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Alternate Pathways of Thyroid Hormone Metabolism

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The major thyroid hormone (TH) secreted by the thyroid gland is thyroxine (T_4). Triiodothyronine (T_3), formed chiefly by deiodination of T_4, is the active hormone at the nuclear receptor, and it is generally accepted that deiodination is the major pathway regulating T_3 bioavailability in mammalian tissues. The alternate pathways, sulfation and glucuronidation of the phenolic hydroxyl group of iodothyronines, the oxidative deamination and decarboxylation of the alanine side chain to form iodothyroacetic acids, and ether link cleavage provide additional mechanisms for regulating the supply of active hormone. Sulfation may play a general role in regulation of iodothyronine metabolism, since sulfation of T_4 and T_3 markedly accelerates deiodination to the inactive metabolites, reverse triiodothyronine (rT_3) and T_2. Sulfoconjugation is prominent during intrauterine development, particularly in the precocial species in the last trimester including humans and sheep, where it may serve both to regulate the supply of T_3, via sulfation followed by deiodination, and to facilitate maternal-fetal exchange of sulfated iodothyronines (e.g., 3,3′-diiodothyronine sulfate [T_2S]). The resulting low serum T_3 may be important for normal fetal development in the late gestation. The possibility that T_2S or its derivative, transferred from the fetus and appearing in maternal serum or urine, can serve as a marker of fetal thyroid function is being studied. Glucuronidation of TH often precedes biliary–fecal excretion of hormone. In rats, stimulation of glucuronidation by various drugs and toxins may lead to lower T_4 and T_3 levels, provocation of thyrotropin (TSH) secretion, and goiter. In man, drug induced stimulation of glucuronidation is limited to T_4, and does not usually compromise normal thyroid function. However, in hypothyroid subjects, higher doses of TH may be required to maintain euthyroidism when these drugs are given. In addition, glucuronidates and sulfated iodothyronines can be hydrolyzed to their precursors in gastrointestinal tract and various tissues. Thus, these conjugates can serve as a reservoir for biologically active iodothyronines (e.g., T_4, T_3, or T_2). The acetic acid derivatives of T_4, tetrac and triac, are minor products in normal thyroid physiology. However, triac has a different pattern of receptor affinity than T_3, binding preferentially to the β receptor. This makes it useful in the treatment of the syndrome of resistance to thyroid hormone action, where the typical mutation affects only the β receptor. Thus, adequate binding to certain mutated beta receptors can be achieved without excessive stimulation of alpha receptors, which predominate in the heart. Ether link cleavage of TH is also a minor pathway in normal subjects. However, this pathway may become important during infections, when augmented TH breakdown by ether-link cleavage (ELC) may assist in bactericidal activity. There is a recent claim that decarboxylated derivates of thyronines, that is, monoiodothyronamine (T_1am) and thyronamine (T_0am), may be biologically important and have actions different from those of TH. Further information on these interesting derivatives is awaited.

Introduction

The alternate pathways of thyroid hormone (TH) metabolism include conjugation (sulfation or sulfonation, and glucuronidation of the phenolic hydroxy group), oxidative deamination of the alanine side-chain leading to the formation of the corresponding iodothyroacetates and ether-link cleavage (ELC; Fig. 1). The goal of this review is to summarize recent advances in these areas and to provide relevant physiologic and pathophysiologic information for thyroidologists in basic research and in clinical practice. This review does not include all details in physiology, biochem-

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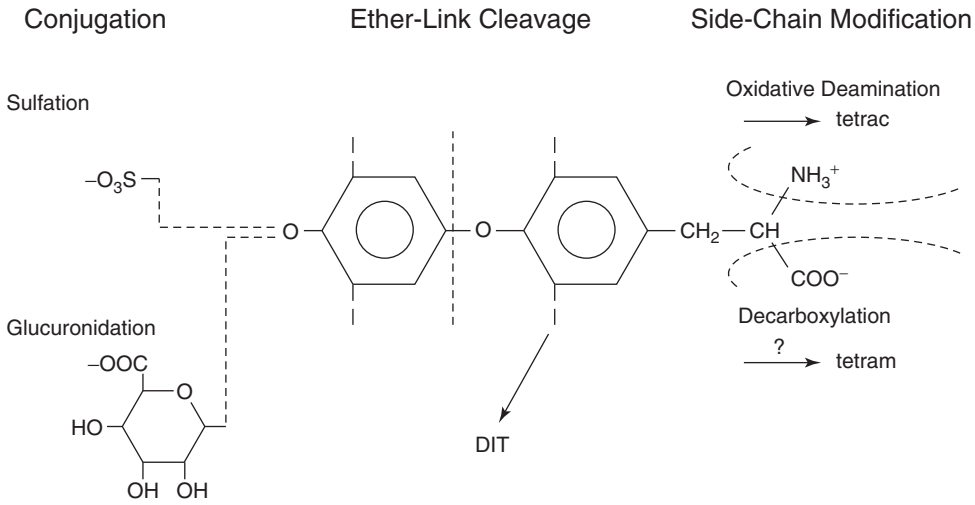

FIG. 1. Alternate pathways of thyroid hormone metabolism. DIT, diiodotyrosine; tetrac, tetraiodothyroacetic acid; tetram, tetraiodothyronamine.

istry, or related background information. The reader is referred to several excellent earlier reviews covering this subject (1–6).

There is general agreement that sequential monodeiodination is the major mechanism regulating the bioavailability of thyroid hormones in tissues. However, the alternate pathways may also play a role in some circumstances. Sulfoconjugation of iodothyronines, for example, is an important pathway in developing animals (2), and sulfated iodothyronines can also be deiodinated, even at a faster rate. Likewise, iodothyroacetates can be sulfated and further deiodinated. Iodothyronine glucuronides are rapidly excreted in the bile. Furthermore, sulfoconjugation and glucuronidation are not irreversible pathways for thyroid hormone metabolism. Glucuronides can be hydrolyzed in the intestine, as well as in other tissues, and then reabsorbed and reutilized. Sulfoconjugates can also be desulfated in selective tissues, for example, liver and brain, and become available to nuclear receptors, especially in fetuses where type 1 deiodinase (D1) activity is low. The *in vivo* occurrence of the decarboxylated metabolites of T_4 and T_3, 3,3′,5,5′-tetraiodothyronamine (tetram) and 3,3′,5-triiodothyronamine (triam) has not been demonstrated (7). However, recently 3-monam (or T_1am) and T_0am have been identified in brain and other tissues in rodents (8) and 3-T_1am was found to be a potent agonist of the G-protein–coupled trace amine receptor TAR1 *in vitro* (8). Iodothyronamines may be derived from iodothyronines by aromatic amino acid decarboxylase (Fig. 1). Finally, ELC in leukocytes may provide cofactors for bacterial killing (9,10).

Sulfoconjugation of Iodothyronines

Sulfoconjugation or sulfonation of iodothyronines is catalyzed by a group of soluble sulfotransferases composed of two subunits, each with a molecular weight of approximately 34 kd, located in the cytoplasmic fraction of different tissues. Sulfation is the transfer of a sulfonate group from the universal sulfonate donor, 3′-phosphoadenosine 5′-phosphosulfate (PAPS), to an appropriate acceptor molecule, the phenolic hydroxyl group for iodothyronines. Many different human and rat sulfotransferase (SULT) genes have been cloned and characterized in recent years (Table 1). They can be grouped into three major superfamilies: SULT1, SULT2, and SULT3. Primarily, the SULT1 and SULT2 families sulfoconjugate phenolic compounds (including TH) and hydroxysteroids respectively (11). One of the SULT3 families mainly catalyzes the sulfation of amines.

Biochemical basis of sulfoconjugation

The different isozymes share a number of conserved domains, including regions I and IV that are proposed to be involved in the binding of PAPS and a number of other key amino acids, especially the conserved histidine that is proposed to function as the catalytic base in the reaction center (12). Many SULTs exhibit overlapping substrate specificities (e.g., estrogen SULT has been shown to sulfate TH). In addition, multiple SULTs in the same organ may be involved in the sulfoconjugation of iodothyronines such as hSULT1A1, hSULT1A3, and hSULT2A1 in liver (13). This represents a clear redundancy of SULTs involved in the sulfoconjugation of iodothyronines so that multiple knockouts of enzymes will be required to evaluate fully the role of SULTs in TH economy.

In humans, SULT1A1 clearly shows the highest affinity for both iodothyronines and PAPS, but it remains to be established whether it is the prominent isozyme for sulfation of TH in human liver and kidney (5). There are at least seven allozymes identified (14). Other human SULTs with documented activities toward TH include hSULT1A3, hSULT1A5, hSULT1B1, hSULT1B2, hSULT1C1, hSULT1E1, and hSULT2A1 (Table 1) (11,12,14–21). They are expressed in a variety of tissues including hSULT1E1 in the uterus and liver as well as hSULT1A1 and hSULT1A3 in normal and diseased thyroid glands (22). A potential role for hSULT1E1 in fetal TH metabolism needs to be considered; in particular the enzyme expressed in the endometrium may be a significant source for the high serum levels of iodothyronine sulfoconjugates in fetuses. However, a similar rat estrogen ST, recombinant rSULT1E1, failed to catalyze iodothyronine sulfation (15).

TABLE 1. BIOCHEMICAL PROPERTIES OF RECOMBINANT HUMAN AND RAT IODOTHYRONINE SULFOTRANSFERASE (SULT) ISOENZYMES

	Human (cDNA expression)					*Rat (cDNA expression)*				
SULT	*Cell line*	*Iodothyronine substrate preferences*	K_m (μM) T_2/T_3	*Note (previous names) specific substrate*	*Ref*	*Cell line*	*Iodothyronine substrate preferences*	K_m (μM) T_2/T_3	*Note (previous names)*	*Ref*
1A1	V79	$T_2 \gg rT_3 > T_3 > T_4$	0.14/29.1	(P-PST-1) (AST IV)	20[a]	S.typhimurim	ND	—	Homodimer and Heterodimer	15
1A1	Cos-1	$T_2 \gg rT_3 > T_3 > T_4$	0.66/84	(Phenol ST) *4-nitrophenol* Thermostable	14[b]					
1A3	V79	$T_2 \gg rT_3 > T_3 > T_4$	33/112	(M-PST) *dopamine* thermolabile	17[a]					
	E.coli		−/413 −/1339		11, 16					
1A5	E.coli		−/180 −/380		11, 16					
1B1	S.typhimurim	$T_2 > rT_3 > T_3 > T_4$	—		17	S.typhimurim	$3,3'\text{-}T_2 \gg T_3 > rT_3 > T_4$	7.74/142	Expressed in female liver, kidney, intestine.	15
1B2	E.coli		−/63.5 −/46.2	Cytosolic liver content. Strongly correlate with T_3 sulfation. Thermostable	11, 16					
1C1	Cos-1	$rT_3 = 3,3'\text{-}T_2 > T_3 > T_4$	10.3/28.7	(HAST-1)	18[b]	V79	$T_2 \gg T_3 = rT_3 > T_4$		Expressed in male liver, kidney, intestine.	15
1C2	—	—	—	Mainly detected in fetal tissues—liver, kidney, lungs, small intestine.	19					
1E1	S.typhimurim	$rT_3 > 3,3'\text{-}T_2 \gg T_3 > T_4$	3.5–6.0/ 15.3–36.1	(EST) *estrogen*	20[a]	S.typhimurim	ND	—	(rEST-1, rEST-3)	15
	Cos-1	$3,3'\text{-}T_2 > rT_3 > T_3 > T_4$	9.3/60.7		21[b]					
1E2	—	—	—		—				(rEST-2, rEST-6)	
1E4	E.coli	—	−/260		011					
2A1	Cos-1	$3,3'\text{-}T_2 > T_3 > rT_3 > T_4$	2.95/14.3	(DHEA-ST) *DHEA*	21[b]	S.typhimurim V79	ND	—		15
2A2	—	—				S.typhimurim	ND	—		15
2A3	E.coli	ND	—	—	11	S.typhimurim	ND	—		15
2B1		?		Two isoforms 2B1a, 2B1b mainly expressed in skin.	12					

Enzyme activities were measured:
[a]PAPS Concentration = 50 μM, pH 7.2, in 0.1 M potassium phosphate buffer.
[b]PAPS Concentration = 0.4 μM, pH 7.0, in 0.06 M potassium phosphate buffer.
[c]PAPS Concentration = 5–100 μM, pH 8.0, in 0.1 M potassium phosphate buffer.
P-PST, phenol-preferring phenol sulfotransferase; AST, aryl ST; M-PST, monamine-preferring PST; HAST, human AST; EST, estrogen ST; DHEA-ST, dehyroepiandrosterone ST; rEST, rat EST; ND, no detectable sulfation.

In rats, as in humans, sulfation of iodothyronines is catalyzed by multiple SULT isozymes in different tissues (Table 1). The higher rate of T_3 sulfation in male versus female rats suggests that rSULT1C1 is a major SULT in liver (15). In contrast, rSULT1B1 expression in rat liver appears to be independent of gender (16). Therefore, sulfation of iodothyronines in female rat liver probably represents predominantly activity of rSULT1B1. It has been reported that rSULT1A1, rSULT2A1, rSULT2A2, and rSULT2A3 do not catalyze iodothyronine sulfation (15). In rats, we found significant activities in uterus with an apparent Km of 0.62 μM for T_2, and activity varied during gestation (23). We also identified rSULT1A1 and rSULT1B1 mRNA in rat uterus but not rSULT1C1 (SY Wu and SH Chen, unpublished data). The role of other rSULTs, for example, rSULT4A1, recently cloned in brain, in TH sulfation is not known (24).

The biochemical properties of SULTs in each organ or tissue presumably reflect the composite effect of different isozymes. The reported Km value for 3,3′-T_2 in hepatic SULT in male rat for example is intermediate between the Km values of rSULT1C1 and rSULT1B1. The molecular weight of the enzymes is between 61,000 and 68,000 consisting of two subunits (25). It should be pointed out that SULT may consist not only of two identical subunits as a homodimer but also of two different subunits (25). The protein-concentration dependency in reaction rate in enzyme kinetics may suggest heterodimer formation in higher concentrations (17).

Biologic significance of sulfoconjugation

The introduction of a sulfate group into the phenolic ring modifies its electronic environment. The sulfoconjugation of thyroid hormones (T_4 and T_3) and their metabolites (rT_3 and 3,3′-T_2) may accelerate further degradation of iodothyronines. Sulfation of T_4 completely blocks the outer ring deiodination to T_3S. On the other hand, sulfated iodothyronine may serve as a reservoir for biologically active hormones such as T_3, which can be recovered from T_3S by sulfatases in selective tissues in which hormone action is required (26,27). In addition, we have demonstrated that sulfoconjugation facilitates fetal to maternal transfer of thyroid hormones and their metabolites, sulfated 3,3′-T_2 in particular (28–30). It is possible that uterine and/or placental (19,23) sulfotransferases may be involved in such a transfer process.

Deiodination of sulfated iodothyronines. Sulfation may be a common event prior to deiodination of T_4 and T_3. In a human hepatoblastoma cell line, HepG2, deficient in sulfotransferase activities, T_3 deiodination was reduced (31). However, it is unlikely that sulfoconjugation is essential prior to all deiodination of iodothyronines *in vivo*. In particular, T_4 can be readily converted to T_3 by D1, whereas sulfation of T_4 completely blocks T_3S formation via D1. Moreover, T_4 is a poor substrate for all SULTs studied thus far. *In vitro*, sulfation of T_4 accelerated 3-deiodination approximately 200 times, because of a decrease in apparent Km as well as an increase in V_{max}. Overall, sulfation markedly facilitates the inner-ring deiodination of T_4, T_3, and 3,3′,5-triiodothyroacetic acid (triac) while outer ring deiodination may either be inhibited (T_4), unaffected (rT_3) or markedly stimulated (3,3′-T_2, 3,3′-diac). As proposed by Visser et al. (4,5), the facilitated deiodination of sulfated iodothyronines by rat liver D1 is the result of an interaction of the negatively charged sulfate group with protonated residues in the active center of this basic protein. However, the exact mechanism by which sulfation stimulates D1 action on the various iodothyronine remains unclear. Also, the phenomenon of accelerated deiodination of sulfated iodothyronines is limited to D1 because deiodination of sulfoconjugates by D2 or D3 was either absent or very limited.

Sulfated iodothyronines serve as a reservoir. Under conditions of low D1 activity, significant amounts of T_3 may be recovered from T_3S (4,5,26). Thus, the sulfated iodothyronines could be deconjugated and serve as a reservoir for parent precursors. 3,3′-T_2 (T_2) is by far the preferred substrate for various mammalian SULTs. The purpose of rapid sulfation of T_2, as well as rT_3 in some tissues, is unknown. T_2 and rT_3 have low affinity for the nuclear thyroid hormone receptor (32). However, T_2 has been found to stimulate mitochondrial respiration in various rat tissues (33) and rT_3 may play a role in regulating actin polymerization in brain cells (34). Thus, the possibility that these T_4 metabolites play a physiologic role in developing animals via sulfation and desulfation cannot be excluded.

During fetal development when D1 is low, little desulfation activity was found in rat hepatic microsomal preparations, but there is a surge of activity after one month postnatally (35). Among rat tissues examined, liver, brain, kidney, testes, and skin were found to have sulfatase activities in decreasing order of strength (26,36). Among the recombinant arylsulfatase (ARS) A, B, and C, expressed in human liver and placenta, only the steroid ARS C, associated with the endoplasmic reticulum, was shown to hydrolyze iodothyronine sulfates (27). In humans, however, significantly higher levels of microsomal sulfatase activity were found, showing 3,3′-T_2S as a preferred substrate, in liver than in placenta although ARS C is expressed at higher levels in placenta. These data suggest that additional arylsulfatase(s) yet to be identified may contribute to the high activity in human liver (27).

Sulfoconjugation of iodothyronines in various physiological and pathophysiological states. Increased serum levels of iodothyronine sulfates are found in developing animals (2,26,29,37–40), in preterm infants (39,41), selenium deficient rats (40,42) and in rats treated with D1 inhibitors (43) as well as in patients on higher T_4-replacement therapy (44) and with systemic illness (26). Although relatively low D1 activity may be involved, the exact mechanism(s) for the increase in serum levels of iodothyronine sulfoconjugates remains to be elucidated. Recently, measurable 3,3′-T_2S levels were found across all brain areas in adult rats, and levels positively correlated with those of rT_3 suggesting a role of tissue D3 that may increase the availability of the substrate, T_2 (45).

Involvement of sulfoconjugates in fetal and maternal transfer of iodothyronines. We have shown high serum concentrations of sulfated iodothyronine analogues in ovine and human fetal and preterm infant serum. These include T_4 sulfate (T_4S), T_3S, rT_3S, and 3,3′-T_2S (T_2S) (2,26,28–30,37,38,46–48). An elevated level of iodothyronine sulfoconjugates is also detectable in amphibians during metamorphosis (49). A kinetic study using the steady-state constant infusion method in sheep showed that the major pathways of TH me-

tabolism in the fetus convert T_4 to inactive metabolites, rT_3, T_4S, rT_3S, and T_3S, via sulfotransferase and D3 enzyme systems in late gestation (2,50).

Thyroid hormone (TH) plays an important role in fetal neurologic maturation. Iodothyronines detected in the fetus before the onset of fetal thyroid function must be maternal in origin. The maternal–fetal transfer of TH and their metabolites is apparently a two-way street. The high gradient between fetal and maternal serum concentrations of iodothyronine sulfates raises the possibility of significant fetal to maternal transfer of iodothyronine sulfoconjugates. Sack et al. (51) showed that umbilical cord cutting, thus removing the lamb from placental D3 and transfer, triggers hypertriiodothyroninemia in the newborn lamb and that the postnatal T_3 peak can be delayed until well after the thyrotropin (TSH) peak by delaying umbilical cord cutting. Recently, Santini et al. (39) found that the placenta plays an important role in maintaining the low serum T_3 in fetuses late in gestation. These findings suggest the importance of the placenta in fetal T_3 metabolism, and it is possible that fetal-to-maternal transfer of the sulfated iodothyronines (presumably via placenta) is one mechanism responsible for reducing serum T_3 concentrations in the fetus. Increasing fetal-to-maternal transfer of iodothyronines may occur in late gestation.

In developing mammals, sulfoconjugation of iodothyronine is an important pathway, in particular, during late gestation when the hypophyseal-pituitary-thyroid system becomes more mature in precocial species including humans and sheep. As term approaches, fetal thyroid gland secretion increases progressively while thyroid hormone effects in many peripheral tissues must be delayed to the postpartum period. D3 and SULTs may serve to moderate the circulating thyroid hormones before parturition. Significant amounts of sulfated iodothyronines in the fetus, including 3,3′-diiodothyronine sulfate (T_2S), appear to be shunted to the maternal circulation through placenta or uterine circulation. The fetal-to-maternal transfer of sulfoconjugated iodothyronine could be a nonselective process as part of a waste management for the fetus or could be a highly selective biologic signal to the mother as a fetal thyroid function indicator. The overall result of the complex fetal–maternal two-way iodothyronine transfer process is to maintain low circulating fetal T_3 concentrations and optimal TH supply for critical tissues such as the central nervous system (CNS).

We observed that when the ovine fetus was infused with ^{125}I-T_3, without disturbing the fetal stable T_3 pool, a mean of 19% of infused radioactive dose was recovered in maternal urine in 4 hours. T_2S was identified as the major radioactive iodothyronine undergoing fetal to maternal transfer; only minimal amounts of T_3S or T_3 were found. We also showed the contribution of fetal TH to the urinary T_2S and T_3S pool in ewes. Maternal urinary T_2S excretion (pmol/g cr) is significantly reduced by fetal thyroidectomy (Tx) but not by maternal Tx (30), providing further evidence that T_2S of fetal origin contributes significantly to the maternal urinary T_2S excretion. 3,3′-T_2 has been found to stimulate mitochondrial respiration (33). The removal of T_2 from fetal compartment may be necessary for normal maturation of mammalian fetuses.

Compound W as a potential marker for fetal thyroid function. In humans, employing the radioimmunoassay for T_2S, we found high levels of "T_2S" in maternal serum (37,38,47,48) and urine (52). Levels increased with the progression of pregnancy and peaked before parturition. At delivery, serum "T_2S" levels were 20-fold higher than levels in nonpregnant women and "T_2S" levels returned to nonpregnant values in 7 to 10 days (47). On closer examination, the radioimmunoassayable "T_2S" did not cochromatograph with synthetic T_2S by high-performance liquid chromatography (HPLC; 47). Over 30 known synthetic thyroid hormone analogues were examined and none was found to be identical to the T_2S-like material in pregnant women's serum. Thus, the name Compound W was given. It is postulated that W is a side-chain modification of T_2S, which cross-reacts with T_2S antibody but is slightly more hydrophobic than T_2S.

In normal pregnancies, both maternal and fetal serum Compound W levels increased progressively with a significant direct correlation in both mothers and fetuses (53). In addition, in 451 paired cord and maternal sera obtained from women at delivery, a highly significant correlation was found between the concentrations of Compound W in newborn cord and maternal serum (SY Wu, L VanMiddlesworth, unpublished data). A significant positive correlation was observed between fetal Compound W and fetal free thyroxine (FT_4) in fetal serum, and between maternal and fetal Compound W (53) whereas no significant correlation was observed between maternal serum Compound W and maternal serum FT_4 in euthyroid or hyperthyroid women (Fig. 2).

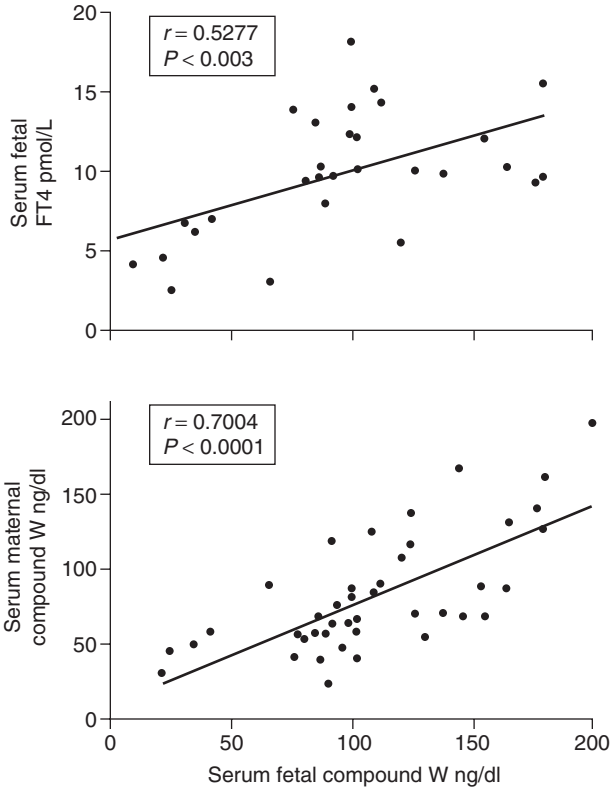

FIG. 2. Correlation of fetal serum compound W levels with (**upper panel**) fetal free thyroxine (FT_4) (pmol/L, $n = 29$) and (**lower panel**) maternal compound W levels (ng/dL in 3,3′-diiodothyronine [T_2S] equivalent, $n = 42$). (Reprinted with permission from Cortelazzi et al. Eur J Endocrinol 141:570–578, 1999, © Society of the European Journal of Endocrinology.)

Thus, these data strongly suggest the fetal origin of Compound W. Furthermore, 9 cordocentesis-proven cases of fetal hypothyroidism (mean serum TSH, 75 mU/L) were found to have maternal Compound W levels (expressed by T_2S-equivalence) significantly below the normal range, as determined in 235 serum samples from normal pregnant women with gestational age of 3 to 40 weeks (49,53–55). These data warrant further evaluation of the use of maternal Compound W to screen for fetal hypothyroidism.

Conclusions

Sulfoconjugation of TH is catalyzed by a group of cytosolic SULTs involved in inactivation and detoxification of both endogenous and xenobiotic compounds. No SULTs have been identified that are specific to thyroid hormones or regulated by thyroid states. Nevertheless, sulfation is an important pathway that facilitates rapid deiodination of T_4S to inactivate metabolite rT_3S while the conversion to T_3S is completely blocked. The sulfoconjugation of iodothyronine could be an important step toward further deiodination by D1 to recover and conserve iodide in terrestrial animals living on iodine-deficient land. Sulfation of TH may also serve to further regulate the bioavailability of TH, especially in developing tissues in addition to deiodinases. Tissue sulfatases may convert sulfated T_3, rT_3, or 3,3′-T_2 to the parent precursors to regain their bioactivities. The significant rise of sulfated iodothyronines in mammalian fetal compartments raises the possibility that significant fetal to maternal transfer of the conjugates occurs in late gestation as the fetal hypothalamic-pituitary-thyroid system become more mature. This transfer may be a novel mechanism to maintain the low T_3 states that is important for normal tissue maturity, especially the fetal brain. The possibility that the transferred iodothyronine sulfate, especially T_2S and its immune-cross-reactive material, Compound W, in maternal serum and urine may serve as a marker of fetal thyroid function needs to be further explored.

Glucuronidation

Phenolic conjugation of the thyroid hormones with glucuronic acid to form their glucuronides has long been recognized as an alternate metabolic pathway, especially for the metabolism of T_4. Although other conjugation sites are also recognized, the primary site of glucuronidation is believed to be the liver where it may precede biliary–fecal excretion of the TH glucuronides (56). In the rat, the glucuronidation pathway is sufficiently prominent that, when the enzyme, an uridine diphosphate-glucuronosyltransferase (UDP-GT or UGT), is stimulated by experimental interventions, the resulting increase in biliary T_4 glucuronide (T_4G) secretion can deplete circulating T_4 levels sufficiently to stimulate TSH and lead to thyroidal hypertrophy. Glucuronidation of T_3 is less important quantitatively and physiologically than is the glucuronidation of T_4 in the rat and is minimal in the human.

While biliary secretion of T_4G into the gut has been considered primarily an excretory mechanism, the intestine can also serve as a T_4 reservoir. Deconjugation back to T_4 occurs in the intestinal lumen, catalyzed by β-glucuronidase in intestinal bacteria. With intestinal absorption of this recovered T_4, the hormone reenters the portal circulation and is again available to the liver. The importance of this hepatoenteric cycle for T_4 and T_4G varies among species and with different experimental interventions. There is evidence of deconjugation of T_4G in tissues other than the liver and the gut lumen, as will be described below. T_4G, as a more polar molecule than T_4, is distributed into a larger volume of distribution than the parent T_4. Deconjugation at tissue sites may serve as a means of delivering T_4 into intracellular sites. Deiodination of T_4G and T_3G has also been shown.

This review focuses on these aspects of the formation and metabolism to the thyroid hormone glucuronides. The reader is also referred to previous reviews of the glucuronidation of the thyroid hormones (4,57).

Biochemical basis of thyroid hormone glucuronidation

T_4 and T_3 are conjugated at their phenolic sites (Fig. 1) by an enzymatic process; UDP-glucuronic acid is a cofactor. Both T_4G and T_3G are prominent in the rat but T_3G formation appears to be minimal in the human. The enzymes that catalyze glucuronidation, the UDP-GTs (UGTs), have been studied extensively, and the isoenzymes have been characterized genetically (56). Isoenzymes UGT1A1 in human liver microsomes and UGT1A9 in human kidney microsomes have been shown to result in T_4 glucuronidation. T_3 conjugation in the rat is catalyzed by the UGT2B isoenzyme (58).

UGT1A1, the key isoenzyme for hepatic glucuronidation of T_4, is found in the liver but not the kidney. It is absent in Gunn rats and also in patients with the Crigler-Najjar (CN) syndrome. The latter is a congenital defect in the conjugation of bilirubin that, in its severe form (type 1) is associated with absent activity in all of the UGT1 isoenzymes not just UGT1A1 (59).

Many agents have been identified that induce the formation of the various UGT isoenzymes. In the 1970s, Bastomsky reported on the enhancement of T_4 glucuronidation in the rat by a variety of toxins (60–64). More recently, McClain et al. (65) reported increases in liver and thyroid size in male rats given phenobarbital for 3 months. T_4 clearance was increased, with increased liver uptake of T_4, increased biliary clearance, and a threefold increase in biliary T_4G. Female rats showed similar but smaller effects (65). Proton pump inhibitors (66), dexamethasone and clofibrate (67) stimulate glucuronide formation to varying degrees, as do a variety of toxins (67–70). These effects have been shown to differ between rats and mice (68,70), indicating considerable species specificity. One should be cautious in extrapolating these findings to the human.

Klaassen's group have studied, in rats, the effects of agents affecting different aspects of glucuronidation. When administered for 21 days, phenobarbital (PB) led to a 190% increase in UDP-GT activity, 3-methylcholanthrene (3MC) to a 290% increase, pregnenolone-16α-carbonitrile (PCN) to a 260% increase and polychlorobiphenyl (PCB) to a 550% increase (71). All four agents resulted in decreased circulating T_4 and increased TSH; these effects were greatest after PCN. Similar changes were also seen after only 7 days' administration (72). All four agents led to increased liver weight and to increased hepatic microsomal UDP-GT activity toward T_4 (73). In studies of these agents' effects on rat liver enzyme mRNA, PCN was found to increase three isoenzymes, UGT1A1, UGT1A2, and UGT1A5, while 3MC and PCB increased UGT1A7 (74). With regard to effects on T_3 glucoconjugation, only PCN in-

creased production of T_3G, resulting in increased biliary secretion of label, 75% as T_3G, after ^{125}I-T_3 intravenously, and probably accounting for the previously observed effect of PCN on stimulating TSH (75).

Visser and coworkers have observed a marked increase in biliary T_4G in rats given propylthiouracil (76) and the formation of T_3G by rat hepatocytes (77). Glucuronide formation by the acetic acid analogues of T_4 and T_3, tetrac and triac were found to be markedly enhanced. They suggested that this would account for the rapid disposal of those T_4 and T_3 products. Unlike the phenol conjugation observed with T_4 and T_3, tetrac and triac are glucuronidated as an ester on the carboxyl group in humans, but not in rats (78).

More recently, Findlay et al. (58) reported the results of studies with microsomes derived from human tissues, from livers of two patients with severe CN syndrome as well as from livers of two control patients and kidneys of four control patients (58). Glucuronide-conjugating capabilities of these microsomes were compared on substrates known to be specific for particular isoenzymes. UGT1A1, absent in CN patients, conjugated bilirubin, T_4 and rT_3. UGT1A9 in the kidney, which conjugates phenols, also conjugated T_4 and rT_3. Glucuronidation of T_3 by the human liver was minimal (58).

Clinical consequences of changes in glucuronidation in humans

Several drugs in common use are inducers of the hepatic glucuronidation mechanism, particularly the anticonvulsants phenytoin and carbamazepine and the antituberculous drug rifampin. As reviewed earlier (4,79), these drugs may accelerate T_4 disposal in humans, lowering T_4 levels, but do not typically affect levels of T_3 or TSH—unlike rats, who do respond with TSH elevations and goiter to such drugs even though T_3 glucuronidation is also often not induced by microsomal enzyme inducers, for example, TCB (3,3′,4,4′-tetrachlorobiphenyl) or dioxin, in rats (4). The difference may reflect weaker enzyme inducing effects in humans, and particularly the failure to accelerate T_3 glucuronidation and clearance. Presumably, increased T_4 secretion compensates for the increased clearance; the fact that some patients have thyroid enlargement (79) suggests at least a transient increase in TSH secretion. Also, there is a recent report that the combination of carbamazepine with valproate may induce subclinical hypothyroidism in epileptic children (80).

A clinical problem does arise, however, when such drugs are given to hypothyroid patients receiving TH therapy, who do have increases in TSH and may need higher doses of T_4 to compensate for the increased rate of T_4 disposal. This has been documented in hypothyroid patients receiving phenytoin, rifampin, and carbamazepine (79), and probably TSH and TH levels should be monitored when hypothyroid patients receive these drugs. Differing recommendations have been made for the management of euthyroid subjects treated with these drugs. Some advise that no routine screening is needed (81); others advise selective screening of those who are known to have thyroid abnormalities or who have suggestive symptoms (82).

Biological significance of T_4G and T_3G

Radioiodinated T_4G and T_3G, derived from ^{125}I-T_4 (T_4*) or from ^{125}I-T_3 (T_3*) incubated with a UDP-GT preparation (83, 84), have been used in a variety of studies in Hays' laboratory (85–87).

Binding to serum proteins. Equilibrium dialysis studies showed the dialyzable fraction for T_4G to be increased 5-fold over that for T_4 in human plasma and 3.7-fold in cat plasma. However, the free fraction of T_3G was almost identical to that of T_3 in both human and cat plasma (85).

Intestinal absorption and hepatoenteric circulation. T_4G administered orally to normal human subjects was found to be absorbed as well as T_4 and to be absorbed primarily as T_4G (87). The presence of a hepatoenteric circulation for T_4G has been postulated, based on the high concentration of T_4G in the bile and the presence of β-glucuronidase in the bacteria of the gut lumen. This assumption was confirmed by members of Visser's group when they demonstrated that fecal suspensions from rats and humans hydrolyzed T_3G, an effect that disappeared in the feces of rats pretreated with antibiotics to sterilize the gut (88). Obligately anaerobic bacteria were found to be responsible for the hydrolyzing effect. A study of the T_3 and T_3G content of the feces from the two groups of rats showed that T_3G was absent from feces of the control rats but present in feces of the decontaminated rats (88).

Deiodination, deconjugation, and distribution volume. T_4G and T_3G were incubated with microsomes derived from euthyroid rat liver (for D1) and hypothyroid rat brain (for D2) prepared in Cavalieri's laboratory. T_4G was deiodinated by both types of microsomes, at about half the rate of deiodination of T_4 studied simultaneously. Both T_4G and T_3G were deconjugated to yield T_4 or T_3 after incubation with all batches of microsomes in a dose-dependent manner. These studies supported the concept that glucuronidation, in addition to being an excretory route, could also produce a T_4 or T_3 reservoir, and that this reservoir is probably present in other tissues in addition to the gut lumen (86).

In human subjects administered T_4G orally or intravenously, very rapid, reversible deconjugation to T_4 occurred, leading to an equilibrium in the ratio between circulating T_4 and T_4G. This unexpected finding leads to the hypothesis that reconjugation is also occurring at various tissue sites. The volume of distribution of the T_4*G and the T_4* derived from it after T_4*G administration was three times that of the T_4* present after T_4* administration. This indicates that the T_4*G-derived T_4* has been carried into intracellular sites to a greater extent than that administered as T_4* (87). In view of the ready deconjugation of T_4G, this may be a mechanism of delivery of T_4 into intracellular compartments that would not have been detected by studies using labeled T_4 alone.

In unpublished studies, rats were given simultaneous doses of ^{125}I-T_4G and ^{131}I-T_4 via the portal vein, with measurement of metabolic products up to 15 minutes after injection. In this short time-frame, no conjugation of the administered ^{131}I-T_4 was detected, but deconjugation of ^{125}I-T_4G occurred in all cases. T_4G was converted to T_4 at approximately 0.5%/minute at the hepatic, biliary, and peripheral sites.

Conclusions

These data suggest that the glucuronidation of TH is quite complicated, with deconjugation and deiodination as potentially important processes, and with the glucuronide conjugate serving as a means of tissue distribution of the parent TH, T_4 in particular. More studies, taking a variety of approaches, are needed. Stimulation of glucuronidation by various drugs and toxins can cause low T_4 levels, high TSH levels, and goiter in rats. In man, however, such effects are not usually seen. A problem does arise when hypothyroid patients on T_4 replacement receive such drugs, and increased T_4 doses are needed.

Deamination and Decarboxylation of the Alanine Side Chain of Thyroid Hormones

Numerous thyroid hormone analogues have been synthesized with modifications of the alanine side chain. The most studied have been triiodothyroacetic and tetraiodothyroacetic acid (triac and tetrac), both of which have been identified in humans, and they are the subject of this review. However, there is a very recent claim that decarboxylated derivatives, or thyronamines (i.e., 3-T_1am and T_0am) may be biologically important, and have actions quite different from those of thyroid hormones (8). 3-T_1am may be derived from monoiodinated iodothyronine by aromatic amino acid decarboxylase (Fig. 1). Further information on these interesting TH derivatives is awaited.

Biochemistry

Enzymes. At least two enzymes have been postulated to convert TH to their acetic acid analogues including TH aminotransferase or transaminase and L-amino acid oxidase (S-amino acid:oxygen-2-oxidoreductase, LAO). The TH aminotransferase is mainly localized in the soluble fraction of liver and kidney whereas the LAO are isolated from various sources including fungi, microorganism, snake venom, turkey liver, and mammalian kidney (89).

Kaiser-Siegrist et al. (89) could not document transamination of T_3. On the other hand, LAO, a member of the flavoenzyme family, converts L-amino acids to their acetic analogues via oxidative deamination. Thus, tetrac and triac are formed from T_4 and T_3. Iodothyronines other than T_4 and T_3 were not found to have such metabolism in any species (1).

Interaction with other metabolic pathways of iodothyronines. Deiodination is the major metabolic pathway for tetrac and triac in humans (90). Both triac and tetrac are better substrates for hepatic D1 than T_3 and T_4 (4,7). The acetic acid derivatives are also conjugated with glucuronic and sulfuric acid in a manner similar to their parent forms. For example, tetrac, triac, reverse triac, and the lesser iodinated analogues are sulfated and glucuronidated in the liver and extrahepatic tissues (1 and this review). These conjugated acetic acid derivatives may be subject to monodeiodination.

In rats, glucuronidation is a major pathway for hepatic triac metabolism (91). Glucuronidated tetrac and triac are also found in human and rat bile (78,90). Both triac and tetrac undergo glucuronidation faster than T_3 and T_4. However, the types of glucuronidation differ in rat and human liver. In rat liver microsomes, triac and tetrac are mainly converted to stable ether glucuronides, whereas in human microsomes mainly labile ester glucuronides are formed (1,78).

Sulfation is an alternate pathway of thyroid hormone metabolism. There are data indicating that sulfated T_3 and T_4, i.e. T_3S and T_4S, can be converted into triac sulfate (triacS) and tetrac sulfate (tetracS) and then deiodinated and desulfated into lower iodinated forms (4,89,92).

In normal subjects, the mean serum concentrations of tetrac are around 50 ng per 100 mL by immunoassay and 8 ng per 100 mL by gas chromatography-mass fragmentography, with a metabolic clearance rate (MCR) of 2.5 L/day, similar to its parent hormone, T_4, and a Production Rate (PR) of 1–2 μg/d (1,89). Thus production of tetrac only accounts for 1%–2% of the total daily T_4 PR. Mean serum concentrations of triac are 2.6 to 8.7 ng per 100 mL in euthyroid subjects, depending on different reports, with a MCR of 215 L/d and a PR of 5.2 μg/d (1,89, and Table 2). In view of tetrac's lower PR, the majority of circulating triac must come via oxidative deamination of T_3, and accounts for 14% of daily T_3 degradation (93). Triac has a blood half-life of approximately

Table 2. Comparison of T_3 and Triac in Metabolism and Biologic Activities

	Kinetic			*TH Receptors*						
	Serum Conc.	$T_{1/2}$	*MCR L/d*	α_1	α_2	β_1	β_2	*Binding protein*	*Metabolism*	*Biologic activity*
T_3	80–180 ng/dL	23 h	37	+	−	+	+	TBG	Deiodination $T_3S \rightarrow$ TriacS	100%
Triac	2.6–8.7 ng/dL	7 h	215	+	−	+++	+++	Trans-thyretin	Deiodination Biliary excretion of triacG	6%
Organ distribution	—	—	—	Heart and skeletal muscle	Brain and testis	(RTH mutation) Kidney Liver Brain	Anterior pituitary Hypothalamus Cochlea	—	—	—

Synthesized from Refs: (86,96–98,105).
RTH, thyroid hormone resistance syndrome; T_3, triiodothyronine; TH, thyroid hormone.

6 to 8 hours (T_3: 23 hours, Table 2) in humans (94) and 5.5 hours in rat (95).

Physiology and pathophysiology

Effect of side chain modification on affinity to receptors for thyroid hormones. Both tetrac and triac have thyromimetic activity in terms of suppression of TSH secretion or calorigenic potency (7). There are two TH receptor (TR) genes, TRα and TRβ (96; Table 2). Each TR gene has subtypes generated by different RNA splicing (97). The TRα_1 is a functional receptor and responds to TH. The TRα_2 does not bind thyroid hormone but can antagonize thyroid hormone. The TRβ_1, TRβ_2, and TRβ_3 differ in their amino termini, but all bind and respond to TH (96,98). These TR subtypes differ in tissue distribution and accessory products resulting in organ-specific thyromimetic responses (Table 2).

The pituitary can take up triac rapidly, inducing TSH suppression, *in vitro* and *in vivo* (99,100). *In vitro* TSH release after exposure to TRH was significantly reduced by triac at 0.01 nM (0.6 ng per 100 mL) and fully blocked at 1–10 nM (101). While there is a shorter binding time on TRs than T_3, triac has a higher binding affinity than T_3 (102) and inhibits circulating TSH as efficiently as T_3 (94). The relative biologic activity *in vivo* of triac/T_3 is 1/18 (89). Approximately 3.5- and 1.5-fold greater affinities of triac than T_3 were reported for *in vitro* translated TRβ_1 and TRα_1 respectively (102), indicating receptor-specific effects of triac. Triac was also reported to selectively augment the function of TRβ_1 without altering TRα_1 (103). Recent data indicate that the major TR isoform expressed in the heart is TRα_1 (98). Notably, mutations in the thyroid hormone resistance syndrome (RTH) mainly occur on the TRβ_1 gene (104). The selectively higher affinity of triac for TRβ_1 but much lower affinity for TRα_1 suggest that triac may be a better choice than T_3 for the treatment of RTH (105). Although the effects of triac on TRH-induced TSH secretion and on hepatic parameters of TH action are similar to those of T_3, triac has significantly different effects on cardiac D1 activity and on cardiac function, resulting in significantly less increase of heart weight with triac than with T_3 or T_4 (95).

In human studies, triac was reported to have a rather selective action at the pituitary level and less effects on peripheral tissues (89,100,106). In an athyreotic patient study, however, triac was found to have distinct augmented thyromimetic effects on hepatic and skeletal but not on cardiac functions as compared with T_4 (107). Triac has a higher affinity for TRβ than for TRα; the liver is β-form predominant whereas the heart and skeleton are α-form predominant (108). However, TRβ has an important role in bone metabolism (107) and development (109). Tetrac has a longer half-life (3–4 days) than triac. In serum, tetrac is mainly bound to transthyretin (101). Available data indicate that tetrac does not inhibit D2, allowing its conversion to triac and excellent inhibition of serum TSH without causing subclinical hyperthyroidism (110,111).

Clinical implications of the acetic acid analogues, tetrac and triac. A significantly increased production of tetrac and triac was found in healthy man during caloric deprivation and in patients with euthyroid sick syndrome (89). Triac is more effective than levothyroxine (LT_4) in reducing goiter size with less adverse events and similar effects on peripheral parameters (112,113). Triac has been effectively applied to treat patients including children with central RTH (114) and pituitary TSH hypersecretion (115). The ability of triac to reduce atherogenic lipoprotein values but not high-density lipoprotein (HDL) cholesterol suggests a potential role in treating patients with hypercholesterolemia (107).

These therapeutic uses of triac are still debated (99,100,107,116,117). Nevertheless, differentiated patients with thyroid cancer with unsuppressed TSH or adverse responses to high doses of LT_4 could benefit from adjuvant triac therapy to improve therapeutic tolerance while suppressing TSH (106).

Conclusions

Acetic acid derivatives of TH are mainly produced by oxidation and deamination of T_3 and T_4. Because triac is more active in TSH suppression than effects on peripheral metabolic parameters, it may be useful, alone or combined with parent TH, in treatment of certain thyroid disorders.

Ether-Link Cleavage

ELC breaks the thyronine nucleus at its ether bridge. One product is diiodotyrosine (Fig. 1), while the phenolic ring iodine is removed in a form that can either iodinate iodoproteins or be converted to iodide. There have been numerous studies of the fate of radioiodine-labeled thyroid hormones and analogues, in humans, animals, and tissue preparations *in vitro*. However, in the majority of these studies, only the phenolic ring has been labeled. Because in these studies the specific product of ELC, DIT formed from the inner ring (see Fig. 1), is unlabeled and the labeled products, iodide and iodoprotein are also formed during monodeiodination, the contribution of ELC to iodothyronine metabolism cannot be accurately assessed.

There has been surprisingly little research on this mechanism since the previous reviews (9,10). However, there have been provocative new findings about the delivery of iodothyronines to tissues via cleavage of thyroxine-binding globulin (TBG; 118). Thus the older literature will be briefly reviewed, and the possible relevance of these new findings discussed.

Ether-link cleavage in vitro

ELC by peroxidases. It has long been known that T_4 and T_3 can be degraded by peroxidases; horseradish peroxidase, and myeloperoxidase have both been studied (119–122). In most reports, when appropriate methods were utilized, diiodotyrosine (DIT) was identified as a product. It was also shown that alternate routes of DIT formation, such as *de novo* iodination of tyrosine, were not operative.

Even the thyroid peroxidase may catalyze ELC. In homogenates of human thyroid tissue, incubated with tyrosyl-labeled T_4 and a peroxide-generating system, DIT was a major product (123). This was not observed when hemi-lobes of thyroid were incubated, and T_3 was the major product from T_4 (124). Thyroid tissue may have a teleologically appropriate mechanism to protect thyroid hormones from degradation by peroxidase. In studies of iodothyronine deiodination by thyroperoxidase, the reaction was strongly

inhibited by glutathione and ascorbate, which are present in large amounts in the thyroid (125). Also, H_2O_2 is said to be excluded from thyroid cells by the action of glutathione peroxidase, further protecting TH from degradation by peroxidase (126). Finally, thyroperoxidase is chiefly localized to the lumenal side of the thyrocyte apical membrane, where it should not encounter free iodothyronines (127).

The postulated mechanism for ELC is an oxidative attack on the phenolic ring, converting it into a quinone which is both cleaved and deiodinated; the iodine liberated is in an oxidation state allowing a portion to bind to protein, and the rest is recovered as inorganic iodide. The remaining moiety, formed from inner ring, is DIT (128).

ELC by leukocytes. Knowledge of iodothyronine breakdown by peroxidases led to study of leukocytes *in vitro*, because of their known myeloperoxidase content and also the fact that halogen ions, including iodide, are cofactors in the killing of bacteria (129). In resting leukocytes, some degree of ELC was observed, as was modest monodeiodinating activity. However, when leukocytes were exposed to particles for phagocytosis, there was a dramatic increase in the rate of breakdown of T_4 and T_3 (130–132). The augmented degradation was shown to be caused by ELC, with DIT identified as a major product, when tyrosyl-labeled T_4 was used (122). Although the prediction was that myeloperoxidase (MPO) would be the responsible enzyme, the discovery that MPO-deficient leukocytes are almost as effective in causing ELC as normal ones (130,132) suggested that other peroxidases may contribute. This group of studies led to the postulate that thyroid hormones may play an important role in the clearing of bacteria by leukocytes.

ELC by tissue preparations in vitro. In several tissues, oxidative breakdown of iodothyronines, and identification of DIT as a product when methods identifying it were applied, have been shown (133–136). Preparations of liver tissue have been most commonly used, and have demonstrated a reciprocal relation between monodeiodination, which occurs under reducing conditions, and ELC, which occurs under oxidizing conditions (137). It may be noteworthy that, in one study of hepatic tissue, abundant DIT formation only occurred when the catalase inhibitor, aminotriazole, was present, while in control incubations DIT was only occasionally found, and then in small amounts (137). This confirms the ability of a hepatic peroxidase to catalyze ELC, but also casts doubt on the importance of hepatic ELC *in vivo*.

Ether link cleavage in vivo

ELC in normal subjects. The question, how important is ELC in the normal disposition of T_4 and T_3, has prompted a number of experimental approaches. One is the bookkeeping approach; from radiotracer experiments estimating rates of T_4, T_3, and rT_3 disposal, what proportion of secreted T_4 can be accounted for by the sum of monodeiodination and conjugation-fecal excretion? The answer, according to several investigations, is that more than 95% is accounted for by these pathways (138), leaving only a small role for ELC. A second approach is based on measuring the recovery in urine of compounds with ether link intact. The studies of Pittman and coworkers (139) and of Chopra et al. (140) suggest that almost all of thyroid secretion in man is matched by recovery of compounds containing an ether link, leaving little room for ELC. Finally, several workers have measured levels of DIT in serum and urine. Obviously, if a large proportion of T_4 and T_3 is undergoing ELC, there should be measurable amounts of DIT in body fluids, and the amount should increase when extra T_4 is given. However, it has now been shown that normal DIT levels are quite low (0.02–0.55 nmol/L), and that they parallel thyroid secretion, that is, are high in hyperthyroidism and low in hypothyroidism (141–143). Furthermore, when large amounts of T_4 are given, DIT production decreases, again suggesting it is related to thyroid secretory activity (141). The conclusion is that most of the DIT reaching the circulation comes from the thyroid, where it is known that DIT is released during thyroglobulin hydrolysis.

ELC during infections. However, some workers, impressed by the several reports of increased T_4 secretion in infections and by the demonstration that labeled hormone becomes concentrated at infected sites (144–147), and encouraged by the findings in phagocytosing leukocytes *in vitro*, have assessed ELC by measuring DIT levels in infections. Although the reports to date come from only one laboratory, they are quite striking—DIT levels in serum and urine increase during sepsis, and can reach extremely high levels (> 5 nmol/L) during severe infections (148,149). Indeed, one problem with the data is that, if metabolic clearance rate of DIT (normally approximately 120 L/d) remains constant during infection, the molar quantity of DIT formed exceeds the T_4 secretory rate (normally about 130 nmol/d) in some patients (149).

There is, however, new information bearing on this problem. It has been shown that the carrier protein for T_4 and T_3, TBG, is a member of the serine protease inhibitor (serpin) family of proteins, and its reactive site loop can be cleaved by leukocyte elastase (118,150–152). The cleaved form has a lower affinity for thyroid hormones, so that larger amounts of T_4 and T_3 can be delivered to sites of infection for ELC possibly followed by bacterial killing. Still, to explain some of the extremely high serum DIT values, up to 100 times normal, other factors, such as altered rates of DIT metabolism, may be involved.

Other instances of increased ELC in vivo. The finding of an apparent association between TBG cleavage and ELC in infections raises a speculative question: Are other instances of TBG cleavage also associated with ELC? Increased TBG cleavage has been reported in pregnant women (153), in cord blood (154), and during cardiac bypass surgery (155). DIT levels are reportedly low during pregnancy (140), arguing against a role for ELC in this circumstance. However, mildly elevated DIT levels have been reported in the newborn (140), perhaps suggesting an association there. As for patients undergoing surgery, the only available report deals with 12 patients undergoing esophageal surgery (156). DIT increased immediately postoperatively to more than tenfold normal levels. In 5 subjects levels returned to normal in 2 or 3 days, while 7 with complications had continuing elevated levels.

Finally, the possibility of a significant role for ELC may be considered in any conditions where total T_4 degradation seems to exceed the sum of deiodination to T_3 and rT_3 plus

fecal T_4 excretion. Persuasive evidence has been presented that in normal individuals there is no accounting gap—processes other than ELC account for all the T_4 degraded (137). However, a gap does exist in several clinical situations. In nonthyroidal illness, T_3 production falls while T_4 and rT_3 production remain constant. In the study showing elevated levels of DIT during sepsis, DIT measurements were made in critically ill nonseptic patients, and the levels were normal (149). Thus, ELC is not the sole explanation for a gap in such patients. During the chronic administration of high doses of T_4, T_3 production does not increase proportionately, again creating a gap (157). However, long-term T_4 treatment of athyrotic individuals, or a single large dose of T_4 in normal subjects, depresses DIT levels (140), making ELC a less attractive explanation for this phenomenon.

One circumstance is of special interest, namely chronic renal failure. T_4 production exceeds the rate of T_3 and rT_3 formation (158,159) and DIT assays have shown elevated levels in both serum and urine (149,160).

Conclusions

ELC is a mechanism for thyroid hormone degradation, presumably a minor pathway in normal hormone economy. It is catalyzed by peroxidases, and can become an important pathway during infections, when leukocytes are activated both to cleave TBG, increasing local hormone delivery, and to cause ELC, thought to provide cofactors for bacterial killing. Elevated DIT levels suggest a role for ELC in chronic renal failure, during major surgery, and in the newborn. These and other situations where the amounts of T_4 degraded appear larger than can be explained by T_3 and rT_3 formation will require further investigation to define the role of ELC.

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References

1. Burger AG 1986 Nondeiodonative pathways of thyroid hormone metabolism. In: Hennemann G (ed) Thyroid Hormone Metabolism. Dekker Marcel, New York, pp. 255–276.
2. Burrow GN, Fisher DA, Larsen PR 1994 Maternal and fetal thyroid function. N Engl J Med **331:**1072–1078.
3. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR 2002 Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev **23:**38–89.
4. Visser TJ 1994 Sulfation and glucuronidation pathway of thyroid hormone metabolism. In: Wu SY, Visser TJ (eds) Thyroid Hormone Metabolism: Molecular Biology and Alternate Pathways. CRC Press, Boca Raton, pp. 85–117.
5. Visser TJ, Kaptein E, Glatt H, Bartsch I, Hagen M, Coughtrie MWH 1998 Characterization of thyroid hormone sulfotransferases. Chem Biol Interact **109:**279–291.
6. Strott CA 2002 Sulfonation and molecular action. Endocr Rev **23:**703–732.
7. Leonard JL, Kohrle J 2000 Intracellular pathways of iodothyronine metabolism. In: Bravermen LE, Utiger RD (eds) Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text, 8th ed. JB Lippincott, New York, pp. 136–173.
8. Scanlan TS, Suchland KL, Hart ME, Chiellini G, Huang Y, Kruzich PJ, Frascarelli S, Crossley II DA, Bunzow JR, Ronca-Testoni S, Lin ET, Hatton D, Zucchi R, Grandy DK 2004 3-Iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. Nat Med **10:** 638–642.
9. Engler D, Burger AG 1984 The deiodination of the iodothyronines and of their derivatives in man. Endocr Rev **5:**151–184.
10. Green WL 1994 Ether-link cleavage of iodothyronines. In: Wu S, Visser T (eds) Thyroid Hormone Metabolism. CRC Press, Boca Raton, pp. 199–221.
11. Fujita K, Nagata K, Shimada M, Yamazoe Y 1999 Bacterial expression and functional characterization of a rat thyroid hormone sulfotransferase, ST1B1. Jpn J Pharmacol **79:**467–475.
12. Coughtrie MW, Johnston LE 2001 Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos **29:**522–528.
13. Richard K, Hume R, Kaptein E, Stanley EL, Visser TJ, Coughtrie MW 2001 Sulfation of the thyroid hormone and dopamine during human development: Ontogeny of phenol sulfotransferases and arylsulfatase in liver, lung, and brain. J Clin Endocrinol Metab **86:**2734–2742.
14. Li X, Clemens DL, Cole JR, Anderson RJ 2001 Characterization of human liver thermostable phenol sulfotransferase (SULT1A1) allozymes with 3,3′,5-triiodothyronine as the substrate. J Endocrinol **171:**525–532.
15. Kester MH, Kaptein E, Roest TJ, van Dijk CH, Tibboel D, Meinl W, Glatt H, Coughtrie MW, Visser TJ 2003 Characterization of rat iodothyronine sulfotransferases. Am J Physiol Endocrinol Metab **285:**E592–E598.
16. Fujita K, Nagata K, Ozawa S, Sasana H, Yamazoe Y 1997 Molecular cloning and characterization of rat ST1B1 and human ST1B2 cDNAs, encoding thyroid hormone sulfotransferases. J Biochem **122:**1052–1061.
17. Kester MH, Kaptein E, Roest TJ, van Dijk CH, Tibboel D, Meinl W, Glatt H, Coughtrie MW, Visser TJ 1999 Characterization of human iodothyronine sulfotransferases. J Clin Endocrinol Metab **84:**1357–1364.
18. Li X, Clemens DL, Anderson RJ 2000 Sulfation of iodothyronines by human sulfotransferase 1C1 (SULT1C1). Biochem Pharmacol **60:**1713–1716.
19. Stanley EL, Hume R, Visser TJ, Coughtrie MW 2001 Differential expression of sulfotransferase enzymes involved in thyroid hormone metabolism during human placental development. J Clin Endocrinol Metab **86:**5944–5955.
20. Kester MHA, Van Dijk CH, Tibboel D, Hood AM, Rose NJM, Meinl W, Pabel U, Glatt H, Falany NC, Coughtrie MWH, Visser TJ 1999 Sulfation of thyroid hormone by estrogen sulfotransferase. J Clin Endcrinol Metab **84:**2577–2580.
21. Li X, Anderson RJ 1999 Sulfation of iodothyronines by recombinant human liver steroid sulfotransferases. Biochem Biophys Res Commun **263:**632–639.
22. Ebmeier CC, Anderson RJ 2004 Human thyroid phenol sulfotransferase enzymes 1A1 and 1A3: activities in normal and diseased thyroid glands, and inhibition by thyroid

hormones and phytoestrogens. J Clin Endocrinol Metab **89:**5597–5605.
23. Wu SY, Fisher DA, Jones G, Florsheim WH, St. Germain D, Galton VA 2000 Characterization of a novel iodothyronine sulfotransferase activity in pregnant rat uterus. Pediatr Res **48:**847–851.
24. Falany CN, Xie X, Wang J, Ferrer J, Falany JL 2000 Molecular cloning and expression of novel sulphotransferase-like cDNAs from human and rat brain. Biochem J **346:**857–864.
25. Kiehlbauch CC, Lam YF, Ringer DP 1995 Homodimeric and hetereodimeric arylsulfotransferases catalyze the sulfuric esterification of N-hydroxy-2-acetylaminofluorene. J Biol Chem **270:**18941–18947.
26. Chopra IJ, Santini F, Wu SY, Hurt RE 1994 The role of sulfation and desulfation in hormone thyroid metabolism. In: Wu SY, Visser TJ (eds) Thyroid Hormone Metabolism: Molecular Biology and Alternate Pathways. CRC Press, Boca Raton, pp. 119–138.
27. Kester MH, Kaptein E, van Dijk CH, Roest TJ, Tibboel D, Coughtrie MW, Visser TJ 2002 Characterization of iodothyronine sulfatase activities in human and rat liver and placenta. Endocrinology **143:**814–819.
28. Wu SY, Polk D, Fisher DA, Huang WS, Reviczky A, Chen WL 1995 Identification of 3,3′-T_2S as a fetal thyroid hormone derivative in maternal urine in sheep. Am J Physiol **268:**E33–E39.
29. Wu SY, Polk DH, Huang WS, Fisher DA 1999 Fetal-to-maternal transfer of 3,3′,5-triiodothyronine sulfate and its metabolite in sheep. Am J Physiol **277:** E915–E919.
30. Wu SY, Huang WS, Fisher DA, Florsheim WH, Kashiwai K, Polk DH 2001 3,3′-Diiodothyronine sulfate excretion in maternal urine reflects fetal thyroid function in sheep. Pediatr Res **50:**358–364.
31. Otten MH, Mol JA, Visser TJ 1983 Sulfation preceding deiodination of iodothyronines in rat hepatocytes. Science **221:**81–83.
32. Oppenheimer JH, Schwartz HL 1997 Molecular basis of thyroid hormone-dependent brain development. Endocr Rev **18:**462–475.
33. Moreno M, Lanni A, Lombardi A, Goglia F 1997 How the thyroid controls metabolism in the rat: Different roles for triiodothyronine and diiodothyronines. J Physiol **505:**529–538.
34. Leonard JL, Farwell A 1997 Thyroid hormone-regulated actin polymerization in brain. Thyroid **7:**147–151.
35. Huang WS, Kuo SW, Chen WL, Shieh KS, Wu SY 1996 The maturation of hepatic sulfatase in developing rats. J Formos Med Assoc **95:**435–439.
36. Santini F, Chopra IJ, Wu SY, Solomon DH, Chua Teco GN 1992 Metabolism of 3,5,3′-triiodothyronine sulfate (T_3S) by tissues of the fetal rat: A consideration of the role of desulfation of T_3S as a source of T_3. Pediatr Res **31:**541–544.
37. Chopra IJ 2004 A radioimmunoassay for measurement of 3,3′-diiodothyronine sulfate: Studies in thyroidal and nonthyroidal diseases, pregnancy, and fetal/neonatal life. Metabolism **53:**538–543.
38. Wu SY, Fisher DA 2004 Measurement of 3,3′-diiodothyronine sulfate (T_2S) in thyroidal and nonthyroidal disease, pregnancy, and fetal/neonatal life. Metabolism **53:**1387.
39. Santini F, Chiorato L, Ghirri P, Lapi P, Mammoli C, Montanelli L, Scartabelli G, Ceccarini G, Coccoli L, Chopra IJ, Boldrini A, Pinchera A 1999 Serum iodothyronine in the human fetus and the newborn: evidence for an important role of placenta in fetal thyroid hormone homeostasis. J Clin Endocrinol Metab **84:**493–498.
40. Wu SY, Huang WS, Chopra IJ, Jordan M, Santini F 1995 Sulfation pathway of thyroid hormone metabolism in selenium deficient male rats. Am J Physiol **268:**E572–E579.
41. Murphy N, Hume R, van Toor H, Wu SY, Visser TJ, Williams FLR 2004 The hypothalamic-pituitary-thyroid axis in preterm infants; changes in the first 24 hours of postnatal life. J Clin Endocrinol Metab **89:**2824–2831.
42. Zimmermann MB, Kohrle J 2002 The impact of iron and selenium deficiencies on iodine and thyroid metabolism: Biochemistry and relevance to public health. Thyroid **12:**867–878.
43. Veronikis IE, Alex S, Fang SL, Wright G, Wu SY, Chanoine JP, Emerson CH, Braverman LE 1996 Serum iodothyronine concentrations in intestinally decontaminated rats treated with a 5′deiodinase type 1 inhibitor, 6-anilino-2-thiouracil. Eur J Endocrinol **134:**519–523.
44. Huang WS, Cherng SC, Wang CH, Shih BF, Kuo SW, Wu SY 1997 Increased urinary thyroxine sulfate excretion in thyroxine therapy. Endocr J **44:**467–472.
45. Pinna G, Brodel O, Visser T, Jeitner A, Grau H, Eravci M, Meinhold H, Baumgartner A 2002 Concentrations of seven iodothyronine metabolites in brain regions and the liver of the adult rat. Endocrinology **143:**1789–1800.
46. Chanoine JP, Neve J, Goyens P, Wu SY, Vanderpas J, Bourdoux P 2001 Selenium supplementation and thyroid hormone metabolism in children with permanent congenital hypothyroidism. J Clin Endocrinol Metab **86:** 1160–1163.
47. Wu SY, Polk DH, Chen WL, Fisher DA, Huang WS, Yee B 1994 A 3,3′-diiodothyronine-sulfate cross-reactive compound in serum from pregnant women. J Clin Endocrinol Metab **78:**1505–1509.
48. Huang WS, Roan CS, Kuo SW, Yan JS, Luo JS, Chen WL 1995 Establishment of the sulfated 3,3′-diiodothyronine radioimmunoassay and its application in pregnant women. Proc Natl Sci Counc Repub China B **9:**201–207.
49. Wu SY, Huang WS, Polk DH, Parker LN, Fisher DA, Galton VA 1998 Sulfoconjugation is a major pathway of thyroid hormone metabolism in developing animals: from tadpoles to mammals. 80th Annual Meeting of the Endocrine Society, New Orleans, LA, p 248.
50. Polk DH, Reviczky A, Wu SY, Huang WS, Fisher DA 1994 Metabolism of sulfoconjugation thyroid hormone derivatives in developing sheep. Am J Physiol **266:**E892–E895.
51. Sack J, Beaudry M, DeLamater PV, Oh W, Fisher DA 1976 Umbilical cord cutting triggers hypertriiodothyroninemia and non-shivering thermogenesis in the newborn lamb. Pediatr Res **10:**169–175.
52. Wu SY, Fisher A, Huang WS, Beck-Peccoz P, Emerson CH, Kuo W, Chen W 1998 Urinary compound W in pregnant women is a potential marker for fetal thyroid function. Am J Obstet Gynecol **178:**886–891.
53. Cortelazzi DP, Morpurgo S, Azmperini P, Fisher DA, Beck-Peccoz P, Wu SY 1999 Maternal Compound W serial measurements in the management of fetal hypothyroidism. Europ J Endocrinol **141:**570–578.
54. VanMiddlesworth L, Guerra SM, Mercer BM, Rose SR, Burstein S, Wu SY 1995 Maternal "Compound W," a possible indicator of fetal thyroid function during maternal hyperthyroidism on PTU therapy. 11th International Thyroid Congress, Toronto, Canada.
55. Abuhamad AZ, Fisher DA, Warsof SL, Slotnick RN, Pyle PG, Wu SY 1995 Antenatal diagnosis and treatment of fetal goitrous hypothyroidism: Case report and review of the literature. Ultrasound Obst Gynecol **6:**368–371.
56. Tukey RH, Strassburg CP 2001 Genetic multiplicity of the

human UDP-glucuronosyltransferases and regulation in the gastrointestinal tract. Mol Pharmacol **59:**405–414.
57. Curran PG, de Groot LJ 1991 The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. Endocr Rev **12:**135.
58. Findlay KA, Kaptein E, Visser TJ, Burchell B 2000 Characterization of the uridine diphosphate-glucuronosyltransferase-catalyzing thyroid hormone glucuronidation in man. J Clin Endocrinol Metab **85:**2879–2883.
59. Sampietro M, Iolascon A 1999 Molecular pathology of Crigler-Najjar type I and II and Gilbert Syndromes. Haematologica **84:**150–157.
60. Bastomsky CH 1974 Effects of a polychlorinated biphenyl mixture (aroclor 1254) and DDT on biliary thyroxine excretion in rats. Endocrinology **95:**1150–1155.
61. Bastomsky CH 1977 Enhanced thyroxine metabolism and high uptake goiters in rats after a single dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Endocrinology **101:**292–296.
62. Bastomsky CH 1977 Goitres in rats fed polychlorinated biphenyls. Can J Physiol Pharmacol **55:**288–292.
63. Bastomsky CH, Murthy PV 1976 Enhanced in vitro hepatic glucuronidation of thyroxine in rats following cutaneous application or ingestion of polychlorinated biphenyls. Can J Physiol Pharmacol **54:**23–26.
64. Bastomsky CH, Papapetrou PD 1973 The effect of methylcholanthrene on biliary thyroxine excretion in normal and Gunn rats. J Endocrinol **56:**267–273.
65. McClain RM, Levin AA, Posch R, Downing JC 1989 The effect of phenobarbital on the metabolism and excretion of thyroxine in rats. Toxicol Appl Pharmacol **99:**216–228.
66. Masubuchi N, Hakusui H, Okazaki O 1997 Effects of proton pump inhibitors on thyroid hormone metabolism in rats: a comparison of UDP-glucuronyltransferase induction. Biochem Pharmacol **54:**1225–1231.
67. Jemnitz K, Veres Z, Monostory K, Vereczkey L 2000 Glucuronidation of thyroxine in primary monolayer cultures of rat hepatocytes: in vitro induction of UDP-glucuronosyltransferases by methylcholanthrene, clofibrate, and dexamethasone alone and in combination. Drug Metab Dispos **28:**34–37.
68. Craft ES, DeVito MJ, Crofton KM 2002 Comparative responsiveness of hypothyroxinemia and hepatic enzyme induction in Lon-Evans rats versus C57BL/6J mice exposed to TCDD-like and phenobarbital-like polychlorinated biphenyl congeners. Toxicol Sci **68:**372–380.
69. Hallgren S, Darnerud PO 2002 Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats-testing interactions and mechanisms for thyroid hormone effects. Toxicology **177:**227–243.
70. Kato Y, Haraguchi K, Yamazaki T, Ito Y, Miyajima S, Nemoto K, Koga N, Kimura R, Degawa M 2003 Effects of polychlorinated biphenyls, kanechlor-500, on serum thyroid hormone levels in rats and mice. Toxicol Sci **72:**235–241.
71. Barter RA, Klaassen CD 1994 Reduction of thyroid hormone levels and alteration of thyroid function by four representative UDP-glucurosyltransferase inducers in rats. Toxicol Appl Pharmacol **128:**9–17.
72. Hood AM, Klaassen CD 2000 Differential effects of microsomal enzyme inducers on in vitro thyroxine (T(4)) and triiodothyronine (T(3)) glucuronidation. Toxicol Sci **55:**78–84.
73. Hood A, Allen ML, Liu Y, Liu J, Klaassen CD 2003 Induction of T(4) UDP-GT activity, serum thyroid stimulating hormone, and thyroid follicular cell proliferation in mice treated with microsomal enzyme inducers. Toxicol Appl Pharmacol **188:**6–13.
74. Vansell NR, Klaassen CD 2002 Increase in rat liver UDP-glucuronosyltransferase mRNA by microsomal enzyme inducers that enhance thyroid hormone glucuronidation. Drug Metab Dispos **30:**240–246.
75. Vansell NR, Klaassen CD 2002 Effect of microsomal enzyme inducers on the biliary excretion of triiodothyronine (T(3)) and its metabolites. Toxicol Sci **65:**184–191.
76. Rutgers M, Pigmans IG, Bonthuis F, Docter R, Visser TJ 1989 Effects of propylthiouracil on the biliary clearance of thyroxine (T4) in rats: Decreased excretion of 3,5,3′-triiodothyronine glucuronide and increased excretion of 3,3′,5′-triiodothyronine glucuronide and T4 sulfate. Endocrinology **125:**2175–2186.
77. Rooda SJ, Otten MH, van Loon MA, Kaptein E, Visser TJ 1989 Metabolism of triiodothyronine in rat hepatocytes. Endocrinology **125:**2187–2197.
78. Moreno M, Kaptein E, Gglia F, Visser TJ 1994 Rapid glucuronidation of tri and tetraiodothyroacetic acid to ester glucuronides in human liver and to ether glucuronides in rat liver. Endocrinology **135:**1004–1009.
79. Green WL 1996 Antithyroid compounds. In: Bravermen LE, Utiger RD (eds) Werner and Ingbars The Thyroid: A Fundamental and Clinical Text, 7th ed. JB Lippincott, New York, pp. 271–272.
80. Eiris-Punal J, Del Rio-Garma M, Del Rio-Garma MC, Lojo-Rocamonde S, Novo-Rodriguez I, Castro-Gago M 1999 Long-term treatment of children with epilepsy with valproate or carbamazepine may cause subclinical hypothyroidism. Epilepsia **40:**1761–1766.
81. Tiihonen M, Liewendahl K, Waltimo O, Ojala M, Valimaki M 1995 Thyroid status of patients receiving long-term anticonvulsant therapy assessed by peripheral parameters: a placebo-controlled thyroxine therapy trial. Epilepsia **36:**1118–1125.
82. Verma NP, Haidukewych D 1994 Differential but infrequent alterations of hepatic enzyme levels and thyroid hormone levels by anticonvulsant drugs. Arch Neurol **51:**381–384.
83. Hazenberg MP, de Herder WW, Visser TJ 1988 Hydrolysis of iodothyronone conjugates by intestinal bacteria. FEMS Microbiol Rev **4:**9–16.
84. Hays MT, Hsu L 1987 Preparation and separation of the glucuronide and sulfate conjugates of thyroxine and triiodothyronine. Endocr Res **13:**215–228.
85. Hays MT, Hsu L 1988 Equilibrium dialysis studies of plasma binding of thyroxine, triiodothyronine and their glucuronide and sulfate conjugates in human and cat plasma. Endocr Res **14:**51–58.
86. Hays MT, Cavalieri RR 1992 Deiodination and deconjugation of the glucuronide conjugates of the thyroid hormones by rat liver and brain microsomes. Metabolism **41:**494–497.
87. Hays MT, Hsu L 1991 Absorption and deconjugation of thyroxine glucuronide (T4G) in man. In: Gordon A, Gross J, Hennenman G (eds) Progress in Thyroid Research. Balkema, Rotterdam, pp. 749–752.
88. de Herder WW, Hazenberg MP, Pennock-Schroder AM, Oosterlaken AC, Rutgers M, Visser TJ 1989 On the enterohepatic cycle of triiodothyronine in rats; Importance of the intestinal microflora. Life Sci **45:**849–856.
89. Kaiser-Siegrist CA, Burger AG 1994 Modification on the side chain of thyroid hormones. In: Wu SY, Visser TJ (eds) Thyroid Hormone Metabolism: Molecular Biology

and Alternate Pathways. CRC Press, Boca Raton, pp. 183–190.
90. Ichikawa K, Hashizume K, Yamada T, Hashmoto T 1987 Effect of thyroid hormone on peroxisomal flavin enzymes in rat liver and kidney. Endocrinol Jpn **34:**245–250.
91. Rutgers M, Heusdens FA, Bonthuis F, Visser TJ 1989 Metabolism of triiodoacetic acid (TA3) in rat liver. II. Deiodination and conjugation of TA3 by rat hepatocytes and in rats *in vivo*. Endocrinology **125:**433–443.
92. Kung MP, Spaulding SW, Roth JA 1988 Desulfation of 3,5,3′-triiodothyronine sulfate by microsomes from human and rat tissues. Endocrinology **122:**1195–1200.
93. Gavin LA, Livermore BM, Cavalieri RR, Hammond ME, Castle JN 1980 Serum concentration, metabolic clearance, and production rates of 3,5,3′-triiodothyroacetic acid in normal and athyreotic man. J Clin Endocrinol Metab **51:**529–534.
94. Menegay C, Juge C, Burger AG 1989 Pharmacokinetics of 3,5,3′-triiodothyroacetic acid and its effect on serum TSH levels. Acta Endocrinol **121:**651–658.
95. Liang H, Juge-Aubry CE, O'Connell M, Burger AG 1997 Organ-specific effects on 3,5,3′-triiodothyroacetic acid in rats. Eur J Endocrinol **137:**537–544.
96. Wagner RL, Huber BR, Shiau AK, Suzana AK, Lima TC, Scanlan TS, Apriletti JW, Baxter JD, West BL, Fletterick RJ 2001 Hormone selectivity in thyroid hormone receptors. Mol Endocrinol **15:**398–410.
97. Lazar MA 1993 Thyroid hormone receptors: multiple forms, multiple possibilities. Endocr Rev **14:**184–193.
98. Ortiga-Carvalho TM, Hashimoto K, Pazos-Moura CC, Geenen D, Cohen R, Lang RM, Wondisford FE 2004 Thyroid hormone resistance in the heart: Role of the thyroid hormone receptors β isoform. Endocrinology **145:**1625–1633.
99. Everts ME, Visser TJ, Moerings EPCM, Docter R, van Toor H, Tempelaars AMP, De Jong M, Krenning EP, Hennemann G 1994 Uptake of triiodothyroacetic acid and its effect on thyrotropin secretion in cultured anterior pituitary cells. Endocrinology **135:**2700–2707.
100. Bracco D, Morin O, Schutz Y, Liang H, Jequier E, Burger AG 1993 Comparison the metabolic and endocrine effects of 3,5,3′-triiodothyroacetic acid and thyroxine. J Clin Endocrinol Metab **77:**221–228.
101. Everts ME, Visser TJ, Moerings EPCM, Tempelaars AMP, van Toor H, Docter R, De Jong M, Krenning EP, Hennemann G 1995 Uptake of 3,3′,5,5′-tetraiodothyroacetic acid and triiodothyronine in cultured rat anterior pituitary cells and its effects on thyrotropin secretion. Endocrinology **136:**4454–4461.
102. Schueler PA, Schwartz HL, Strait KA, Mariash CN, Oppenheimer JH 1990 Binding T3 and its analogs to the in vitro translational products of c-erb A protooncogenes: differences in the affinity of the α- and β-forms for the acetic acid analog and failure of the human testis and kidney α-2 products to bind T3. Mol Endocrinol **4:**227–234.
103. Takeda T, Suzuki S, Liu RT, DeGroot LJ 1995 Triiodothyroacetic acid has unique potential for therapy of resistance to thyroid hormone. J Clin Endocrinol Metab **80:**2033–2040.
104. Yen PM 2003 Molecular basis of resistance to thyroid hormone. Trends Endocrinol Metab **14:**327–333.
105. Messier N, Laflamme L, Hamann G, Langlois MF 2001 In vitro effect of triac on resistance to thyroid hormone receptor mutants: potential basis for therapy. Mol Cell Endocrinol **174:**59–69.
106. Pujol P, Osman A, Bringer J, Jaffiol C 1997 Letter to the Editors. Clin Endocrinol **46:**121–122.
107. Sherman SI, Ringel MD, Smith MJ, Kopelen HA, Zoghbi WA, Ladenson PW 1997 Augmented hepatic and skeletal thyromimetic effects of tiratricol in comparison with levothyronine. J Clin Endocrinol Metab **82:**2153–2158.
108. Bassett JH, Williams GR 2003 The molecular actions of thyroid hormone in bone. Trends Endocrinol Metab **14:**356–364.
109. Freitas FR, Capelo LP, O'Shea PJ, Jorgetti V, Moriscot AS, Scanlan TS, Williams GR, Zorn TM, Gouveia CH 2005 The thyroid hormone receptor beta-specific agonist GC-1 selectively affects the bone development of hypothyroid rats. J Bone Miner Res **20:**294–304.
110. Lameloise N, Siegrist-Kaiser C, O'Connell M, Burger A 2001 Differences between the effects of thyroxine and tetraiodothyroacetic acid on TSH suppression and cardiac hypertrophy. Eur J Endocrinol **144:**145–154.
111. Safran M, Farwell AP, Rokos H, Leonard JL 1993 Structural requirements of iodothyronines for the rapid inactivation and internalization of type II iodothyronine 5′-deiodinase in glial cells. J Biol Chem **268:**14224–14229.
112. Alvarez L, Burgueño A, Zeni S, Randi AS, Hernândez S, Hockl P, Pisarev MA, Kleiman de Pisarev DL 2004 Comparison of the effect of 3,5,3′-triiodothyroacetic acid and triiodothyronine on goiter prevention and involution and on hepatic and skeletal parameters in rats. Horm Metab Res **36:**291–297.
113. Brenta G, Schnitman M, Fretes O, Facco E, Gurfinkel M, Damilano S, Pacenza N, Blanco A, Gonzalez E, Pisarev MA 2003 Comparative efficacy and side effects of the treatment of euthyroid goiter with L-thyroxine or triiodothyroacetic acid. J Clin Endocrinol Metab **88:**5287–5292.
114. Radetti G, Persani L, Molinaro G, Mannavola D, Cortelazzi D, Chatterjee VK, Beck-Peccoz P 1997 Clinical and hormonal outcome after two years of triiodothyroacetic acid treatment in a child with thyroid hormone resistance. Thyroid **7:**775–778.
115. Beck-Peccoz P, Piscitelli G, Cattaneo MG, Faglia G 1983 Successful treatment of hyperthyroidism due to nonneoplastic pituitary TSH hypersecretion with 3,5,3′-triiodothyroacetic acid (TRIAC). J Endocrinol Invest **6:**217–223.
116. Beck-Peccoz P, Sartorio A, De Medici C, Grugni G, Morabito F, Faglia G. 1988 Dissociated thyromimetic effects of 3,5,3′-triiodothyroacetic acid (TRIAC) at the pituitary and peripheral tissue levels. J Endocrinol Invest **11:**113–118.
117. Mechelany C, Schlumberger M, Challeton C, Comoy E, Parmentier C 1991 TRIAC (3,5,3′-triiodothyroacetic acid) has parallel effects at the pituitary and peripheral tissue levels in thyroid cancer patients treated with L-thyroxine. Clin Endocrinol **35:**123–128.
118. Robbins J 2000 Editorial: New ideas in thyroxine-binding globulin biology. J Clin Endocrinol Metab **85:**3994–3995.
119. Mayrargue-Kodja A, Bouchilloux S, Lissitzky S 1958 The action of a plant peroxidase on various hydroxyphenyl amino acids: Tyrosine, thyronine, and certain of their iodized or hydroxylated derivatives. Bull Soc Chim Biol (Paris) **40:**815–831.
120. Bjorksten F, Grasbeck R, Karlsson R, Lamberg BA 1963 Peroxidase-catalysed iodination and deiodination of iodotyrosines and iodothyronines. Ann Med Exp Biol Fenn **41:**156–165.
121. Jolin T, Morreale de Escobar G 1971 Deiodination of L-thyroxine and its activity on the oxidation in vitro of reduced nicotinamide-adenine dinucleotide by peroxidase plus hydrogen peroxide. Biochem J **125:**869–878.

122. Burger AG, Engler D, Buergi U, Weissel M, Steiger G, Ingbar SH, Rosin RE, Babior BM 1983 Ether link cleavage is the major pathway of iodothyronine metabolism in the phagocytosing human leukocyte and also occurs in vivo in the rat. J Clin Invest **71:**935–949.
123. Kubota K, Uchimura H, Mitsuhashi T, Chiu SC, Kuzuya N, Ito K, Nagataki S 1985 Peroxidatic degradation and ether link cleavage of thyroxine in a particulate fraction of human thyroid. Life Sci **36:**1033–1039.
124. Green WL 1978 Metabolism of thyroid hormones by rat thyroid tissue in vitro. Endocrinology **103:**826–837.
125. Nakamura M, Yamazaki I, Ohtaki S 1990 Iodothyronine-induced catalatic activity of thyroid peroxidase. J Biochem (Tokyo) **108:**804–810.
126. Nilsson M 2001 Iodide handling by the thyroid epithelial cell. Exp Clin Endocrinol Diabetes **109:**13–17.
127. Taurog A 2000 Hormone synthesis: thyroid iodine metabolism. In: Braverman LE and Utiger RD (eds) The Thyroid: A Fundamental and Clinical Text. Lippincott Williams and Wilkins, Philadelphia, pp. 61–85.
128. Wynn J, Gibbs R 1964 Thyroxine degradation. IV. The product from the beta-phenyl ring following incubation of thyroxine with microsomes. J Biol Chem **239:**527–529.
129. Klebanoff SJ 1967 Iodination of bacteria: A bactericidal mechanism. J Exp Med **126:**1063–1078.
130. Klebanoff SJ, Green WL 1973 Degradation of thyroid hormones by phagocytosing human leukocytes. J Clin Invest **52:**60–72.
131. Woeber KA, Doherty GF, Ingbar SH 1972 Stimulation by phagocytosis of the deiodination of L-thyroxine in human leukocytes. Science **176:**1039–1041.
132. Woeber KA, Ingbar SH 1973 Metabolism of L-thyroxine by phagocytosing human leukocytes. J Clin Invest **52:**1796–1803.
133. Wynn J, Gibbs R 1962 Thyroxine degradation. II. Products of thyroxine degradation by rat liver microsomes. J Biol Chem **237:**3499–3505.
134. Plaskett LG 1962 Catabolism of doubly labelled thyroxine in vivo. Nature **195:**961–963.
135. Roche J, Nunez J, Jacquemin C 1962 Nature of the deiodination products of thyroid hormones labelled simultaneously with tritium and radioactive iodine. Biochim Biophys Acta **64:**475–486.
136. Ushijima Y, Suwa K, Nakano M 1973 Degradation of thyroxine by microsomal particles from rat liver. II. Purification of Fe2+-dependent particles and some of their properties. Biochim Biophys Acta **320:**284–294.
137. Balsam A, Sexton F, Borges M, Ingbar SH 1983 Formation of diiodotyrosine from thyroxine. Ether-link cleavage, an alternate pathway of thyroxine metabolism. J Clin Invest **72:**1234–1245.
138. Faber J, Kirkegaard C, Jorgensen B, Kludt J 1989 The hidden, nonexchangeable pool of 3,5,3′-triiodothyronine and 3,3′,5′-triiodothyronine in man: Does it exist? Acta Endocrinol (Copenh) **120:**667–671.
139. Pittman CS, Buck MW, Chambers JB Jr 1972 Urinary metabolites of 14 C-labeled thyroxine in man. J Clin Invest **51:**1759–1766.
140. Chopra IJ, Boado RJ, Geffner DL, Solomon DH 1988 A radioimmunoassay for measurement of thyronine and its acetic acid analog in urine. J Clin Endocrinol Metab **67:**480–487.
141. Meinhold H, Beckert A, Wenzel KW 1981 Circulating diiodotyrosine: Studies of its serum concentration, source, and turnover using radioimmunoassay after immunoextraction. J Clin Endocrinol Metab **53:**1171–1178.
142. Faber J, Kirkegaard C, Meinhold H, Bregengaard C 1988 Metabolic clearance and production of diiodotyrosine in healthy man. Scand J Clin Lab Invest **48:**747–750.
143. Mohammed MN, Farmer M, Ramsden DB 1983 3,5-Diiodotyrosine excretion in human urine in individuals of differing thyroidal status. Biomed Mass Spectrom **10:**507–511.
144. Gregerman RI, Solomon N 1967 Acceleration of thyroxine and triiodothyronine turnover during bacterial pulmonary infections and fever: Implications for the functional state of the thyroid during stress and in senescence. J Clin Endocrinol Metab **27:**93–105.
145. Woeber KA 1971 Alterations in thyroid hormone economy during acute infection with *Diplococcus pneumoniae* in the rhesus monkey. J Clin Invest **50:**378–387.
146. DeRubertis FR, Woeber KA 1973 Accelerated cellular uptake and metabolism of L-thyroxine during acute Salmonella typhimurium sepsis. J Clin Invest **52:**78–87.
147. Adelberg HM, Siemsen JK, Jung RC, Nicoloff JT 1971 Scintigraphic detection of pulmonary bacterial infections with labeled thyroid hormones and pertechnetate. Radiology **99:**141–146.
148. Meinhold H, Schwander J, Gramm HJ 1988 Ether bond cleavage of thyroxine to diiodotyrosine (DIT). DIT in serum, a possible new marker of leukocyte activity in sepsis and severe infections. Acta Med Austriaca **15**(Suppl 1)**:**25–30.
149. Meinhold H, Gramm HJ, Meissner W, Zimmermann J, Schwander J, Dennhardt R, Voigt K 1991 Elevated serum diiodotyrosine (DIT) in severe infections and sepsis: DIT, a possible new marker of leukocyte activity. J Clin Endocrinol Metab **72:**945–953.
150. Schussler GC 2000 The thyroxine-binding proteins. Thyroid **10:**141–149.
151. Jirasakuldech B, Schussler GC, Yap MG, Drew H, Josephson A, Michl J 2000 A characteristic serpin cleavage product of thyroxine-binding globulin appears in sepsis sera. J Clin Endocrinol Metab **85:**3996–3999.
152. Janssen OE, Golcher HM, Grasberger H, Saller B, Mann K, Refetoff S 2002 Characterization of T(4)-binding globulin cleaved by human leukocyte elastase. J Clin Endocrinol Metab **87:**1217–1222.
153. Khan NS, Schussler GC, Gabbur N, Finkelstein A 2002 Cleavage of thyroxine-binding globulin during pregnancy [Abstract]. 84th Annual Meeting of the Endocrine Society, San Francisco, CA, p. 92.
154. Khan NS, Schussler GC, Holden JB, Finkelstein A 2002 Thyroxine-binding globulin cleavage in cord blood. J Clin Endocrinol Metab **87:**3321–3323.
155. Jirasakuldech B, Schussler GC, Yap MG, Zirkind R, Afandi B, Michl J 2001 Cleavage of thyroxine-binding globulin during cardiopulmonary bypass. Metabolism **50:**1113–1116.
156. Gramm HJ, Meinhold H, Voigt K, Dennhardt R 1989 Diiodotyrosine (DIT): A new marker of leukocyte phagocytic activity in sepsis and severe infections. Prog Clin Biol Res **308:**711–713.
157. Nicoloff JT, LoPresti JS 1991 Alternate pathways of thyroid hormone metabolism. In:Wu SY (ed) Thyroid Hormone Metabolism, Regulation and Clinical Implication. Blackwell Scientific Publication, Boston, pp. 55–64.
158. Faber J, Heaf J, Kirkegaard C, Lumholtz IB, Siersbaek-Nielsen K, Kolendorf K, Friis T 1983 Simultaneous turnover studies of thyroxine, 3,5,3′ and 3,3′,5′-triiodothyronine, 3,5-, 3,3′-, and 3′,5′-diiodothyronine, and

3′-monoiodothyronine in chronic renal failure. J Clin Endocrinol Metab **56:**211–217.
159. Kaptein EM, Feinstein EI, Nicoloff JT, Massry SG 1983 Serum reverse triiodothyronine and thyroxine kinetics in patients with chronic renal failure. J Clin Endocrinol Metab **57:**181–189.
160. Ramsden DB, Farmer M, Mohammed MN, McGonigle RS, Sheppard MC 1986 3,5-Diiodotyrosine and thyronine in the urine of patients with chronic renal disease. Clin Endocrinol (Oxf) **24:**491–495.

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2. Barae JomaaThyroid Toxicogenomics 159-189. [CrossRef]
3. Craig M. Butt, Heather M. Stapleton. 2013. Inhibition of Thyroid Hormone Sulfotransferase Activity by Brominated Flame Retardants and Halogenated Phenolics. *Chemical Research in Toxicology* **26**:11, 1692-1702. [CrossRef]
4. Béatrice B. Roques, Julien Leghait, Marlène Z. Lacroix, Frédéric Lasserre, Thierry Pineau, Catherine Viguié, Pascal G.P. Martin. 2013. The nuclear receptors pregnane X receptor and constitutive androstane receptor contribute to the impact of fipronil on hepatic gene expression linked to thyroid hormone metabolism. *Biochemical Pharmacology* **86**:7, 997-1039. [CrossRef]
5. P. A. Dawson. 2013. Role of sulphate in development. *Reproduction* **146**:3, R81-R89. [CrossRef]
6. AlberTinka J. Murk, Eddy Rijntjes, Bas J. Blaauboer, Rebecca Clewell, Kevin M. Crofton, Milou M.L. Dingemans, J. David Furlow, Robert Kavlock, Josef Köhrle, Robert Opitz, Theo Traas, Theo J. Visser, Menghang Xia, Arno C. Gutleb. 2013. Mechanism-based testing strategy using in vitro approaches for identification of thyroid hormone disrupting chemicals. *Toxicology in Vitro* **27**:4, 1320-1346. [CrossRef]
7. Margarita Gkotsina, Marina Michalaki, Irene Mamali, Georgios Markantes, George C. Sakellaropoulos, Fotios Kalfarentzos, Apostolos G. Vagenakis, Kostas B. Markou. 2013. Improved Levothyroxine Pharmacokinetics After Bariatric Surgery. *Thyroid* **23**:4, 414-419. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
8. Jacqueline Jonklaas, Kenneth D. Burman, Antonio C. Bianco for the American Thyroid Association Spring 2013 Program Committee. 2013. Treatment of Hypothyroidism: Possibilities on the Horizon. *Thyroid* **23**:4, ix-xi. [Citation] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
9. G. Morvan-Dubois, J.B. Fini, B.A. DemeneixIs Thyroid Hormone Signaling Relevant for Vertebrate Embryogenesis? **103**, 365-396. [CrossRef]
10. Daozhen Chen, Huixin Yu, Jiandong Bao, Wenqun Xue, Yuan Xing, Li Zhang, William L. Green, Delbert A. Fisher, Sing-Yung Wu. 2012. 3,3′-Diiodothyronine sulfate cross-reactive material (compound W) in human newborns. *Pediatric Research* **72**:5, 521-524. [CrossRef]
11. Sarah A. Hackenmueller, Thomas S. Scanlan. 2012. Identification and quantification of 3-iodothyronamine metabolites in mouse serum using liquid chromatography–tandem mass spectrometry. *Journal of Chromatography A* **1256**, 89-97. [CrossRef]
12. B. B. Roques, M. Z. Lacroix, S. Puel, V. Gayrard, N. Picard-Hagen, I. Jouanin, E. Perdu, P. G. Martin, C. Viguie. 2012. CYP450-Dependent Biotransformation of the Insecticide Fipronil into Fipronil Sulfone Can Mediate Fipronil-Induced Thyroid Disruption in Rats. *Toxicological Sciences* **127**:1, 29-41. [CrossRef]
13. Huayun Deng, Haibei Hu, Ye Fang. 2012. Multiple tyrosine metabolites are GPR35 agonists. *Scientific Reports* **2**. . [CrossRef]
14. Maarten Buitendijk, Valerie Anne Galton. 2012. Is the Kidney a Major Storage Site for Thyroxine as Thyroxine Glucuronide?. *Thyroid* **22**:2, 187-191. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
15. Carolin S. Hoefig, Kostja Renko, Susanne Piehl, Thomas S. Scanlan, Mariarita Bertoldi, Thomas Opladen, Georg Friedrich Hoffmann, Jeannette Klein, Oliver Blankenstein, Ulrich Schweizer, Josef Köhrle. 2012. Does the aromatic l-amino acid decarboxylase contribute to thyronamine biosynthesis?. *Molecular and Cellular Endocrinology* **349**:2, 195-201. [CrossRef]
16. Jae Won Yang, Seung Tae Han, Shin Han Song, Min Keun Kim, Jae Seok Kim, Seung Ok Choi, Byoung-Geun Han. 2012. Serum T3 Level Can Predict Cardiovascular Events and All-Cause Mortality Rates in CKD Patients with Proteinuria. *Renal Failure* 1-9. [CrossRef]
17. J.-B. Fini, A. Riu, L. Debrauwer, A. Hillenweck, S. L. MEVEL, S. Chevolleau, A. Boulahtouf, K. Palmier, P. Balaguer, J.-P. Cravedi, B. A. Demeneix, D. Zalko. 2011. Parallel biotransformation of Tetrabromobisphenol A in Xenopus laevis and mammals: Xenopus as a model for endocrine perturbation studies. *Toxicological Sciences* . [CrossRef]
18. Ami R. Zota, June-Soo Park, Yunzhu Wang, Myrto Petreas, R.Thomas Zoeller, Tracey J. Woodruff. 2011. Polybrominated Diphenyl Ethers, Hydroxylated Polybrominated Diphenyl Ethers, and Measures of Thyroid Function in Second Trimester Pregnant Women in California. *Environmental Science & Technology* 110819141408066. [CrossRef]
19. Lester Vanmiddlesworth, N. Rue Vanmiddlesworth, Robert S. Egerman, Andrew J. Bush, Risa D. Ramsey, Lucinda P. Delmar, Eugene C. Ho, Sing-yung Wu. 2011. Thyroid Function and 3,3'-Diiodothyronine Sulfate Cross-Reactive Substance (Compound W) in Maternal Hyperthyroidism with Antithyroid Treatment. *Endocrine Practice* **17**:2, 170-176. [CrossRef]

20. Domenico Salvatore, Terry F. Davies, Martin-Jean Schlumberger, Ian D. Hay, P. Reed LarsenThyroid Physiology and Diagnostic Evaluation of Patients with Thyroid Disorders 327-361. [CrossRef]
21. Karen C. dos Santos, Maria Fátima G. F. da Silva, João B. Fernandes, Paulo C. Vieira, Igor Polikarpov, Valtencir Zucolotto, Moacir R. Forim. 2011. Development and validation of a fast RP-HPLC method to determine the analogue of the thyroid hormone, 3,5,3′-triiodothyroacetic acid (TRIAC), in polymeric nanoparticles. *Analytical Methods* . [CrossRef]
22. Patricia Villalobos, Aurea Orozco, Carlos Valverde-R. 2010. Molecular cloning and characterization of a type 3 iodothyronine deiodinase in the pine snake Pituophis deppei. *General and Comparative Endocrinology* **169**:2, 167-173. [CrossRef]
23. M. Paris, A. Hillenweck, S. Bertrand, G. Delous, H. Escriva, D. Zalko, J.-P. Cravedi, V. Laudet. 2010. Active Metabolism of Thyroid Hormone During Metamorphosis of Amphioxus. *Integrative and Comparative Biology* **50**:1, 63-74. [CrossRef]
24. Farhana Babli Rahman, Kiyoshi Yamauchi. 2010. Characterization of iodothyronine sulfotransferase activity in the cytosol of Rana catesbeiana tadpole tissues. *General and Comparative Endocrinology* **166**:2, 396-403. [CrossRef]
25. Riccardo Zucchi, Sandra Ghelardoni, Grazia Chiellini. 2010. Cardiac effects of thyronamines. *Heart Failure Reviews* **15**:2, 171-176. [CrossRef]
26. W. Edward Visser, Wing S. Wong, Alies A.A. van Mullem, Edith C.H. Friesema, Joachim Geyer, Theo J. Visser. 2010. Study of the transport of thyroid hormone by transporters of the SLC10 family. *Molecular and Cellular Endocrinology* **315**:1-2, 138-145. [CrossRef]
27. F. Illouz, S. Laboureau-Soares, S. Dubois, V. Rohmer, P. Rodien. 2009. Tyrosine kinase inhibitors and modifications of thyroid function tests: a review. *European Journal of Endocrinology* **160**:3, 331-336. [CrossRef]
28. Nicholas J. Bernier, Gert Flik, Peter H.M. KlarenChapter 6 Regulation And Contribution Of The Corticotropic, Melanotropic And Thyrotropic Axes To The Stress Response In Fishes **28**, 235-311. [CrossRef]
29. Mathilde Paris, Frédéric Brunet, Gabriel V. Markov, Michael Schubert, Vincent Laudet. 2008. The amphioxus genome enlightens the evolution of the thyroid hormone signaling pathway. *Development Genes and Evolution* **218**:11-12, 667-680. [CrossRef]
30. D FISHER. 2008. Thyroid System Immaturities in Very Low Birth Weight Premature Infants. *Seminars in Perinatology* **32**:6, 387-397. [CrossRef]
31. Lutz Schomburg, Josef Köhrle. 2008. On the importance of selenium and iodine metabolism for thyroid hormone biosynthesis and human health. *Molecular Nutrition & Food Research* **52**:11, 1235-1246. [CrossRef]
32. Mathilde Paris, Vincent Laudet. 2008. The history of a developmental stage: Metamorphosis in chordates. *genesis* **46**:11, 657-672. [CrossRef]
33. Susanne Piehl, Thomas Heberer, Gabor Balizs, Thomas S. Scanlan, Josef Köhrle. 2008. Development of a validated liquid chromatography/tandem mass spectrometry method for the distinction of thyronine and thyronamine constitutional isomers and for the identification of new deiodinase substrates. *Rapid Communications in Mass Spectrometry* **22**:20, 3286-3296. [CrossRef]
34. Anita Boelen, Jeffrey Boorsma, Joan Kwakkel, Catharina W. Wieland, Rosemarijn Renckens, Theo J. Visser, Eric Fliers, Wilmar M. Wiersinga. 2008. Type 3 Deiodinase Is Highly Expressed in Infiltrating Neutrophilic Granulocytes in Response to Acute Bacterial Infection. *Thyroid* **18**:10, 1095-1103. [Abstract] [Full Text PDF] [Full Text PDF with Links]
35. Shaker A. Mousa, Joel J. Bergh, Emie Dier, Abdelhadi Rebbaa, Laura J. O'Connor, Murat Yalcin, Ahmad Aljada, Evgeny Dyskin, Faith B. Davis, Hung-Yung Lin, Paul J. Davis. 2008. Tetraiodothyroacetic acid, a small molecule integrin ligand, blocks angiogenesis induced by vascular endothelial growth factor and basic fibroblast growth factor. *Angiogenesis* **11**:2, 183-190. [CrossRef]
36. SING-YUNG WU, DANIEL H. POLK, WEN-SHENG HUANG, EUGENE HO, JAFFER M. KATTAN, DELBERT A. FISHER. 2008. 3′-Monoiodothyronine Sulfate and Triac Sulfate Are Thyroid Hormone Metabolites in Developing Sheep. *Pediatric Research* **63**:2, 149-153. [CrossRef]
37. L. Todini. 2007. Thyroid hormones in small ruminants: effects of endogenous, environmental and nutritional factors. *animal* **1**:07, 997. [CrossRef]
38. Andrea L. Yoder Graber, Jacqueline Ramírez, Federico Innocenti, Mark J. Ratain. 2007. UGT1A1*28 genotype affects the in-vitro glucuronidation of thyroxine in human livers. *Pharmacogenetics and Genomics* **17**:8, 619-627. [CrossRef]
39. P KLAREN, J GUZMAN, S REUTELINGSPERGER, J MANCERA, G FLIK. 2007. Low salinity acclimation and thyroid hormone metabolizing enzymes in gilthead seabream (Sparus auratus). *General and Comparative Endocrinology* **152**:2-3, 215-222. [CrossRef]
40. Josef Köhrle. 2007. Thyroid hormone transporters in health and disease: advances in thyroid hormone deiodination. *Best Practice & Research Clinical Endocrinology & Metabolism* **21**:2, 173-191. [CrossRef]

41. SING-YUNG WU, WEN-SHENG HUANG, EUGENE HO, ELIZABETH S.C. WU, DELBERT A. FISHER. 2007. Compound W, a 3,3???-Diiodothyronine Sulfate Cross-Reactive Substance in Serum from Pregnant Women???A Potential Marker for Fetal Thyroid Function. *Pediatric Research* **61**:3, 307-312. [CrossRef]
42. Sabine M. van der Heide, Brian J.L.J. Joosten, Bieuwke S. Dragt, Maria E. Everts, Peter H.M. Klaren. 2007. A physiological role for glucuronidated thyroid hormones: Preferential uptake by H9c2(2-1) myotubes. *Molecular and Cellular Endocrinology* **264**:1-2, 109-117. [CrossRef]
43. Sumit Bhattacharyya, Joanne K. Tobacman. 2007. Steroid sulfatase, arylsulfatases A and B, galactose-6-sulfatase, and iduronate sulfatase in mammary cells and effects of sulfated and non-sulfated estrogens on sulfatase activity. *The Journal of Steroid Biochemistry and Molecular Biology* **103**:1, 20-34. [CrossRef]
44. R Zucchi, G Chiellini, T S Scanlan, D K Grandy. 2006. Trace amine-associated receptors and their ligands. *British Journal of Pharmacology* **149**:8, 967-978. [CrossRef]
45. K. Yamauchi,, A. Ishihara,. 2006. Thyroid System-Disrupting Chemicals: Interference with Thyroid Hormone Binding to Plasma Proteins and the Cellular Thyroid Hormone Signaling Pathway. *Reviews on Environmental Health* **21**:4, 229-252. [CrossRef]
46. A PINGITORE, G IERVASI, A BARISON, C PRONTERA, L PRATALI, M EMDIN, D GIANNESSI, D NEGLIA. 2006. Early Activation of an Altered Thyroid Hormone Profile in Asymptomatic or Mildly Symptomatic Idiopathic Left Ventricular Dysfunction. *Journal of Cardiac Failure* **12**:7, 520-526. [CrossRef]
47. E. A. GRAVES, H. C. SCHOTT II, J. V. MARTENIUK, K. R. REFSAL, R. F. NACHREINER. 2006. Thyroid hormone responses to endurance exercise. *Equine Veterinary Journal* **38**:S36, 32-36. [CrossRef]
48. SING-YUNG WU, DANIEL H. POLK, WEN-SHENG HUANG, WILLIAM L. GREEN, BECKY THAI, DELBERT A. FISHER. 2006. Fetal-to-Maternal Transfer of Thyroid Hormone Metabolites in Late Gestation in Sheep. *Pediatric Research* **59**:1, 102-106. [CrossRef]
49. DELBERT A. FISHER, ANNETTE GRUETERSThyroid Disorders in Childhood and Adolescence 227-253. [CrossRef]
50. DELBERT A. FISHER, ANNETTE GRUETERSDisorders of the Thyroid in the Newborn and Infant 198-226. [CrossRef]