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Thyroid hormone transport across the placenta☆

Transport transplacentaire des hormones thyroïdiennes

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1. Introduction

Thyroid hormone (TH) is a common term for the compounds secreted by thyroid follicles, 3,3′,5,5′-tetraiodothyronine (thyroxine, T4) and 3,3′,5-triiodothyronine (T3). The thyroid is the only source of T4 in the body but most T3 is produced by deiodination of T4 in peripheral tissues [1]. Most actions of TH are initiated by binding of T3 to nuclear receptors encoded by the *THRA* and *THRB* genes [2,3]. The resultant change in receptor conformation leads to the dissociation of co-repressor complexes and the recruitment of co-activator complexes, changing the expression of TH-responsive genes. T4 may have T3-independent non-genomic actions [4] and its affinity for the nuclear T3 receptors may not be negligible particularly in view of the higher free T4 than T3 levels in serum and perhaps also in tissues. Nevertheless, it is generally accepted that T4 functions predominantly as a prohormone for the active hormone T3 [1]. TH is essential for tissue development, in particular of the brain, and for the regulation of the metabolic activities of the tissues throughout life [3,5].

The biological activity of TH is regulated importantly at the level of target tissues. This involves the local expression of iodothyronine deiodinases, in particular D2 and D3 [1]. D2 converts T4 by outer ring deiodination to T3, whereas D3 converts T4 and T3 by inner ring deiodination to the receptor-inactive metabolites 3,3′,5′-triiodothyronine (reverse T3) and 3,3′-diiodothyronine (3,3′-T2), respectively. D2 and D3 have very different spatiotemporal patterns of expression. D2 is expressed among other tissues in brain, pituitary, brown adipose tissue (BAT), where it usually reaches highest activities after birth. D3 is also expressed in brain but its activity is highest during fetal development. D3 is also highly expressed in other fetal tissues such as the liver but also at very high levels in the placenta and the pregnant uterus. During early development, low D2 and high D3 expression result in low local T3 levels in favor of tissue growth. Ultimately, decreased D3 expression and increased D2 expression allow an increase in local T3 levels, stimulating cellular differentiation. This local regulation of TH action is an autocrine mechanism in tissues such as BAT where T3 functions in the same cell where it is produced by D2 [6], or a paracrine mechanism in tissues such as the brain where T3 is generated by D2 in astrocytes and provided to neuronal target cells [7]. These neurons may also express D3 to terminate T3 action when this is no longer required.

The deiodinases are membrane proteins with their active sites localized in the cytoplasm. TH is also metabolized by sulfation and glucuronidation by intracellular enzymes. Therefore, not only the nuclear action but also the metabolism of TH require the transport of the hormone across the plasma membrane. This does not take place by passive diffusion as was assumed for a long time but is mediated by transporter proteins [7–9]. In addition to the deiodinases, these transporters are crucial in the regulation of local TH activity.

2. Thyroid hormone transporters

In the last two decades, several transporters have been identified which are capable of transporting T4, T3 and other iodothyronine derivatives [7,9]. They belong to two main classes of transporters, namely the organic anion transporters and amino acid transporters (Table 1). Among the organic anion

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Table 1
Thyroid hormone transporters.

Organic anion transporters
NTCP (Na/taurocholate co-transporting polypeptide)
OATPs (organic anion transporting polypeptides)
Amino acid transporters
LAT1,2 (L-type amino acid transporters)
MCT8,10 ("monocarboxylate transporters")

transporters, the Na-taurocholate co-transporting polypeptide (NTCP, SLC10A1) and several members of the Na-independent organic anion transporting polypeptide (OATP, SLCO) family facilitate transport of iodothyronines and/or their sulfate conjugates [10,11]. Among the latter family, OATP1C1 deserves special mention in view of its high selectivity for T4 as the substrate and its specific tissue distribution, with particularly high expression in different brain structures [12,13]. As mentioned above, in human brain, OATP1C1 is especially expressed in astrocytes where it facilitates entry of T4 to allow its conversion to T3 [5,14].

Regarding the amino acid transporters, our group has recently made a detailed characterization of the transport of different iodothyronines and iodotyrosines by the L-type amino acid transporters LAT1-4 [15]. LAT1 and LAT2 are heterodimeric transporters composed of a common heavy chain, SLC3A2, and different light chains, SLC7A5 and SLC7A8, respectively [16]. LAT3 and LAT4 are monomeric proteins from another transporter family; their formal codes are SLC43A1 and SLC43A2, respectively [17]. Although there is little homology between the LAT1/2 and LAT3/4 transporters, they share their preference for large aromatic and branched-chain aliphatic amino acids. With regard to iodothyronine substrates, LAT1 facilitates cellular uptake of T4, T3, rT3, and 3,3′-T2, and LAT2 mediates uptake of T3 and 3,3′-T2. LAT3 and LAT4 do not facilitate uptake of iodothyronines but they mediate the efflux of rT3 and 3,3′-T2 [15].

Particularly effective TH transporters are MCT8 (SLC16A2) and MCT10 (SLC16A10), which belong to the monocarboxylate transporter (MCT) family although they do not transport monocarboxylates but amino acid derivatives [18–20]. MCT10 is also referred to as TAT1 for T-type amino acid transporter 1, as it shows high specificity for the aromatic amino acids Phe, Tyr and Trp [21]. In addition to these amino acids, MCT10 also effectively facilitates uptake and efflux of iodothyronines, in particular T3. MCT10 is expressed at high levels in liver, intestine, kidney and skeletal muscle and at lower levels in many other tissues.

The pathophysiological relevance of TH transporters has been best demonstrated for MCT8. The MCT8 protein is highly homologous to MCT10, in particular in its 12 transmembrane domains. In contrast to MCT10, MCT8 does not facilitate transport of any amino acid but it is very effective in the transport of both T4 and T3 as well as other iodothyronines [18,19]. The *MCT8* gene is located on the X chromosome and mutations in MCT8 have been associated with severe X-linked psychomotor retardation, also known as the Allan-Herndon-Dudley syndrome (AHDS) [22,23]. Patients with AHDS also have abnormal serum TH profiles, including low T4 and high T3 levels. MCT8 is highly expressed in liver, adrenal, kidney, thyroid and brain. In the thyroid, it is involved in TH secretion. In the brain, it is especially expressed in endothelial cells of the blood-brain barrier, in epithelial cells of the choroid plexus and in neurons in different brain regions [5,24]. The pathogenesis of AHDS is explained by the important role of MCT8 in brain TH transport. Since TH is essential for brain development, impaired MCT8-mediated supply of TH to important target cells in the brain causes severe damage to the developing brain.

3. Thyroid hormone transport across the placenta

TH is crucial for fetal and neonatal development. Since the fetal thyroid starts to secrete significant amounts of TH towards mid-gestation, maternal-fetal transfer of TH across the placenta is particularly important in the first half of pregnancy [5]. However, analysis of serum TH levels in newborns with thyroid agenesis indicates that also later in pregnancy, maternal TH remains an important source for the fetus [25].

Table 2
Thyroid hormone transporters in human placenta.

Transporter	Localization	Findings	Ref.
Placenta			
MCT8	CTBs, STBs, EVTBs	Highest expression in TM3	[32,33]
MCT10	CTBs, STBs, EVTBs	Highest expression in TM3	[21,33–36]
LAT1	–	Similar expression in TM1-3	[33,36]
LAT2	–	Similar expression in TM1-3	[33,34,36]
OATP1A2	CTBs, STBs, EVTBs	Similar expression in TM1-3	[33]
OATP4A1	STBs (apical)	Similar expression in TM1-3	[33,37]
CTBs, STBs			
MCT8	MVM	CTB→STB: expression ↓	[38–40]
MCT10	MVM		[38,39]
LAT1		CTB→STB: expression ↓	[38–40]
LAT2	MVM		[38,39]
OATP1A2	MVM	CTB→STB: expression ↑	[38–40]
OATP4A1	MVM	CTB→STB: expression =	[38–40]

CTB: cytotrophoblast; STB: syncytiotrophoblast; EVT: extravillous trophoblast; TM: trimester; MVM: microvillous membrane.