Chapter 5

Maternal-Fetal Thyroid Interactions

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Additional information is available at the end of the chapter

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1. Introduction

Life is getting complicated in the world of local thyroid hormones (THs) regulation. On account of TH action can be controlled in individual cells through selective TH uptake and intracellular TH metabolism, the placenta is an important link in the maternal-fetal communication network for THs which are essential for the normal development and differentiation of the fetus [1-3]. Generally, intracellular activation or inactivation of L-thyroxine (T4) and 3,5,3'-triiodothyronine (T3) in turn is determined by three types of iodothyronine deiodinases (Ds), namely DI, DII, and DIII [4-7]. The placenta transports and metabolizes maternal THs, and mainly expresses DIII, which inactivates T4 and other iodothyronines and thus limits the transfer of maternal active THs to the fetus in the late pregnancy [8]. DII is also active in the placenta and locally provides active T3 from the maternal prohormone T4 for placental metabolic functions [1,2]. The placental expression of DI, which also activates T4 to T3, is still controversial. Because of the lipophilic nature of THs, it was thought that they traversed the plasma membrane by simple diffusion [9,10]. The transport of T4 and T3 in and out of cells is controlled by several classes of transmembrane TH-transporters (THTs) [11], including members of the organic anion transporter family (OATP), L-type amino acid transporters (LATs), Na^+/Taurocholate cotransporting polypeptide (NTCP), and monocarboxylate transporters (MCTs) [10,12]. Particularly, monocarboxylate transporter 8 (MCT8) has recently been identified as an active and specific TH transporter. Also, placental membranes are also involved in 4'-OH-sulfation reactions of iodothyronines [8]. Sulfation (S) plays a role in TH metabolism by interacting between the deiodination and sulfation pathways of TH [13]. Interestingly, placental cells express high affinity, stereo-specific, energy-dependent uptake systems for T4 and T3. On the other hand, the cellular activity of THs is usually classified as genomic (nuclear) and non-genomic (initiated either at cytoplasm or at membrane TH receptors) [14-21]. Binding of T3 to its nuclear thyroid receptors (TRs) directly affects transcription of many genes that are important in development [22].

In general, pregnancy is accompanied by profound alterations in the thyroidal economy (hypo- or hyper-thyroidism), resulting from a complex combination of factors specific to the pregnant state, which together concur to stimulate the maternal thyroid machinery [1,23]. Also, clinical studies showed that maternal TH deficiency during the first trimester of pregnancy can affect the outcome of human neurodevelopment [24,25]. Experiments in rats showed that early maternal TH deficiency affects neuronal migration in the cortex [26], while maternal hyperthyroidism too can disturb fetal brain development [27]. Experimental data on the mechanisms regulating intracellular TH availability and action prior to the onset of fetal TH secretion, however, remain scarce. Thus, in this chapter will be aware about the significant roles of THs, their metabolism by Ds and sulfotransferases, their transport by THTs and their binding to TRs from the mother via the placenta to the fetal compartment especially during the gestation period in both human and animals.

2. Placental transport of thyroid hormones

2.1. By thyroid hormone-deiodinases (Table 1 and Figure 1)

The synthesis of THs is regulated through the hypothalamus–pituitary–thyroid (HPT) axis [28] and the follicular cells of the thyroid gland synthesize and secrete T4 and T3 [1,2,21]. This process is under the control of the circulating TH levels through negative feedback loops of this axis [28]. The availability of the active ligand T3 within tissues is locally determined by the action of the iodothyronine deiodinases (Ds) [29]. There are three selenocysteine monodeiodinase subtypes (DI, DII and DIII) [30]. Whilst T3 is generated by the activity of DI and DII, via 5'- reductive or outer ring deiodination (ORD) of the T4 [31], DIII activity (and to a lesser extent that of DI) convert T4 to 3,3',5'-tri-iodothyronine (reverse T3; rT3) and T3 into 3,3'-T2 via inner ring deiodination (IRD), in effect acting as a deactivating enzyme for THs [13,32].

Activities of all three iodothyronine deiodinase subtypes have been demonstrated in most rat placenta [33]. However, in contrast to man, rodent total serum T3 and T4 increase with gestation [34] and the predominant subtype expressed appears to be DIII [35], although DII is also present with significant activity [36]. Placental DIII activity is much greater (approx. 200 times) than DII activity; however, the activity and expression of both DII and DIII fall as gestation progresses [37-40]. Placental DII provides T3 for 'housekeeping' processes, and as indicated above, its activity is much less than that of D3 [40]. DII has been localized to the villous cytotrophoblasts in the first trimester and syncytiotrophoblasts in the third trimester, whereas DIII has been localized to the villous syncytiotrophoblasts in both the first and third trimesters of pregnancy [39]. Both DIII mRNA and activity are present at the implantation site in rodents, as early as gestational day 9 (GD 9), being expressed in mesometrial and antimesometrial decidual tissue [41]. Also, in rabbit [42] and pig [43], the placenta appears to express DIII activity predominantly. The positioning of the deiodinases, particularly DIII, suggests that they might regulate the amount of maternal TH reaching fetal circulation [40]. Interestingly,

however, fetuses with total thyroid agenesis but with evidence of circulating maternal TH have normal placental DIII activity, suggesting that there might be other factors modulating T4 access to the deiodinases, such as intracellular protection of TH by TH-binding protein (THBP) [40,44]. Collectively, express placental Ds (II, III) may play a critical role in delivery of TH to the fetus as summarized in figure1 [2,45-47] and table 1 [1,2,31,48].

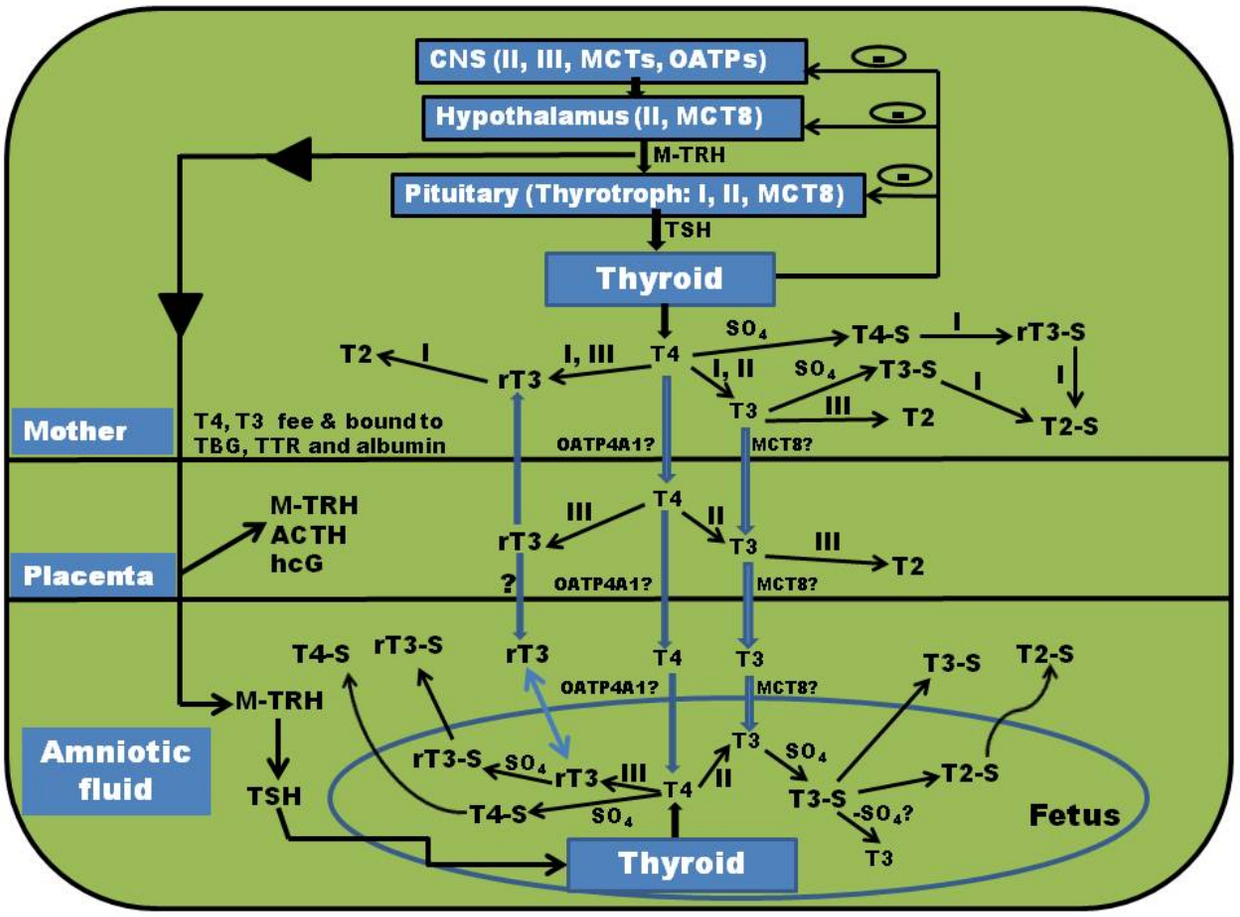


Figure 1. Summary about the interactions of maternal, placental and fetal thyroid metabolism. I, II and III denote deiodinases type 1 (DI), type two (DII) and type three (DIII). SO_4 is a sulfation pathway and $-SO_4$ is a desulfation pathway. CNS is central nervous system, TRH is thyroid releasing hormone, M-TRH is maternal thyroid releasing hormone, TSH is thyrotrophin, T2 is diiodothyronine, T3 is triiodothyronine, rT3 is reverse triiodothyronine, T4 is thyroxine, T2S is diiodothyronine sulfate, T3S is triiodothyronine sulfate, T4S is thyroxine sulfate, rT3S is reverse triiodothyronine sulfate, MCT8 is monocarboxylate transporter 8, OATP4A1 is organic anion transporter 4A1, TBG is thyroxin binding globulin, TTR is transthyretin, ACTH is adrenocorticotrophin and hCG is human chorionic gonadotrophin.

Characteristic	DI	DII	DIII
Reaction kinetics	Ping-pong	Sequential	
Reaction catalyzed (Deiodination)	5 or 5' (ORD+IRD)	5' (ORD)	5 (IRD)
Main form	T4-T3, rT3- T2	- T4- rT3, T3- T2	- T4- rT3- T2
Substrate preference	5: T4S>T3S>>T3, T4 5': rT3, rT3S>T2S>>T4	T4>rT3	T3>T4
Sulfation of substrates	Stimulation	Inhibition	
Substrate limiting *K*M	0.5 mM	1–2 nM	5–20 mM
In vitro cofactor limiting *K*M	1–10 Mm DTT	>10 mM DTT	=70 mM DTT
Molecular mass (kDa)	29	30	32
Selenocysteine	present		
Homodimer	Yes		
Location	- Liver, kidney, thyroid and pituitary.	- Pituitary, brain, BAT, thyroid[a], heart[a] and skeletal muscle[a].	- Brain, skin, uterus, placenta, fetus and in other sites of the maternal- fetal interface, such as the umbilical arteries and veins.
Subcellular location	- Liver: endoplasmic reticulum. - kidney: basolateral plasma membrane	- Microsomal membranes	
Functions	- Production serum T3 and the clearance of serum rT3.	- Catalyzes the outer ring deiodination of T4 to T3 and is thus important for the local production of T3.	- Catalyzes the inner ring deiodination of T4 to rT3 and of T3 to 3,3'-T2.
Activity in hypothyroidism	- Decrease in liver and kidney. - increase in thyroid.	- Increase in all tissues.	- Decrease in brain.
Activity in hyperthyroidism	- Unknown in liver and kidney. - Increase in thyroid.	- Decrease in most tissues. - Increase in thyroid[a].	- Increase in brain.
Low-T3 syndrome	- Decrease	- No change	

Active site residues	- Selenocysteine histidine and phenylalanine.	- (Seleno-)cysteine?	- Selenocysteine
Human gene structure and location	- 1p32-p33, 17.5 kb and 4 exons.	- 14q24.3, 2 exons, and 7.4-kb intron.	- 14q32
Promoter elements	- TRE, RXR, no CAAT or TATA box.	--	
Propylthiouracil inhibitor	++++	+	+/-
Aurothioglucose inhibitor		++	
Iopanoic acid inhibitor	+++	++++	+++
Thiouracils	++++	-/+	-
iodoacetate		+	?
flavonoids	+	+++	

[a] Humans only. T2 is diiodothyronine, T3 is triiodothyronine, rT3 is reverse triiodothyronine, T4 is thyroxine, T2S is diiodothyronine sulfate, T3S is triiodothyronine sulfate, T4S is thyroxine sulfate, rT3S is reverse triiodothyronine sulfate, ORD is outer ring deiodination, IRD is inner ring deiodination, TRE is T3-responsive element, RXR is retinoid X receptors and DDT is dithiols.

Table 1. General characteristics of the iodothyronine deiodinases.

2.2. By thyroid hormone-transporters (THTs) (Tables 2 & 3 and Figure 1)

Membrane transporters mediate cellular uptake and efflux of TH [12,40,49]. The ability to transport TH has been described in members of different transporter groups including the monocarboxylate transporters (MCT), L-type amino acid transporters (LAT), Na^+/Taurocholate cotransporting polypeptide (NTCP), and organic anion transporting polypeptides (OATP) [50]. With the exception of MCT8, these transporters do not exclusively transport TH and they all have slightly different affinities for specific forms of TH. To date six different THTs are known to be present in the placenta: MCT8, MCT10, LAT1, LAT2, OATP1A2 and OATP4A1 but their relative contributions to placental TH transport are unknown [50-55]. Also, their anatomical localization, ontogeny in the human placenta and relative affinity for the TH and thyronines are very complex. MCT8, MCT10, OATP1A2, OATP4A1 and LAT1 are expressed in villous syncytiotrophoblasts, and MCT8, MCT10 and OATP1A2 in cytotrophoblasts [50]. Although transporters in the apical syncytiotrophoblast membrane are well placed to maximize maternal cellular TH uptake early in gestation, the large numbers and variety of THTs are intriguing [51,53,55]. Moreover, the expression of MCT8 mRNA increased with advancing gestation [55] but there is limited information regarding the ontogeny of the other THTs. In addition, it is likely that the lower expression of MCT8, MCT10, OATP1A2 and LAT1 before 14 week compared to term, as well as the nadir in OATP4A1 expression in the late 1st and early 2nd trimester, may play a role in the necessary limitation of maternal-fetal TH transfer, particularly around the time of onset of endogenous fetal TH production in the early 2nd trimester [56]. Increased expression of THTs in late gestation is consistent with the proposal

that there is continued/ increased maternal to fetal supply of TH in the 3rd trimester despite increasing fetal TH production [57]. It is also likely that increased expression of these transporters with gestation may also fulfil the increased need for other biological substances for fetal growth and development, such as amino acids. The most factors regulating the placental expression of these transporters are unknown until now. There are suggestions in rodents that the activity of system-L and the expression of MCT8 in non-placental tissues are influenced by thyroid status [58] suggesting that TH may be a regulator of its own transporters [50]. During the passage of THs from the maternal circulation to the fetal circulation, each THT is likely to have a specific role in each different plasma membrane layer, which might include cellular influx, efflux, or both [59]. To sum, THTs of the various placental cell types serve as channels that help to maintain the differences in the composition of THs and their metabolites between maternal and fetal circulations (figure1 [2,45-47] and tables 2 & 3 [51,52,55,59,60,61]). The relative contributions of these THTs to the transplacental transport of thyroid hormones are still a subject for research.

Transporter[a]	Iodothyronine derivates	Specificity[b]
MCT8	T3, T4, rT3, T2	+++
MCT10	T3, T4	++
OATP1A1	T3, T4, rT3, T2, T4S, T3S, rT3S, T2S	+
OATP1A2	T4, T3, rT3	
OATP1A3	T4, T3	
OATP1A4		
OATP1A5		
OATP1B1	T4, T3, T3S, T4S, rT3S	
OATP1B2	T3, T4	
OATP1B3	rT3, T4S, T3S, rT3S	
OATP1C1	T4, rT3, T3, T4S	++
OATP2B1	T4	+
OATP3A1 (V1/V2)		++
OATP4A1	T3, T4, rT3	+
OATP4C1	T3, T4	
OATP6B1		
OATP6C1		
LAT1	T3, T4, rT3, T2	
LAT2		
NTCP	T4, T3, T4S, T3S	++

[a] The human protein symbol is presented, if TH transport has been demonstrated in different species including humans. [b] If a transporter only transports iodothyronine derivatives, specificity is high (+++). If fewer than five other ligands are known, specificity is moderate (++). If more than five ligands are known, the transporter is denoted as multispecific (+).

Table 2. Types of thyroid hormone transporters and their iodothyronine derivates.

Transporter family	Monocarboxylate transporters		System L amino acidtransporters		Organic anion transporting polypeptides	
	MCT8	MCT10	LAT1	LAT2	OATP1A2	OATP4A1
Heterodimer	N/A		4F2hc		N/A	
Additional molecules transported	N/A	Aromatic amino acids	Large neutral amino acids		Amphipathic organic compounds	
Localization in first and second trimester[a]	ST, CT, EVT	N/A				
Localization in third trimester[b]	ST	N/A	ST^{ap}	N/A		ST^{ap}
Km T4 (μM)	4.7[c]	>Km T3[d]	7.9		8.0	>Km T3
Km T3 (μM)	4.0[c]	≤4.0[d]	0.8		6.5	0.9
Km rT3 (μM)	2.2[c]	N/A	12.5		N/A	
Km T2 (μM)	N/A		7.9	N/A		

[a]Only MCT8 has been localized in the placenta in all three trimesters of pregnancy. [b]LAT1 and OATP4A1 have been localized only at term. [c] These Km values were determined for the rat MCT8 protein expressed in Xenopus laevis oocytes. The other Km values shown are mainly from studies using the human gene expressed in X. laevis oocytes. [d]Human MCT8 or MCT10 transporters expressed in COS1 cells both showed a greater preference for T3 than T4 uptake. Whereas MCT10 showed a greater capacity than MCT8 to transport T3, MCT8 was found to be a more active transporter of T4.
Abbreviations: CT is cytotrophoblast cells, EVT is extravillous trophoblast cells, N/A is no data available, rT3 is reverse T3, ST is syncytiotrophoblast layer and ST^{ap} is predominantly at apical surface of the ST.

Table 3. Expression of the thyroid hormone transporters in human placenta.

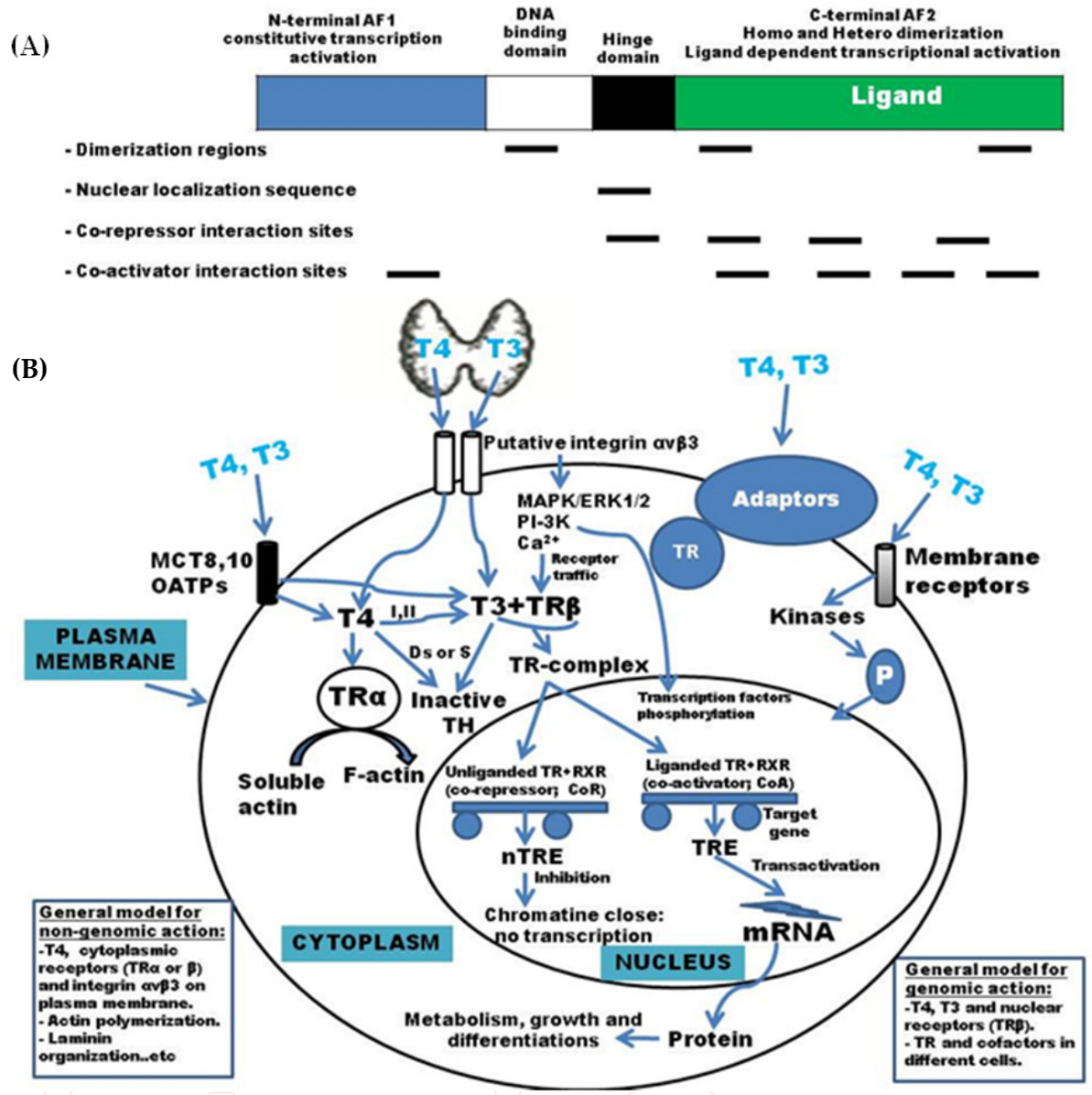
2.3. By thyroid hormone-sulfotransferases (Figure 1)

Sulfation (S) appears to be an important pathway for the reversible inactivation of THs during fetal development [2,13,45-47]. Monique Kester and the group from Erasmus University have used a rat model to study the regulation of fetal TH status and have also extended their studies to human pregnancy [62]. The sulfotransferases catalyze the sulfation of the hydroxyl group of compounds, using 3'-phosphoadenosine-5'-phosphsulfate (PAPS) as the universal sulfate donor [63]. This co-factor PAPS is synthesized from two ATP molecules and inorganic sulfate. Neither the DII or DIII iodothyronines catalyze the deiodination of sulfated iodothyronines nor sulfation strongly facilitates the inner ring deiodination of T4 and T3 by DI, but blocks the outer ring deiodination of T4 (activation) [13,64]. The outer ring deiodination of rT3 by DI is not affected by sulfation [64]. Sulfation thus induces the irreversible degradation of TH. Thus, rapid inner ring deiodinations of T4S, T3S and out ring deiodination of rT3S lead to high concentrations of these sulfates in plasma of adult humans [13,65].

High concentrations of the different iodothyronine sulfates, T4S (thyroxine sulfate), T3S (triiodothyronine sulfate), rT3S (reverse triiodothyronine sulfate) and T2S (diiodothyronine sulfate), have been documented in human fetal and neonatal plasma as well as in amniotic fluid [65,66], and similar findings have been reported for sheep [67]. This has classically been explained by the low hepatic DI expression in the human fetus until the postnatal period [68] and lack of hepatic DI expression until birth in rats [69]. Also, in the rat placenta, where there are insignificant sulfotransferases activities but high DIII activity, irreversible inactivation of DIII appears to be the predominant pathway of iodothyronine metabolism [13]. In the rat fetal liver, sulfotransferase activity is present from the end of the third trimester (GD 17), a time when DI activity is relatively absent [69]. The TH-sulfates may accumulate under such circumstances to form a 'reservoir' of inactive TH from which active hormone may be liberated, in a tissue specific and gestational dependent manner by the action of arylsulfases [13]. To date, six members of this family (ARSAeARSF) have been identified in humans [13,70]. It is interesting that DIII is abundantly expressed in the human placenta [39] and deiodinates T4 and T3 to 3,3'-T2 and rT3, respectively, thus providing substrates for these actions. In the human fetal circulation, T4S and in particular T3S, may represent a reservoir of inactive TH, from which active hormone may be liberated as required (vide supra) [13]. The iodothyronine sulfates in human fetal circulation and amniotic fluid may be derived, at least in part, from sulfation of THs by thermostabile phenol sulfotransferases in the uterus and placenta [13,45]. This may provide a route for the supply of maternal TH to the fetus in addition to placental transfer. Alternatively, iodothyronine sulfates may accumulate in the fetal circulation because of the absence of hepatic transporters which mediate their removal from plasma. It has been demonstrated recently that hepatic uptake of the different iodothyronine sulfates in rats is mediated at least in part through the NTCP and OATP families [71]. Thus, the TH-sulfation mechanism might be useful for non-invasive prenatal diagnostics of fetal thyroid function which is autonomously regulated. The overviews presented here are consistent with the evolving view that sulfation is a major chemical defense system in the maternal-fetal thyroid axis and will hopefully provide a basis for understanding more about these enzymes.

2.4. By thyroid hormone-genomic and non-genomic actions (Tables 4 & 5 and Figure 2)

Although the thyroid gland predominantly secretes T4, T3 is the most active TH, since it has a higher affinity by the nuclear thyroid hormone receptors (TRs; α, β) (Figure 2A) [75], which mediate most actions of these hormones [72,73]. THs are released by the thyroid gland to the circulation where they are carried bound to proteins such as thyroxin binding globulin (TBG), transthyretin (TTR) or serum albumin (Table 4) [74]. The level of albumin, which has the lowest T4 affinity and enables a fast release of T4 [76], gradually decreases during pregnancy [77]. TBG is an active carrier and has a possibility to switch between the high-affinity and the low-affinity form [78]. TBG levels are the highest in the second and third trimester of pregnancy [79,80] and the same holds true for TH-binding ratio [81] and thyroid-binding capacity [82], which decreases as soon as 3-4 days after delivery.



Abbreviations: T3 is triiodothyronine, T4 is thyroxine, TR is thyroid hormone receptor, RXR is retinoid X receptors, TRE is T3-responsive element, nTRE is none T3-responsive element, Ds is deiodonases, S is sulfotransferases, MCT is monocarboxylate transporter, OATP is organic anion transporter, MAPK/ERK1/2 is mitogen-activated protein kinase, P is phosphorylation and PI-3K is phosphatidylinositol 3-kinase.

Figure 2. (A) Schematic representation of major thyroid hormone receptors (TRα, β) domains and functional sub-regions. (B) General model for genomic and non-genomic actions of TH in both adult and fetus; Schematic representation of thyroid hormones (THs; T4 and T3) genomic actions, initiated at the nuclear receptors (TRβ), and non-genomic actions, initiated at cytoplasmatic receptors (TRβ, TRα) and at the plasma membrane on the membrane receptors, particularly integrin αvβ3 receptor. T4 binding (but not T3) to cytoplasmic TRα may cause a change of state of actin. T3 binding (but not T4) to cytoplasmic TRβ activates the phosphatidylinositol 3-kinase (PI-3K) pathway leading to alteration in membrane ion pumps and to transcription of specific genes. TH binding to the integrin receptor results in activation of mitogen-activated protein kinase (MAPK/ERK1/2). Phosphorylated MAPK (pMAPK) translocates to the nucleus where it phosphorylates transcription factors including thyroid receptors (TRβ), estrogen receptor (ER) and signal transducer activators of transcription (STAT). Generally, activity is regulated by an exchange of corepressor (CoR) and coactivator (CoA) complexes.

TH-binding protein	Cellular location
Transthyretin	Plasma
T4-binding globulin	
Serum albumin	
Lipoproteins	
Myosin light chain kinase	Cytoplasmic
Pyruvate kinase, subtype M1	
Pyruvate kinase, subtype M2	
Prolyl 4-hydroxylase, b-subunit	
Aldehyde dehydrogenase	

Table 4. Types of thyroid hormone-binding proteins.

2.4.1. General genomic action (Table 5 and Figure 2)

T4 and T3 enter the cell through transporter proteins such as MCT8 and 10 or OATPs. Inside the cells, deiodinases (DI, II) convert T4, the major form of thyroid hormone in the blood, to the more active form T3. DIII produces rT3 and T2 from T4 and T3, respectively [1,73,83]. T3 binds to nuclear TRs, TRα and TRβ, that activate transcription by binding, generally as heterodimers with the retinoid X receptor (RXR) (Table 5) [87], to thyroid hormone response elements (TREs) located in regulatory regions of target genes [84]. Activity is regulated by an exchange of corepressor (CoR) and coactivator (CoA) complexes. Negative TREs (nTRE) can mediate ligand-dependent transcriptional repression, although in this case the role of coactivators and corepressors is not well defined [73,85]. TRs can also regulate the activity of genes that do not contain a TRE through "cross-talk" with other transcription factors (TF) that stimulate target gene expression [28,86]. Both receptors and coregulators are targets for phosphorylation (P) by signal transduction pathways stimulated by hormones and growth factors [84,85]. Thus, the nuclear actions of T3 are sensitive to inhibitors of transcription and translation and have a latency of hours to days [9,73]. Thus, the genomic action will play a critical role in the cellular proliferations and differentiations.

2.4.2. General non-genomic action (Table 5 and Figure 2)

Although T3 is known to exert many of its actions through the classical genomic regulation of gene transcription, a number of T3 effects occur rapidly and are unaffected by inhibitors of transcription and protein synthesis [88,89]. However, the levels of circulating THs are tightly regulated and stable and thus rapidly mediated responses must involve regulation of pre-receptor ligand metabolism, ligand membrane transport or receptor availability leading to local cell type specific variation in thyroid hormone signaling [87]. Non-genomic actions of THs have been described at the plasma membrane, in the cytoplasm and in cellular organelles [15,21,83,90,91]. They have included the modulation of Na^+, K^+, Ca^{2+} and glucose transport, activation of protein kinase C (PKC), protein kinase A (PKA) and mitogen-activated protein kinase (ERK/MAPK) and regulation of phospholipid metabolism by

activation of phospholipase C (PLC) and D (PLD) [92-94]. Generally, binding of T3 to a subpopulation of receptors located outside the nuclei can also cause rapid "non-genomic" effects through interaction with adaptor proteins, leading to stimulation of signaling pathways. T4 can also bind to putative membrane receptors such as integrin receptor (αVβ3) inducing MAPK activity [18,73,95,96]. Thus, several observations suggest that the rapid nongenomic effects of TH are widespread and may be involved in multiple physiological processes in many different cell types [87]. However, no specific membrane associated TR isoform or thyroid hormone binding G protein-coupled receptors (GPCR) have been identified or cloned and thus the area remains controversial.

Compare face	Ligand	Receptor	Dimerization partners	Associated factors or signalling pathways	Actions
Classical, genomic actions (hours to days)					
Nuclear transcription	T3	TRα and TRβ	RXR and TRs	- NCoR/SMRT Basal	- Transcriptional repression
				- SRC/p160/TRAPs	- Transcriptional activation and repression
Non-classical non-genomic actions (seconds to minutes)					
Cell surface receptor	T4/T3	Putative GPCR		Raf1/MEK/MAPK	TR phosphorylation and altered transcriptional activity p53 phosphorylation and general transcriptional activity
				MEK/STATs	Increased STAT mediated transcription
Mitochondrial gene transcription	T3	TRαp43	mtRXR and mtPPAR	Co-factors?	Increased mitochondrial gene expression
Mitochondrial oxidation	T3	TRαp28		ANT, UCPs	Increased thermogenesis
	T2	Cytochrome -*c* Va			Increased oxidative phosphorylation

Abbreviations: T4 is Thyroxine, T3 is triiodothyronine, T2 is diiodothyronine, RXR is retinoid X receptor, TR is thyroid hormone receptor, GPCR is G protein coupled receptor, mtRXR is mitochondrial retinoid X receptor α isoform, mtPPAR is mitochondrial peroxisome proliferator activator receptor γ2 isoform, NCoR is nuclear receptor co-repressor, SMRT is silencing mediator of RAR and TR, SRC is steroid receptor cooactivator, TRAPs is thyroid receptor associated protein, Raf1 is Raf serine/threonine kinase, MEK is mitogen activated protein kinase kinase, MAPK is mitogen activated protein kinase, STAT is signal transducers and activators of transcription, ANT is adenine nucleotide translocase and UCP is uncoupling protein.

Table 5. General thyroid hormone actions.

There also are reports of nongenomic effects on cell structure proteins by THs. Actin depolymerization blocks DII inactivation by T4 in cAMP-stimulated glial cells, suggesting that an intact actin cytoskeleton is important for this downregulation of deiodinase activity [9,97]. Interestingly, T4, but not T3, can promote actin polymerization in astrocytes [98] and thus may influence the downregulation of DII activity by a secondary mechanism, perhaps by targeting to lysosomes [9,99]. Moreover, the regulation of actin polymerization and F-actin contents also could contribute to the effects of TH on arborization, axonal transport, and cell-cell contacts during brain development, where the regulation of these factors is fundamental for the organization of guidance molecules such as laminin on the astrocyte plasma membrane and modulates integrin–laminin interactions [3]. T4 was required for integrin clustering and attachment to laminin by integrin in astrocytes [100]. These data suggest that the non-genomic action may play an important role in promoting the normal development.

3. Maternal-fetal thyroid in normal state

THs are essential for normal neonatal development in both humans and rodents [3,23,101-104] and the experimental work indicated that THs are transported from the mother to the fetus, albeit in limited amounts, and that the fetal brain is exposed to THs before initiation of fetal TH synthesis [1]. In addition, the maternal TH regulates early fetal brain development in human and animal models [2]. The TH of maternal origin can cross the placenta and reach the fetus [2,105,106] and that TRs are expressed in the fetal rat brain before the onset of fetal thyroid function [107]. Thus, the THs are essential for brain maturation from early embryonic stages onward [103,104,108]. However, TH-dependent stages of fetal brain development remain to be characterized. Notably, the maternal thyroid is the only source of T4 and T3 for the brain of the fetus because its thyroid gland does not start contributing to fetal requirements until midgestation in man, and days 17.5–18 in rats [109]. Therefore, the amount of maternal T4 that the fetus receives early in pregnancy will determine TH action in its brain because it depends on maternal T4 for its intracellular supply of the active form of the hormone, T3. However, fetal brain total T3 levels are low (ca. 100 pM) at this time [1], but receptor occupancy approximates 25% since free T3 concentrations are high in the nucleus relative to the cytosol [110]. In general, materno-fetal transfer of THs has been demonstrated in early fetal stages [111] and continues, at least in the case of fetal inability, to produce sufficient TH until term [44]. Actually, brain cells can protect themselves against higher fetal T4 and T3 values by decreasing DII and increasing DIII activity [2]. Taken together, thyroid activity undergoes many changes during normal pregnancy including [1,112-115]: (a) a significant increase in serum thyroxine-binding globulin, thyroglobulin, total T4, and total T3; (b) an increase in renal iodide clearance; and (c) stimulation of the thyroid by human chorionic gonadotropin (hCG). These changes can make diagnosis of thyroid dysfunction during pregnancy difficult.

4. Maternal-fetal thyroid in hypothyroid state

THs are important for growth and differentiation of a variety of organs, including the brain. In developing brain, THs stimulate and coordinate processes such as neuronal proliferation, migration, growth of axons and dendrites, synapse formation and myelination [1,2].

Disturbance of these processes leads to abnormalities in the neuronal network and may result in mental retardation and other neurological defects, including impaired motor skills and visual processing [115]. If TH deficiency occurs at the perinatal stage, such as in congenital hypothyroidism, timely treatment may rescue most of the symptoms. A shortage of THs starting at the early stages of pregnancy, such as in cretinism, results in neurological deficits that cannot be rescued by exogenous TH addition at later stages [25].

The role of THs in brain development has been studied most extensively in the cerebellum [23,116]. The cellular proliferation and migration processes are disturbed by TH deficiency as investigated predominantly in rodents, where most of cerebellar maturation occurs in the early postnatal period [2]. In the hypothyroid cerebellum, the number and length of Purkinje cell dendrites is severely reduced [1]. At the same time the granule cell parallel fiber growth is reduced, leading to a reduction in axodendritic connections between the Purkinje cells and the granule neurons [117]. Additionally, other cell types such as astrocytes, Golgi epithelial cells, basket cells, and oligodendrocytes show abnormalities under hypothyroid conditions [116]. Several TH target genes have been identified over the years, including genes coding for myelin proteins, cytoskeletal proteins, neurotrophins and their receptors, transcription factors, and intracellular signaling proteins [118] and recent transcriptome analyses continue to increase their number [119-121]. Some of these genes only respond to thyroid status for a short and specific period during development, a feature that is typical for many TH target genes in brain [122]. Interestingly, a reduction or absence of TH during brain maturation yields molecular, morphological and functional alterations in the cerebral cortex, hippocampus and cerebellum [123-132].

5. Maternal-fetal thyroid in hyperthyroid state (Figure 3)

Neonatal hyperthyroidism was described as a critical disease marked mainly by cardiac symptoms, poor weight gain and severe neurological manifestations [1,133-137]. Fetal thyrotoxicosis is the result of thyroid-stimulating antibody transfer to the fetus in the setting of maternal Grave's disease [2,138]. It may present with a variety of clinical features, which include persistent sinus tachycardia, fetal hydrops, intrauterine growth restriction, goiter and fetal demise [1,139]. The vast majority of cases of excessive serum TH concentration seen in pregnancy are due to the overproduction of THs (Graves' disease, toxic nodular goiter); in the postpartum period, thyrotoxicosis may be due to exacerbation of Graves' hyperthyroidism or to the release of thyroid hormone due to an acute autoimmune injury to the thyroid tissue (postpartum thyroiditis-PPT) [2,140].

The management of hyperthyroidism in pregnancy, which most often is caused by Graves' disease, has been reviewed recently [141,142]. Hyperthyroidism occurs in about 0.2–0.4% of all pregnancies. Hyperthyroidism should be distinguished from gestational transient thyrotoxicosis, which is due to the TSH-receptor stimulating effects of hCG [143,144]. This hCG-induced hyperthyroidism is mostly mild and need not be treated. Only rare cases with extremely high hCG (i.e. due to a hydatidiform mole) might induce severe thyrotoxicosis [145]. The signs and symptoms of hyperthyroidism due to Graves' disease may aggravate in the first trimester and thereafter may become mild. Untreated hyperthyroidism is associated with severe

effects on maternal and neonatal outcome. The risk for premature fetal loss, preeclampsia, preterm delivery, intrauterine growth retardation and low birth weight is significantly increased [144]. It has to be considered that the transfer of stimulating receptor antibodies (TSAbs) are transferred from the mother to the child, and therefore the fetus is at risk to develop Graves' disease. Close monitoring of the fetus is, therefore, strictly recommended, even in mothers treated by thyroidectomy before pregnancy but have still elevated TSAbs [142].

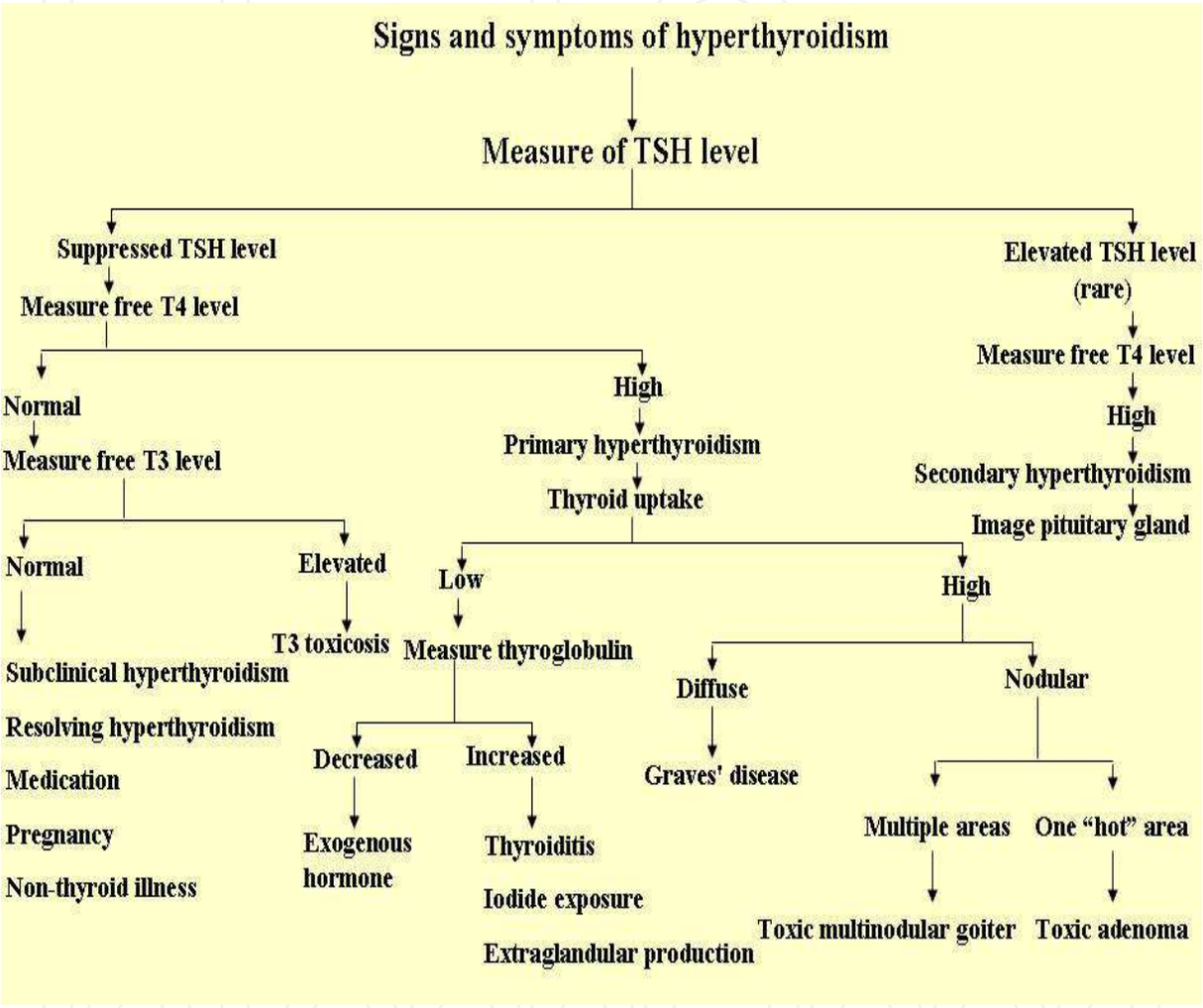


Figure 3. Different cases of hyperthyroidism.

Taken together, there are two known causes of central hyperthyroidism [1,146]; (1) TSH-producing pituitary tumors (TSHomas) and (2) the syndrome of pituitary resistance to thyroid hormone (PRTH). In general, thyrotoxicosis is the syndrome resulting from an excess of circulating free T4 and/or free T3 [147,148]. Babies likely to become hyperthyroid have the highest TSH receptor antibody titer whereas if TSH receptor antibodies are not detectable, the baby is most unlikely to become hyperthyroid (Figure 3) [1,2,149]. In the latter case, it can be anticipated that the baby will be euthyroid, have transient hypothalamic-pituitary suppression or have a transiently elevated TSH, depending on the relative contribution of maternal hyperthyroidism versus the effects of maternal antithyroid medication, respectively [150].

6. Summary

about the developmental thyroid hormone mechanisms (deiodinases, transporters, sulfotransferases and receptors) in human [1,2,50,52,127,130,151-154], rat [1,2,41,60,135,154-156] and chicken [7,157-170]. Note that the chicken is born early compared to the rat and human, as well as the rat is born early compared to the human (Table 6).

Human		Rodent (rat)		Chicken	
Week post conception		Day post conception		Incubation day	
1 W	- DIII is detected in uterine wall.	1 GD	DII and DIII are observed in uterine wall.	5 h (blastula stage)	- TRα mRNA is noticed and the levels markedly increased during neurulation.
3 W	- Thyroid gland begins.	7 -8.5 GD	- Time of implantation process. - Very high DIII activity is detected in decidual tissue.	24 h	- mRNA levels of DI, DII and DIII are detected in whole embryos.
4-6 W	- TBG is observed in thyroid follicle cells at GD 29. - TRH is detected in fetal whole-brain at 4.5 weeks of gestation. - T4 is transferred *via* the placenta and has been found in the gestational fluid sac from 4 to 6 W.	9 GD	- Thyroid gland is first visible as an endodermal thickening in the primitive buccal cavity. - TH is detected in rat embryotrophoblasts	48 h	- OATP1c1 expression appears.
5-11 W	- Maternal-embryo transfer of THs has been detected in embryonic coelomic fluid and amniotic fluid. - All the mRNAs encoding THTs are expressed in placenta from 6 W and throughout pregnancy.				

8 W	- T4, T3 and rT3 are detected in coelomic/amniotic fluids. - TRs, DII and DIII are noticed in fetal brain.	10 GD	- T4, T3 and TRβ are detected in embryo/trophoblast unit.	E2-E4	- T3, THTs, Ds and TRs are expressed in whole embryos.
10 W	- TSH is first detected in the fetal pituitary.			E4	- OATP1c1 expression is more than 10-fold higher in the telencephalon and diencephalon compared to the mesencephalon and rhombencephalon. - DII mRNA levels are highest in the diencephalon.
8-10 W	- The fetus is able to produce THs during this period, but prior to that time, is totally dependent on maternal THs.			E5	- TRα mRNA is widely distributed in fore-, mid- and hind-brain.
11 W	- TBG levels are detected in fetal serum and increased through gestation.			E6	- T4 and T3 are detected in embryonic brain.
8-11 W	- TRH is detected in fetal hypothalamus.			E7	- DII activity is observed in the brain before the onset of thyroid function and increases significantly.
12 W	- T4 and T3 are observed in serum and brain. - Total serum T4 and T3 are low, free T4 is relatively high. - rT3 is noticed in serum relatively high. - TH synthesis begins in fetal thyroid.	13 GD	- Placental circulation established. - TRs and TH are observed in fetal brain. - DIII and DII are detected in uterus and placenta.	E8	- DII mRNA is noticed in cell clusters throughout the brain, particularly in rhombencephalon. - OATP1c1 levels are declined substantially in all brain regions.

	- Decreased mRNA expression of OATP1A2 but no change for OATP4A1 at 9–12 W compared to term.				
14 W	- Expressions of mRNAs encoding MCT8, MCT10, OATP1A2 and LAT1 are significantly lower prior to 14 W compared to term	14 GD	- TRH mRNA is detected in neurons of the fetal hypothalamus.	E4-E8	- DIII mRNA levels are markedly different in the telencephalon and diencephalon but remain stable, while the levels in mesencephalon and rhombencephalon show a sharp decrease and increase, respectively, during these days.
		15 GD	- Pituitary TSH mRNA expression begins. - TRH mRNA is detected in the developing paraventricular nuclei of the hypothalamus.	E9-10	- Several elements of the TH action cascade are present in the brain of embryos long before their own thyroid gland starts hormone secretion.
16 W	- DIII is observed in placenta and fetal epithelial cells. - DIII and TRs are detected in fetal liver. - DI is noticed in heart and lung. - Significant fetal TH secretion begins.	16-19.5 GD	- TRs are observed in liver, heart and lung. - DI and DII are noticed in fetal tissues. - TRH is produced in low levels in hypothalamus and increases approximately threefold by GDI9.5.	E10	- The thyroid gland is fully functional.
16-20 W	- Duplication of TBG concentrations.	17 GD	- TH synthesis begins in fetal thyroid	E13	- Brain DII is elevated at the peak of neuroblast proliferation.

			- TSH protein and Sulfotransferase are observed.		
		18 -22 GD	- The total T4 and T3 concentrations in fetuses are increased dramatically because of maturation of hormone synthesis of the fetal thyroid gland. - The coordination between THTs and Ds is regulated both transplacental TH passage from mother to fetus and the development of the placenta itself through the progress of gestation.	E14	- The strong increase in intracellular T3 has been observed.
20 W	- A steady increase in serum TH levels begins and continues to term.	19 GD	- Significant fetal TH secretion begins. - Marked rise in serum TH but levels at birth still below those in adult.	E15	- Plasma T4 levels start rising markedly around this day.
22-32 W	- Serum total and free T4 and T3 near and below adult levels, respectively. - The HPT axis begins to mature during the second half of gestation.	22 GD	- Birth state. - Thyroid system is less developed. - As much as 17.5% of THs found in the newborn are of maternal origin.	E16	- The decrease in DI activity in gonads is combined with the relatively high DIII activity. - A significant increase in T3 production and in DII-activity and -mRNA expression are combined with a decreased in DIII activity.

	- LAT1 and OATP4A1 have been localized only during the third trimester.				
40 W	- Birth state. - Complete maturation of thyroid system. - MCT8 has been localized in the placenta in all three trimesters of pregnancy. - High concentrations of the different iodothyronine sulfates, T4S, T3S, rT3S and T2S, have been documented in human fetal and neonatal plasma as well as in amniotic fluid during the pregnancy.	10 PND	- Brain development equivalent to human birth.	E13/14–E17 (synaptogenesis)	- Brain DII activity is moderately elevated, whereas DIII activity and mRNA expression are highest between these days, followed by a dramatic decrease thereafter.
		10-20 PND	- Serum TH levels continue to rise and are higher than adult levels between these days.	E18	- DI and DIII are expressed in the granule cells, whereas DII is found mostly in the molecular layer and the Purkinje cells at that time.
		14-50 PND	- The levels of pituitary and serum TSH slowly decrease from PND 14–16 until reaching adult levels at PND 40. - TRH levels increase to adult levels by PNDI7–29, then decrease transiently between PND 31–41; adult levels are once again reached at PND 50. - Adult TRH mRNA expression patterns are present at PND 22.	E19	- The increase in brain T3 production correlates with the appearance of TRβ expression in the cerebellum, telencephalon and optic lobes.
				E20 (at the moment of pipping)	- The brain is quite well developed at the time of hatching. - The gradual increases in plasma T4 and hepatic DI are detected. - DIII levels are decreased in spleen and increased in skin and the lungs towards hatching. - T3 production seems to be elevated markedly in liver. - The rise of T4 is much more pronounced than in plasma. - Diminished T4 sulfation is detected.

		30 PND	Complete maturation of thyroid gland.	E14-E19/20	- The T3 breakdown capacity by DIII is high in liver but low in kidney.
				E15/16-E20	- T4 levels in plasma increase gradually during these days. - In contrast to TRα expression which increases gradually towards hatching, expression of TRβ shows an abrupt elevation in late development, especially in the cerebellum. - The majority of tissues express DIII together with either DI or DII.
				E17-E20	- The levels of DIII activity present in liver are rapidly drop by more than 90%. - DI levels in testis and ovary strongly decrease around hatching.
				E18–E20	- Brain DII activity is moderately decreased, whereas DIII activity is low.
				E19-E20	- The low T3/T4 ratio is associated with high T3 breakdown in liver and with high T4 inactivation or T3 secretion in kidney.
				E20-C0	- DI activity gradually increases, reaching a maximum around these period, and decreases slowly to posthatch levels thereafter.
				C1 (first day post-hatch)	- The expression of DI is limited to the mature granule cells and that of DIII to the Purkinje cells exclusively, whereas DII remains clearly present in the molecular layer.

				C2	- Highest DI-activities and -mRNA expressions are detected in the liver, kidney, and intestine.
				C1-C7	- The circulating T3/T4 ratio started to increase gradually during the first week after hatching.

Abbreviations: W is week, GD is gestation day, E is incubation day, PND is postnatal day, C is posthatch day, THs is thyroid hormones, TRH is thyroid releasing hormone, TSH is thyroid stimulating hormone, THTs is thyroid hormone transporters, MCT is monocarboxylate transporter, OATP is organic anion transporter, Ds is deiodinases (DI, II, III), TRs is thyroid hormone receptors (TRα, β), T4 is Thyroxine, T3 is triiodothyronine, rT3 is reverse triiodothyronine, T2S is diiodothyronine sulfate, T3S is triiodothyronine sulfate, T4S is thyroxine sulfate, rT3S is reverse triiodothyronine sulfate, HPT is hypothalamic-pituitary-thyroid axis and TBG is thyroxin binding globulin.

Table 6. Summary about the developmental thyroid hormone mechanisms (deiodinases, transporters, sulfotransferases and receptors) in human, rat and chicken.

7. Conclusion

The actions of THs are highly pleiotropic, affecting many tissues at different developmental stages. As a consequence, their effects on proliferation and differentiation are highly heterogeneous depending on the cell type, the cellular context, and the developmental or transformation status.

Maternal THs are important in promoting normal fetal development especially the placental and CNS development. Clinical epidemiological and basic findings clearly show that maintaining normal TH regulation from the beginning of pregnancy is important to reduce the risk of obstetric complications and to ensure optimal neurodevelopment of the offspring.

In normal pregnancy, transplacental TH passage is modulated by plasma membrane THTs, Ds, sulfotransferases, TRs and several different proteins within placental cells.

In pathological/abnormal pregnancies with either maternal or fetal THs disturbances (hypo- or hyper-thyroidism), the placenta lacks the full compensatory mechanisms necessary to optimize the maternal–fetal transfer of THs to achieve the normality of TH levels in the fetus.

8. Future challenges

Further studies are still needed to improve our understanding of the mechanisms mediating the transplacental transport of THs in both human and animals, particularly the role of the different THTs, and the mechanisms that ensure that sufficient amounts of THs are protected from D3 inactivation during their transit across the placenta. Such knowledge would facilitate the development of interventions to increase TH passage in pathological situations, in order to ensure normal fetal development. A better understanding of these mechanisms would also permit us to refine the timing and dosage of the increase in

levothyroxine therapy in hypothyroid pregnant women and to establish whether thyroxine on its own is indeed the best form of TH replacement in pregnancy.

Elucidation of tissue-, cell-, and sex-specific expression of individual Ds and THTs during the development of both human and animals, in the adult, during aging and when sick.

I hope that new insights into the complex actions by which the THs and their receptors control cell proliferation and differentiation will be provided in the near future.

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