroid hormone action during brain development: More questions than answers

Sigrun Horn, Heike Heuer*

Leibniz Institute for Age Research/Fritz Lipmann Institute, Beutenbergstr. 11, D-07745 Jena, Germany

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ABSTRACT

Thyroid hormone is essential for proper brain development since it acts on processes such as neuronal migration and differentiation, myelination and synaptogenesis. In this review, we summarize the consequences of thyroid hormone deficiency for brain development with special focus on the cerebellum, an important target of thyroid action. In addition, we discuss the role of iodothyronine deiodinases and thyroid hormone transporters in regulating local thyroid hormone concentrations as well as current knowledge about the function of thyroid hormone receptors and their target genes during brain maturation. Despite considerable progress in recent years in deciphering thyroid hormone signaling pathways we still know very little on the molecular level by which mode of action thyroid hormone exerts its cell-specific effects. Hence, we will particularly address the open questions that remain to be addressed in order to better understand the role of thyroid hormone in brain development.

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Contents

1. Introduction

Thyroid hormone (the prohormone thyroxine T4, and its active metabolite 3,5,3′-triiodothyronine T3) is an essential factor during all stages of brain development. Children who develop under condition of severe thyroid hormone deprivation suffer after birth from severe mental retardation, deaf-mutism, spastic diplegia and extrapyramidal rigidity (DeLong et al., 1985). The most prevalent cause for thyroid hormone insufficiency particularly during gestation is the lack of dietary iodine that prevents thyroid hormone synthesis and may cause these neurological symptoms also known as neurological cretinism (Berbel et al., 2007). Even a mild reduction in maternal thyroxine production during gestation (maternal hypothyroxinemea) greatly increases the risk for neurodevelopmental abnormalities and may lead to a decreased IQ in the progeny (de Escobar et al., 2004). Children can also develop hypothyroidism after birth due to an agenesis or dysgenesis of the thyroid gland (De Felice and Di Lauro, 2004). Congenital hypothyroid newborns are usually diagnosed within the first weeks of life during a neonatal TSH screening which is common practice in many countries (American Academy of Pediatrics et al., 2006). However, if thyroid hormone replacement therapy is not instituted immediately after birth, these children will also exhibit cognitive impairment demonstrating that even during postnatal periods of brain

* Corresponding author. Tel.: +49 3641 656021; fax: +49 3641 656040.
E-mail address: hheuer@fli-leibniz.de (H. Heuer).

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maturation thyroid hormone must be present to ensure normal development.

Despite the wealth of clinical findings underscoring the importance of thyroid hormone for brain development it is surprising that we know very little about the cellular and molecular mechanism by which thyroid hormone influences structure and function of the central nervous system (CNS). The limitations in defining the exact role of thyroid hormone are due to a rather complex interplay of thyroid hormone with thyroid hormone receptors that includes genomic actions as well as rapid activation of cytosolic signaling cascades. Other reasons for the limitations include cell-specific differences in cellular availability that are largely determined by the activities of thyroid hormone activating and inactivitating enzymes (in particular the iodothyronine deiodinases type 2 (D2) and type 3 (D3) as well as by the cell-specific repertoire of thyroid hormone transporters, and also challenges in discriminating cell-autonomous effects of thyroid hormone versus indirect effects that might be due to a systemic action of thyroid hormone that in turn affects the CNS.

This review will briefly assess the current knowledge as well as the open questions that still need to be addressed in order to better understand the role of thyroid hormone during brain development with a special focus on the cerebellum. For more in-depth description the reader is referred to excellent reviews published elsewhere (Anderson, 2008; Bernal, 2005; Bernal, 2007; Nunez et al., 2008; St Germain et al., 2009). Moreover, we will not discuss the role of thyroid hormone in retina and cochlea development which has been addressed in a number of interesting papers published elsewhere (Ng et al., 2004; Roberts et al., 2006; Lu et al., 2009; Ng et al., 2009).

2. Ontogenesis of thyroid hormone action

A wealth of studies have revealed that thyroid hormone already acts during early stages of development. In humans as well as in rodents, thyroid hormones as well as their receptors are present in the fetus prior to the onset of fetal thyroid hormone production underscoring the relevance of maternal thyroid hormone production for fetal development (Bernal and Pekonen, 1984; Obregón et al., 1984; Contempré et al., 1993; de Escobar et al., 2004). For instance, already at week 12 of gestation both T4 and T3 can be detected in the human developing cortex but not in the serum and other fetal tissues. At week 18 when fetal thyroid hormone synthesis has just started thyroid hormone levels in the cerebral cortex reach peak concentrations that are comparable to those found in the adult cortex (Kester et al., 2004). Local concentrations of thyroid hormones are controlled at various levels of synthesis and secretion. In this respect, the ontogenic profile of deiodinases may play an important role by modulating T3-bioavailability in a time- and region-specific manner. Whether the transport of thyroid hormones is also spatially and temporally controlled during ontogenesis still remains to be elucidated. However, the severe neurological phenotype of patients in which the thyroid hormone transporter MCT8 is inactive (see below) indicates an important role of thyroid hormone transporters in regulating the access of thyroid hormone to its target cells during prenatal stages.

Studies on thyroid hormone action in brain development have been performed mainly in rodents in which thyroid hormones, receptors and deiodinases are also expressed in the developing brain well before the onset of the fetal thyroid gland activity. However, when comparing thyroid hormone action in human and rodent brain development one has to keep in mind that the rat brain at birth approximates the developing human brain at 6 months of gestation whereas the human brain at birth exhibits a stage of differentiation that is similar to a rat brain at postnatal day P6–P10 (Porterfield and Hendrich, 1993; Oppenheimer et al., 1995). (A detailed comparison of the developmental timing between rodents and humans is displayed at http://www.translatingtime.net.) As a consequence, brain development may be influenced by the maternal thyroidal state more in humans than in rodents. For a more detailed time-line describing the ontogenesis of the thyroid hormone system in relation to human and rodent brain development the reader is referred to excellent reviews published elsewhere (Anderson et al., 2003; Bernal, 2007).

In order to study the consequences of severe hypothyroidism, pregnant rats were rendered hypothyroid by the treatment with *n*-propylthiouracil (PTU) which blocks thyroid hormone synthesis by inhibiting the iodination of thyroglobulin and by decreasing the activity of deiodinase D1. Alternatively, animals can be treated with MMI (1-methyl-2-mercapto-imidazol)/Perchlorate in order to decrease significantly thyroid hormone production. For monitoring thyroid hormone effects during postnatal neurodevelopment the Pax8 ko mouse represents a very suited animal model (Mansouri et al., 1998). Pax8 is an essential transcription factor for the development of thyroid follicular structure and the expression of thyroid-specific genes. As a consequence, Pax8 ko mice born to euthyroid Pax8 heterozygous mothers are completely athyroid after birth. Neither in tissues nor in the serum thyroid hormones can be detected indicating that at least in mice maternal thyroid hormones are not provided via the milk (Friedrichsen et al., 2003). Due to their athyroidism Pax8 ko mice are strongly growth retarded, deaf and exhibit an ataxic phenotype indicating that among other brain structures particularly the maturation of the cerebellum is impaired. However, since *in utero* Pax8 ko mice are provided with maternal thyroid hormone this animal model is not suited to assess the consequences of thyroid hormone deficiency for prenatal neurodevelopmental events.

3. Metabolism of thyroid hormones by brain deiodinases

Since the major thyroid hormone produced by the thyroid gland is the receptor inactive T4, extrathyroidial conversion of T4 to T3 is needed for any action that is signalled via the classical thyroid hormone receptors. Studies in animal models have revealed that approximately up to 80% of the active thyroid hormone T3 is produced locally in the CNS (Crantz et al., 1982) suggesting a prominent role of the activating enzyme D2 which exclusively catalyses outer ring deiodination. In contrast to thyroid hormone receptors that are highly enriched in oligodendrocytes and neurons, D2 is predominantly found in astrocytes throughout the brain (Guadano-Ferraz et al., 1997). In the rat, D2 expression is first detectable at E16.5 and increases successively until postnatal day 15. Ontogenic profiling of D2 in the fetal human brain revealed the occurrence of D2 in the developing cerebral cortex during the first trimester of pregnancy just at a time point when also the cortical T3 concentration can first be detected (Chan et al., 2002). The similar ontogenic profile of D2 expression and T3 content in different developing brain structures has led to the hypothesis that D2 is particularly important in providing developing brain structures with T3 produced from maternally derived T4. Another remarkable feature of D2 is that its activity is highly regulated by the thyroid status via both pre- and post-translational mechanisms. Hypothyroidism results in markedly upregulated D2 activities and hyperthyroidism leads to a decrease in D2 expression levels (Burmeister et al., 1997; Escobar-Morreale et al., 1997). These changes have been interpreted as a protective mechanism to maintain the brain T3 content as normal as possible in light of altered serum thyroid hormone levels.

Recently, the generation and analysis of a D2 deficient mouse model revealed surprising results that challenged the current concept of D2 as an essential gate keeper in the CNS (Galton et al., 2007). D2 knockout mice exhibit normal serum T3 but increased

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