Molecular and Cellular Endocrinology xxx (2017) 1–7

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Traversing barriers – How thyroid hormones pass placental, blood-brain and blood-cerebrospinal fluid barriers

Kelly Landers [a], Kerry Richard [a, b, c, *]

[a] Conjoint Endocrine Laboratory, Chemical Pathology, Pathology Queensland, Queensland Health, Herston, Qld 4029, Australia
[b] School of Medicine, University of Queensland, Herston, Qld 4029, Australia
[c] School of Biomedical Sciences, Queensland University of Technology, Brisbane, Qld 4000, Australia

ARTICLE INFO

Article history:
Received 13 October 2016
Received in revised form
19 January 2017
Accepted 24 January 2017
Available online xxx

Keywords:
Thyroid hormone
Placenta
Brain
Blood–brain barrier
Blood-cerebrospinal fluid barrier

ABSTRACT

Thyroid hormone is essential for normal human fetal growth and brain development. As the fetal thyroid does not secrete thyroid hormones until about 18 weeks gestation, early fetal brain development depends on passage of maternal hormone across the placenta into the fetal circulation. To reach the fetal brain, maternally derived and endogenously produced thyroid hormone has to cross the blood-brain and blood-cerebrospinal fluid barriers. In this review we will discuss the complex biological barriers (involving membrane transporters, enzymes and distributor proteins) that must be overcome to ensure that the developing human brain has adequate exposure to thyroid hormone.

1. Introduction

Thyroid hormones (TH) are essential for normal human fetal development and especially important in the development of the central nervous system. The hypothalamic-pituitary-thyroid (HPT) axis begins to develop at around 5 weeks gestation and while there is some TH synthesis at about 12 weeks, significant amounts of TH are not produced until after the 18th week of gestation. This means that the developing fetus requires an adequate and timely supply of TH from its mother through the placenta. In order to reach the developing fetal brain, TH in the fetal circulation then must traverse the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB). Each of these barriers (placental and brain) have unique structures comprised of cells that express different TH membrane transporters, metabolising enzymes and distributor proteins.

1.1. Membrane transporters

Due to the lipophilic nature of THs, it was historically believed that THs could passively traverse membranes. However, THs are charged and cannot cross a phospholipid bilayer (Schweizer and Kohrle, 2013). Over the last two decades several membrane transporters capable of transporting TH have been identified (see (Visser, 2000; Visser et al., 2008, 2011)) including the organic anion transporting polypeptides OATP1A2, OATP4A1 and OATP1C1, the L-type amino acid transporters LAT1 and LAT2 (Friesema et al., 2001) and the more recently described specific TH transporter monocarboxylate transporters MCT8 and MCT10 (Friesema et al., 2003).

1.2. Metabolising enzymes

During vertebrate development, the action of TH is coordinated by three iodothyronine deiodinases: Type 1 (D1), Type 2 (D2) and Type 3 (D3), that differ in substrate specificity and tissue distribution. D2 is an outer ring deiodinase that converts transcriptionally inactive thyroxine (T4) to active triiodothyronine (T3). Conversely D3 is an inner ring deiodinase that inactivates T3 to diiodothyronine (T2) or T4 to reverse triiodothyronine (rT3). D1 has both inner and outer ring deiodinase activity. For a review on deiodinases see (Dentice and Salvatore, 2011). The balance of D2 and D3 activity plays an important role in fetal development by ensuring safe levels of TH are maintained (Richard et al., 1998).

In addition to deiodination, THs are metabolised by conjugation

* Corresponding author. Conjoint Endocrine Laboratory, Level 9, Bancroft Centre, 300 Herston Road, Herston, Queensland 4029, Australia.
E-mail address: kerry.richard@qimrberghofer.edu.au (K. Richard).

http://dx.doi.org/10.1016/j.mce.2017.01.041
0303-7207/

of the phenolic hydroxyl group with sulfate or glucuronic acid (Wu et al., 2005). Sulfation and glucuronidation increase water-solubility of the substrates, which facilitates biliary and/or urinary clearance. Sulfation of TH is catalysed by sulfotransferases and desulfation by arylsulfatases. TH sulfates are the preferred substrates for deiodination (Visser, 1994) and are rapidly degraded in liver by D1. In the presence of low D1 activity, T3 sulfate may function as a reservoir of inactive hormone from which active T3 may be recovered by arylsulfatases (Visser, 1994). Glucuronidation of TH is catalysed by UDP-glucuronyltransferases that utilise UDP-glucuronic acid as a cofactor. Glucuronidation of TH appears to be more important in rodents than in humans (Visser et al., 1993).

1.3. TH distributor proteins

In serum, TH is bound to three hepatically synthesised distributor proteins, which are, in order of their affinity for T4, thyroxine binding globulin (TBG), transthyretin (TTR) and albumin (Chopra, 1996). The extent of overall binding is great such that the free T4 concentration in serum is less than 0.1% of total T4. TTR is also synthesised by several other cell types including placenta (McKinnon et al., 2005) and choroid plexus (Herbert et al., 1986) and plays a role in transporting TH into cells (Landers et al., 2009, 2013a,b; Schreiber et al., 1990). Several intracellular TH binding proteins have also been identified that may modify TH transport and access to nuclear TH receptors including alpha-1-antitrypsin, alpha-1-acid glycoprotein and mu-crystallin (Barsano and DeGroot, 1993; 2012; McKinnon et al., 2005; Suzuki et al., 2007).

2. The placental barrier

2.1. Placental structure

The human placenta is a highly specialised organ that actively exchanges nutrients and waste between the maternal and fetal circulations. During the first 10–12 weeks of gestation, the fetus is bathed in amniotic fluid and is completely surrounded by the placenta through which maternal-fetal exchange occurs (Gude et al., 2004). During this time, the placenta is primarily made up of cytotrophoblasts, which undergo proliferation and differentiation into a multinucleated syncytium called the syncytiotrophoblast (Gude et al., 2004; Huppertz and Peeters, 2005) and transport of nutrients and waste between maternal and fetal circulations occurs across these two layers of cells (Gude et al., 2004). By the 13th week of pregnancy (Foidart et al., 1992) the hemochorial plate is formed allowing chorionic villi to be perfused by maternal blood (Huppertz and Peeters, 2005). At this time, the placental barrier consists of four layers, the maternal facing syncytiotrophoblasts, a layer of cytotrophoblasts, connective tissue and the endothelial cells lining the fetal capillaries. The utero-placental unit consists of the chorionic plate derived from the fetal chorionic sac and the basal plate derived from maternal endometrium. In between these two regions is the intervillous space where chorionic villi are bathed in maternal blood introduced through maternal spiral arteries. The placental barrier is formed by the tight layer of multinucleated syncytiotrophoblasts, located on the chorionic villi that separate maternal blood from fetal capillaries and is the layer of cells through which maternal-fetal exchange occurs (Fig. 1).

2.2. Placental TH transport

For many years it was thought that the placenta was impermeable to thyroid hormones (TH) despite early studies demonstrating that radiolabeled TH crossed the placenta (Fisher et al., 1964). Later, the discovery of high D3 activity suggested that intracellular deiodination may provide the barrier to placental TH transport (Roti et al., 1981). However in 1989, Vulsma et al. (1989) demonstrated that fetuses unable to produce TH had significant (but low) circulating TH levels at birth providing evidence of materno-fetal transfer of TH.

Since then the presence of both T3 and T4 have been identified in the fetal exocoelomic cavity and in fetal tissues from 5 weeks

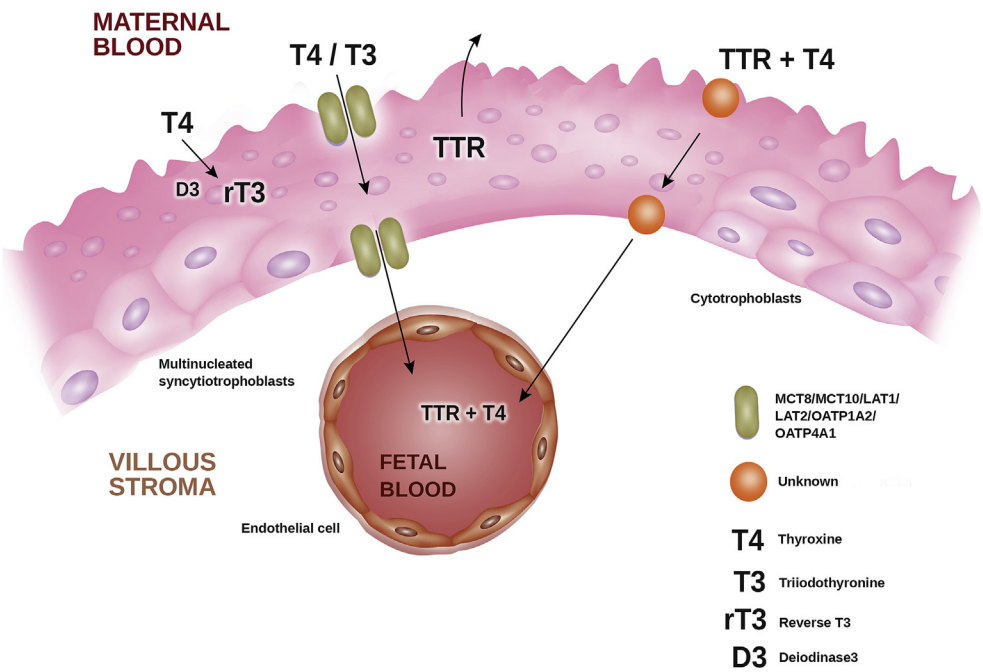

Fig. 1. Proposed route of TH transfer across placenta. Several transporters are capable of transporting TH across placenta including MCT8, MCT10, LAT1, LAT2, OATP1A2 and OATP4A1. However placental deiodinase 3 (D3) is expressed at high levels and can convert T4 to rT3. Placenta synthesises and secretes transthyretin (TTR) that can bind maternal TH. TTR is taken up by trophoblasts and may chaperone T4 to the fetal capillaries.

Please cite this article in press as: Landers, K., Richard, K., Traversing barriers – How thyroid hormones pass placental, blood-brain and blood-cerebrospinal fluid barriers, Molecular and Cellular Endocrinology (2017), http://dx.doi.org/10.1016/j.mce.2017.01.041