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The relationship between ingested thyroid hormones, thyroid homeostasis and iodine metabolism in humans and teleost fish

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A B S T R A C T

Oral L-thyroxine (T4) therapy is used to treat human hypothyroidism but T4 fed to teleost fish does not raise plasma thyroid hormone (TH) levels nor induce growth, even though oral 3,5,3′-triiodo-L-thyronine (T3) is effective. This suggests a major difference in TH metabolism between teleosts and humans, often used as a starting thyroid model for lower vertebrates. To gain further insight on the proximate (mechanistic) and ultimate (survival value) factors underlying this difference, the several steps in TH homeostasis from intestinal TH uptake to hypothalamic-hypophyseal regulation were compared between humans and teleosts, and following dietary TH challenges. A major proximate factor limiting trout T4 uptake is a potent constitutive thiol-inhibited intestinal complete T4 deiodination that is ineffective for T3. At the hepatic level, T4 deiodination, conjugation and extensive biliary excretion with negligible T4 enterohepatic recycling can further block teleost T4 uptake to plasma. Such protection of plasma T4 from dietary T4 may be particularly critical for piscivorous fish consuming thyroid tissue, rich in T4 but not T3. It would prevent disruption by unregulated ingested T4 of the characteristic acute and transient changes in teleost plasma T4 due to diel rhythms, food intake and stress-related factors. These marked natural short-term fluctuations in teleost plasma T4 levels are enabled by the relatively small and rapidly-cleared plasma T4 pool, stemming largely from properties of the plasma T4-binding proteins. Humans, however, due mainly to plasma T4-binding globulin, have a relatively massive circulating pool of T4 and an extremely well-buffered free T4 level, consistent with the major TH role in regulating basal metabolic rate. Furthermore, this large well-buffered and slowly-cleared plasma T4 pool, in conjuction with enterohepatic recycling and relaxation of hypothalamic-hypophyseal negative feedback, allows humans to temporarily 'store' ingested T4 in plasma, thereby sparing endogenous TH secretion and conserving thyroidal iodine reserves. Indeed, iodine conservation is likely the key ultimate factor determining the divergent evolution of the human and teleost systems. For humans, ingested iodine in the form of I^-, or TH and their derivatives, is the sole iodine source and may be limiting in many environments. However, most freshwater teleosts, in addition to their ability to assimilate dietary I^-, can derive sufficient I^- from their copious gill irrigation, with no selective advantage in absorbing dietary T4 which would disrupt their natural acute and transient changes in plasma T4. Thus T4 may act also as a vitamin (vitamone) in humans but not in teleosts; in contrast, T3, naturally ingested at much lower levels, may act as a vitamone in both humans and teleosts.

1. Introduction

Thyroid homeostasis is defined in the present context as maintaining plasma free T4 (L-thyroxine = 3,5,3′,5′-tetraiodo-L-thyronine) and free T3 (3,5,3′-triiodo-L-thyronine) levels appropriate for a given physiological state. Early studies emphasized the central role of the hypothalamo-hypophyseal-thyroidal axis and secretion of thyroid stimulating hormone (TSH) in T4 regulation. Later studies demonstrated the importance of peripheral thyroid hormone (TH) deiodination in regulating both plasma and tissue levels of T4 and T3, its more bioactive derivative with a greater affinity for nuclear receptors. It is now recognized that both central and peripheral controls are complementary in TH homeostasis (McNabb, 1992). Implicit in most studies is the fundamental but rarely-stated assumption that the thyroid is the sole source of TH.

However, the thyroid may not be the sole source of TH, which also

Abbreviations: T4, L-thyroxine; T3, 3,5,3′-triiodo-L-thyronine; rT3, 3,3′,5′-triiodo-L-thyronine = reverse T3; TSH, thyroid stimulating hormone; TH, thyroid hormones; DIO1, type 1 deiodinase; DIO2, type 2 deiodinase; DIO3, type 3 deiodinase; MCR, metabolic clearance rate; DR, degradation rate; TBG, thyroxine binding globulin; TBA, thyroxine-binding albumin; TBPA, thyroxine-binding prealbumin = transthyretin = TTR; GIT, gastrointestinal tract; DTT, dithiothreitrol

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traverse the food chain and can have vitamin-like (vitamone) properties (Eales, 1997; Heyland and Moroz, 2005; Miller and Heyland, 2010). This concept was first established for certain invertebrates (see reviews Davey (2007) and Flatt et al. (2006)) but also applies to vertebrates. Any vertebrate eating vertebrate tissues will ingest *some* TH (Eales, 1997; Villalobos et al., 2010). Viscera may contain significant TH but the main source will be the thyroid with its considerable store of iodothyronines, mainly as T4 in humans (Dunn et al., 2000) and solely as T4 in teleost fish studied to date (Chan and Eales, 1975; Grau et al., 1986; Inui et al., 1989; Kuhn, 1993; Milne and Leatherland, 1980; Swanson et al., 1988). Thus ingestion of TH, and particularly T4, will be routine in those vertebrates (eg piscivorous fish) consuming the whole carcass of their vertebrate prey. Even humans are not exempt. The effect of ingested TH was demonstrated dramatically by the potentially lethal consequence of a prolonged diet of thyroid-contaminated hamburger (Hedberg et al., 1987). Thus dietary TH can contribute significantly to the human plasma TH pool.

The effective TH transfer from gastrointestinal tract (GIT) to systemic circulation has been exploited clinically and it is standard practice to treat certain hypothyroid conditions by prescribing T4 or T3 pills (Brent et al., 2000; Singer et al., 1995). Consequently, an unexpected observation for teleost fish studied to date is the inability of orally-administered T4, as opposed to orally-administered T3, to enhance growth (Higgs et al., 1979; Higgs et al., 1982). It was found subsequently that while orally-administered T3 raised plasma T3 levels, orally-administered T4, at comparable doses, did not raise systemic plasma levels of T4 or T3. This was observed in at least three taxonomically diverse teleosts – rainbow trout, *Oncorhynchus mykiss* (Kohel, 2004; MacLatchy and Eales, 1993; Sweeting and Eales, 1992), red drum, *Sciaenops ocellatus* (MacKenzie et al., 1993; Moon et al., 1994) and Nile tilapia, *Oreochromis niloticus* (Van der Geyten et al., 2005). However, if T4 is administered to rainbow trout by injection (Fok and Eales, 1984) or to Atlantic salmon, *Salmo salar,* or rainbow trout by addition to the ambient water (Morin et al., 1995; Plate et al., 2002) then plasma T4 increases predictably. Thus, at the T4 or T3 doses used, only orally-administered T4 did not raise salmonid plasma TH levels. Clearly, aspects of TH metabolism differ between humans and at least some fish. What are these differences and how might they relate to thyroid homeostasis in humans and fish following sudden unpredictable and potentially disrupting influxes of dietary TH?

Thyroid homeostasis following TH ingestion could involve regulation at the following levels in the thyroid hierarchy:

- Uptake of TH from the gastrointestinal tract (GIT)
- Deiodination of TH by the GIT
- Deiodination of TH by the liver
- Conjugation and excretion of TH by the enterohepatic system
- Plasma TH kinetics and buffering by plasma proteins
- Exchanges of TH with tissues
- Thyroid secretion of TH through the brain-pituitary axis

Humans and teleosts have been compared at each of the above levels and with the following interrelated objectives:

- To highlight differences between the fish thyroid system and that of humans, often used as a starting model for studies on lower vertebrates
- To determine how this comparison might explain the species difference in the ability of ingested TH to raise plasma TH levels
- To speculate on the various factors that may have led to divergent evolution of the human and fish systems
- To assess the impact of environmental iodine availability on the above

2. Uptake of TH from the gastrointestinal tract

The mechanism of intestinal TH uptake does not appear to have been studied in humans. T4 and T3 were absorbed equally well from rat intestinal loops and since both T4 and T3 are lipophilic their uptake was considered passive (DiStefano et al., 1992). Later studies on other tissues have established transport systems for both T4 and T3 (Henneman et al., 2001; Visser, 2013). The general consensus is that transporters (MCT8 and MCT10) are responsible for most TH transmembrane movement (Visser, 2016). TH transport systems exist for trout hepatocytes (Riley and Eales, 1994), and erythrocytes (McLeese and Eales, 1996) with properties differing between T4 and T3, but the transporters were not studied. Transporters MCT8, MCT10 and OATP1C1 have been established for developing zebrafish, *Brachydanio rerio* (Arjona et al., 2011; Heuijlen et al., 2013) but GIT tissue was not studied. Indeed GIT TH transport has received little attention for any vertebrate. This is surprising considering the GIT is a large organ with a vast surface area and human oral TH therapy for hypothyroidism depends on efficient TH uptake from its lumen. Furthermore, from an evolutionary standpoint, the GIT is the primitive recipient of TH discharged from the endostyle of the larval lamprey lacking internally-secreting thyroid follicles (Wright and Youson, 1976). In these instances is diffusion the only mechanism for TH uptake or do TH have GIT transporters like other amino acids (Broer, 2008)?

Early studies on various mammals showed significant GIT uptake of T4 to the systemic circulation (Albert et al., 1952; Clayton et al., 1950; Cottle and Veress, 1965; Mixner and Lennon, 1960; Myant and Pochin, 1950; Yatvin et al., 1965). In humans the bioavailabilities of ingested T3 and T4 from the lumen of the GIT were estimated as 95.8% and 49.3% respectively (DiStefano and Mak, 1979). For T4 ingested by fasted humans the time of maximum concentration is approximately 2 h and the bioavailability is 60–80% (Hays and Nielsen, 1994; Ianiro et al., 2014).

Experimentally-administered T3 is absorbed from the teleost GIT to the systemic circulation (Kohel, 2004; MacLatchy and Eales, 1993; Moon et al., 1994; Van der Geyten et al., 2005) and stimulates growth (Higgs et al., 1982). However, ^{125}I-T4 introduced by injection into a doubly-ligated gut loop or by an anal catheter into the small intestine of fasted brook trout, *Salvelinus fontinalis* (Eales and Sinclair, 1974) or channel catfish, *Ictalurus punctatus* (Collicutt and Eales, 1974) suggested limited uptake to the systemic circulation. Furthermore, the situation could be more complex when T4 is administered with food as T4 can bind to luminal ingesta/feces (Chung and van Middlesworth, 1967; Ruegamer et al., 1967) and could be metabolized and/or bound by gut bacteria (DiStefano et al., 1993a; Nguyen et al., 1993a,b; Rutgers et al., 1989). Thus differential binding of T4 and T3 to luminal contents or differential bacterial degradation of T4 and T3 in the intestine could also contribute to a less effective T4 absorption (Hazenburg et al., 1988). There are few data on these topics for teleosts (Benedict et al., 2007), although some species may have a prolific bacterial flora (Al-Harbi and Uddin, 2004; Spanggaard et al., 2000; Van Kessel et al., 2011). Diet could also influence bioavailability of orally-administered T4. However, negligible T4 uptake from the GIT to the systemic circulation occurred in three taxonomically diverse teleosts fed a variety of diets (MacLatchy and Eales, 1993; Moon et al., 1994; Van der Geyten et al., 2005) and therefore would not appear to be diet dependent. In summary, in contrast to T3, T4 ingested with or without food appears unlikely to gain ready access to the systemic circulation of teleosts studied to date.

Greater absorption of T3 than T4 by the GIT was theorized for Nile tilapia (Van der Geyten et al., 2005). This appeared consistent with a comparison of ^{125}I-T4 and ^{125}I-T3 uptakes from the GIT of acutely-fasted rainbow trout (Whitaker and Eales, 1993). But up to 24 h after ^{125}I-T4 introduction into the trout intestinal lumen most plasma radioactivity was inorganic $^{125}I^-$ and most luminal radioactivity was also $^{125}I^-$. Thus the less effective luminal absorption of ^{125}I-T4, as

opposed to ^{125}I-T3, could be due to preferential ^{125}I-T4 deiodination by the GIT and with uptake of the released $^{125}I^-$ to plasma.

In conclusion, although the mechanism is not yet understood, both T4 and T3 are efficiently absorbed from the human GIT. In teleost fish T3 is absorbed but there is apparent limited T4 absorption. Several factors could underlie this difference. However, at least for trout, T4 might be degraded to a greater extent than T3 by GIT deiodination.

3. Deiodination of TH by the gastrointestinal tract

Deiodination in vertebates is accomplished primarily by three classes of deiodinases (Darras and Van Herck, 2012; Orozco and Valverde, 2005; Visser, 1996). Type 1 (DIO1) has a high-K_m and removes iodines from both inner and outer rings and may serve mainly to degrade TH and salvage iodine (St Germain et al., 2009); Type 2 (DIO2) has a low-K_m and removes one outer-ring iodine converting T4 to T3 and is an activating step; Type 3 (DIO3) also has a low-K_m but removes a single inner-ring iodine converting either T4 to reverse T3 (rT3 = 3,3′,5′-triiodo-L-thyronine) or T3 to a T2 (3′,3, diiodo-L-thyronine) as inactivating steps. The deiodinases usually require a thiol cofactor (e.g. glutathione or dithiothreitrol (DTT)). DIO2 and/or DIO3 activities have been reported for the GIT of mammals (Bates et al., 1999), birds (Survana et al., 1993), reptiles (Shepherdley et al., 2002a,b) amphibia (Galton, 1988) and several fish and cyclostomes. These include DIO2-like activity in blue tilapia, *Oreochromis aureus* (Mol et al., 1997); sea lamprey, *Petromyzon marinus* (Eales et al., 1997; Eales et al., 2000; Stilborn et al., 2013); Atlantic cod, *Gadus morhua* (Cyr et al., 1998); American plaice, *Hippoglossoides platessoides* (Adams et al., 2000); Atlantic hagfish, *Myxine glutinosa* (McLeese et al., 2000); red drum (Moore-Vanputte et al., 2001) and lake sturgeon, *Acipenser fulvescens* (Plohman et al., 2002) and DIO3-like activity in American plaice (Adams et al., 2000) and lake sturgeon (Plohman et al., 2002). In contrast, GIT DIO1 has received less attention.

GIT deiodination was studied in rainbow trout held at 12C and fed 1% of body weight/day once each day for 7 days with chow containing 12 ppm T3 or T4 (Kohel, 2004). In agreement with previous studies (MacLatchy and Eales, 1993; Sweeting and Eales, 1992) plasma T3 increased due to T3 feeding but there were no changes in plasma T3 or T4 due to T4 feeding. T3 feeding also induced changes in intestinal DTT-dependent T4 or T3 deiodination, indicating some adaptation of GIT DIO2 and DIO3 to the T3 challenge. In contrast there were small and inconsistent changes for these intestinal deiodinases due to the T4 challenge. However, regardless of any T4 or T3 challenge, high T4 deiodinating activity, but only in the *absence* of DTT, occurred in all three intestinal regions (pyloric ceca, middle intestine and distal intestine). T3 deiodination in the *absence* of DTT was negligible, presumably due to inner-ring iodine removal as the first step in T4 deiodination. This DTT-inhibited deiodination, effective for T4 but not for T3, appeared complete as no potential intermediate ^{125}I-containing products (T_3, reverse T_3, 3,3′-diiodothyronine, 3′,5′-diiodothyronine or 3′-monoiodothyronine) other than $^{125}I^-$ and a small quantity of protein-bound ^{125}I were detected by HPLC. This agrees with an earlier study (Law and Eales, 1973) in which ^{125}I-T_4 deiodination in the absence of DTT occurred in intestine and stomach homogenates of brook trout, *Salvelinus fontinalis,* and where $^{125}I^-$ was the only labelled end-product. The detailed properties of this intestinal DTT-inhibited T4 deiodination were not explored but it likely represents DIO1 activity. In support of this, complete DTT inhibition of DIO1 activity has been shown for liver and kidney of the gilthead bream, *Sparus auratus* and common carp, *Cyprinus carpio,* with properties that varied depending on tissue type (Klaren et al., 2005; Klaren et al., 2012). Also, DIO1 activity has low optimal thiol requirements in other fish tissues (Finnson et al., 1999; Orozco et al., 1997).

Most tissues have TH receptors and the GIT itself may be a target tissue for TH. If so, the trout GIT constitutive T4-specific complete deiodination could have added relevance as: a) it destroys T4, the precursor of bioactive T3, thereby preventing local excess T3 formation; b) only T4, and not T3, can act as a substrate and so it will not disrupt local T3 metabolism by degrading T3; c) due to its capacity for 'complete' deiodination it will not generate T3 and raise GIT T3 levels; d) since T4 in sufficiently high concentrations also binds to T3 receptors, it is eliminating T4 from this potential interference with T3 action; e) should plasma-borne T4 be a ligand for its own GIT T4-specific receptors it could protect these receptors from an otherwise unregulated luminal T4 source.

In conclusion, a potent, selective and apparently complete intestinal DTT-inhibited T4 deiodination, likely a form of DIO1, may act as a constitutive ready-to-act "gate keeper" blocking T4 uptake from the trout GIT to the hepatic portal system but without effect on T3 uptake. This T4 deiodination releases iodide of potential use for regulated endogenous TH synthesis. Although intestinal DIO3 was induced by a dietary T3 challenge it did not prevent a rise in plasma T3 at the experimental T3 dose employed.

4. Deiodination of TH by the liver

Some regulation of plasma T4 levels could occur in any tissue with deiodinating activity. However, in its strategic location the liver has the greatest potential to regulate delivery of ingested T4 from hepatic-portal to systemic blood by adjusting its deiodinating activity. No evidence appears to exist for this in humans and indeed is unexpected under normal circumstances, since T4 is transferred so effectively from the GIT to the systemic circulation. However, the situation may differ for teleosts. Hepatic deiodination responses to dietary T4 or T3 challenges have been studied for both rainbow trout and tilapia.

Rainbow trout acclimated at 12C were fed for 3 or 7 days with TH-supplemented chow (1% of body weight containing 12 ppm T4; once each day) (Kohel, 2004; MacLatchy and Eales, 1993; Sweeting and Eales, 1992). The T3 challenge raised plasma T3 levels and induced autoregulatory hepatic responses by depressing hepatic T4 to T3 conversion and increasing T4 to rT3 conversion and T3 to 3,3′-T2 conversion. In contrast, the T4 challenge did not change plasma T4 levels and was without effect on any hepatic deiodination pathway. However, if T4 is administered to various teleosts by addition to the ambient water then the anticipated compensating changes in hepatic T4 deiodination do occur (Garcia-G et al., 2004; Morin et al., 1995; Plate et al., 2002). Thus it appears that at the dosage used negligible ingested T4 was reaching the trout liver.

Nile tilapia, *Oreochromis nilotica* acclimated at 27C were fed to satiation four times a day for 3 or 14 days with food containing up to 48 ppm T4 or T3 (Mol et al., 1999; Van der Geyten et al., 2005). In most respects the results resembled those for the trout. T3 feeding increased systemic plasma T3 but T4 feeding did not increase systemic plasma T4. However, T4 feeding did increase both the hepatic T4 level and hepatic DIO1 activity. This shows that some T4 had been taken up by the hepatic portal vessels and induced compensatory hepatic deiodination.

This difference in response between trout and tilapia could be due to the much higher T4 burden fed to tilapia but could also reflect a difference due to species and/or natural diet. The trout is a piscivore/carnivore but tilapia is a herbivore/omnivore. Tilapia may not have the potent GIT T4 deiodination of trout and rely more on hepatic deiodination for T4 homeostasis. However, the end result is the same; both species are effectively protected from a dietary T4 challenge but less so from a T3 challenge.

In conclusion, hepatic deiodination in humans is likely not routinely prominent in degrading dietary T4. However, in teleosts it has the potential, and for tilapia the demonstrated capacity, to degrade a dietary T4 excess and contribute to T4 homeostasis following a dietary T4 challenge. Although hepatic DIO3 was induced in trout and tilapia by a dietary T3 challenge it did not prevent a rise in plasma T3 at the experimental T3 doses employed.

5. Conjugation and excretion of TH by the enterohepatic system

In addition to the deiodinases the liver has two other TH-metabolizing enzyme systems in the phenol sulfotransferases and uridine-diphospho-glucuronyl transferases. Both conjugate TH at their phenolic group forming more water-soluble sulfate or glucuronide conjugates, inactive as receptor ligands. Mammals have several sulfotransferases with an efficiency inversely related to the number of iodothyronine iodines (Sekura et al., 1981; Visser et al., 1990). Sulfate conjugates are preferred substrates for DIO1, resulting in negligible loss of sulfated TH in bile or urine (Bollman et al., 1965; Visser, 1994). Thus the iodine stripped from sulfate-TH conjugates is conserved.

Glucuronide conjugates in mammals are mainly excreted in bile via the gall bladder to the intestine where they may be hydrolysed by intestinal bacteria and the liberated TH reabsorbed to complete an enterohepatic cycle (Briggs et al., 1953; De Herder et al., 1986). Thus glucuronidation temporarily removes TH from "active service" by shunting them in inactive and more water-soluble forms to the bile and gall bladder (DiStefano, 1988; DiStefano et al., 1988). However, this classic model may be an oversimplification. Further studies in the rat involving injection or infusion of labelled TH followed by detailed kinetic and compartmental analyses of their subsequent distribution, exchanges and loss established the GIT as a key component in TH metabolism (DiStefano et al., 1993a,b; Hays, 1968; Nguyen et al., 1993b). It not only receives TH into its lumen via biliary discharge but also receives an ongoing non-luminal supply of TH directly to its tissues via the mesenteric arteries. This direct non-luminal source is considerable. Consequently, the GIT acts as a major dynamic reservoir of TH that can exchange not only with the food/fecal matter in the GIT lumen but also with the systemic blood supply and acts as a complex buffer and conserver in regulating plasma TH levels.

Glucuronide and sulfate conjugates of T4, T3 and rT3 are formed in all fish studied to date (Collicutt and Eales, 1974; Eales, 1970; Eales et al., 1983; Geven et al., 2007; Klaren et al., 2007; Leloup and Fontaine, 1960; Osborn and Simpson, 1969). The proportions of TH and their conjugates in bile vary with species but in general glucuronides are more prevalent than sulfates or the parent TH (Sinclair and Eales, 1972). The hepatic intracellular sites, kinetics and properties of the teleost glucuronide and sulfate conjugating systems generally resemble those of mammals (Finnson and Eales, 1996; Finnson and Eales, 1997; Finnson and Eales, 1998; Schnitzler et al., 2012). However, in marked contrast to mammals, sulfated TH in rainbow trout do not undergo preferential DIO1 deiodination with iodide recovery (Finnson et al., 1999). This explains TH-sulfate presence in teleost bile and also suggests that iodine conservation may not be as high a priority in fish (trout) as it is in mammals.

As in mammals, the teleost enterohepatic system is prominent in TH metabolism. Following intracardiac or intraperitoneal injection of ^{125}I-labelled TH, and depending on species, the maximum percentage of the administered dose occurring in the combined enterohepatic tissues (gall bladder + intestine) ranged from approximately 10–65%. In rainbow trout rT3 was particularly prone to enterohepatic uptake (~65%), followed by T4 (~40%) and T3 (~35%) (Eales, 1979; Eales et al., 1983). In brook trout from 40 to 50% of the injected ^{125}I-T4 dose was captured by the gall bladder and intestine (Eales, 1970; Higgs and Eales, 1976; Higgs and Eales, 1978; Higgs and Eales, 1979). In chronically-fasted channel catfish an average of 60% of an injected ^{125}I-T4 dose was recovered from the gall bladder, ligated to prevent discharge via the bile duct (Collicutt and Eales, 1974). However, appreciably lower enterohepatic uptakes of injected ^{125}I-T4 occurred in non-predatory goldfish, *Carassius auratus* (~10%) and sucker, *Catastomus commersoni* (~20%) (Eales, 1972).

Following ^{125}I-T4 injection into acutely-fasted brook trout (Higgs and Eales, 1978) or rainbow trout (Eales, 1979) there was a negligible loss over several days of the ^{125}I label from the enterohepatic organs. However, feeding caused a rapid enterohepatic ^{125}I 'washout' and plasma clearance, showing that the trout enterohepatic system represents a major route for *elimination,* rather than *recycling*, of TH. This is supported by negligible reabsorption to plasma of biliary excreted ^{125}I-T4 from the GIT of acutely-fasted brook trout after they were fed (Eales and Sinclair, 1974). Thus available data indicate that luminal T4 uptake and hence T4 recycling occur to a negligible degree in teleosts studied to date. This could be due in part to the previously described DTT-inhibited intestinal T4 deiodination. There is less information on the fate of biliary-excreted T3, but significant uptake of unconjugated T3 is predicted from the studies with orally-administered T3.

TH-glucuronide and TH-sulfate excretions in teleosts are not confined to bile. In Mozambique tilapia, *Oreochromis mossambicus,* appreciable TH-glucuronides occur in plasma (DiStefano et al., 1998; Geven et al., 2007) and alternative TH-conjugate excretory routes exist. Both T4 and T3 glucuronide and sulfate conjugates are lost in rainbow trout urine (Parry et al., 1994) and branchial metabolism and loss of TH conjugates may occur in gilthead sea bream (*Sparus auratus*) (Klaren et al., 2007). Significant loss of TH conjugates by extra-biliary routes further supports the view that recovery of enterohepatic-excreted TH (or iodine) is not as high a priority in teleosts as it is in humans.

In conclusion, teleosts resemble mammals in having potent hepatic T4 glucuronide and sulfate conjugating activities and in processing a high proportion of total body T4 through the enterohepatic system, although this traffic may be greater for predatory than omnivorous/herbivorous fish. However, trout differ from mammals in i) not deiodinating T4-sulfate conjugates, which are excreted in bile without hepatic reclamation of iodide, and ii) their negligible enterohepatic recycling of biliary-excreted T4 and its conjugates, which are excreted with feces. Thus for trout, the bile T4 pathway appears exclusively excretory and would contribute to T4 homeostasis following a dietary T4 challenge. In contrast, some biliary-excreted T3 is reabsorbed. Furthermore, unlike humans, the considerable loss by teleosts of conjugated and unconjugated TH by enterohepatic or other routes suggests that iodine conservation is not a priority.

6. Plasma TH kinetics and buffering by plasma proteins

Two key TH plasma kinetic parameters are Metabolic Clearance Rate (MCR) and Degradation Rate (DR). MCR, the volume of plasma cleared of T4 or T3/unit time/unit body weight, measures plasma T4 or T3 turnover. DR (MCR × plasma T4 or T3 concentration) represents the amount of T4 or T3 irreversibly leaving the plasma pool/unit time/unit body weight. At a steady-state, and assuming no influx of exogenous TH, the T4DR equals the thyroid T4 secretion rate, while T3DR represents the sum of any thyroidal T3 secretion and extrathyroidal T3 production by T4 deiodination.

The euthyroid human T4MCR is 1.2 L/day/70 kg body weight) while the T3MCR = 24 L/day/70 kg) (Chopra and Sabatino, 2000) indicating a 20-fold faster plasma turnover for T3 than T4. However, due to the high plasma T4 concentration, the T4DR is 130 nmols T4/24 h/70 kg (or 7.7 pmol T4/h/100 g), exceeding the T3DR of 48 nmol/24 h/70 kg (or 2.9 pmol/h/100 g) (Chopra and Sabatino, 2000). Thus humans have a rapid turnover of a small plasma T3 pool and a very slow turnover of a much greater T4 pool. The net result is a T3 production rate from all sources that is about 40% of the T4 secretion rate.

This striking difference in T4 and T3 kinetics is largely dictated by properties of TH-binding plasma proteins. In humans, TH bind mainly to three plasma proteins: TBA (TH-binding albumin), TBPA (TH-binding prealbumin = TTR = transthyretin) and TBG (T4-binding globulin) (Refetoff, 2015; Robbins et al., 2000). In combination, with TBG predominating, they bind about 99.97% of human circulating T4 leaving 0.03% in the free exchangeable fraction. This explains the large plasma pool of total T4 that turns over very slowly, allowing the physiologically-relevant free T4 level (0.7–2.1 ng/dL (10–25 pM) (Stockigt et al., 2000) to be extremely well buffered against either a diminished thyroid T4 secretion or a sudden T4 influx from dietary sources.

Importantly, due to this slow turnover of bound T4, there can be a temporary, but physiologically significant, plasma storage of a dietary T4 excess with a negligible effect on the free T4 level (Refetoff, 2015; Robbins et al., 2000). This spares thyroidal T4 secretion and thereby contributes to iodine conservation. In contrast, human plasma free T3 levels (0.2–0.5 ng/dL (3–8 pM) (Stockigt et al., 2000) are somewhat lower than free T4 levels and the binding characteristics differ greatly due mainly to the much lower affinity of T3 than T4 for TBG. Thus the concentration of total plasma T3 (75–175 ng/dL) is considerably less than that for T4 (4–11 μg/dL) (Stockigt et al., 2000). A major consequence is that plasma free T4 would be buffered far better than plasma free T3 against an influx of exogenous (dietary) hormone.

Temperate teleost TH kinetics are highly dependent on acclimation temperature (Eales et al., 1982; Eales et al., 1986; Sefkow et al., 1996). The behaviourally-preferred temperature for rainbow trout is 13C (Garside and Tait, 1958). Kinetic estimates for fed rainbow trout acclimated at 11-12C, close to this preferred temperature, indicate a T4MCR of 1.6 ml/h/100 g and a T3MCR of 0.83 ml/h/100 g (Eales et al., 1982; Eales et al., 1986). Thus, in marked contrast to humans, trout plasma T3 is turned over half as fast as plasma T4, and in many instances T4 is present at lower plasma levels than T3. However, on account of the more rapid T4MCR, the T4DR at 11–12 C is 4.8 pmol/h/100 g whereas the T3DR is 2.8 pmol/h/100 g, resulting in a trout T3 production that is 60% of total T4 production. Under other conditions (differences in acclimation temperature, nutritional state or age) the trout T4DR ranges from 2.4 to 6.0 pmol T4/h/100 g (Sefkow et al., 1996). Of additional parenthetic interest, based on a standardized body weight of 100 g, the T4DR estimates are generally comparable for homeothermic humans at 37C and heterothermic trout at 11-12C.

What are the properties of the teleost TH-binding plasma proteins and what impact do they have on plasma TH levels and their kinetics? The primary plasma TH-binding sites in teleosts studied to date comprise albumin and prealbumin (Falkner and Eales, 1973; Refetoff, 2015; Refetoff et al., 1970), the latter now identified as TTR (Power et al., 2000; Santos and Power, 1999) A TBG-like protein has not been identified. Analyses on salmonid plasma involving heterologous ligand displacements suggested that the capacity and affinity for T3 binding sites might exceed those for T4 sites (Eales, 1987). A subsequent study (Power et al., 2000) showed that, in contrast to mammals, fish TTR binds T3 more avidly than T4. More recent studies on recombinant TTR in the little skate (*Leucoraja erinacea*) (Suzuki et al., 2015) and the brown hagfish (*Paramyxine atami*) (Suzuki et al., 2017) show that TTR affinity for T3 exceeds that for T4; a 190-fold difference for the brown hagfish. Significantly, despite the major effect that plasma TH-binding proteins may have on the plasma TH levels and kinetics, the plasma free T4 and free T3 levels do not differ greatly between humans and fish (as measured by equilibrium dialysis on Arctic charr, *Salvelinus alpinus*, at 12C (Eales and Shostak, 1985). Thus while plasma TH-binding proteins have major effects on plasma total TH levels, plasma TH kinetics and plasma TH buffering they exert little influence on the physiologically relevant free TH levels.

TBG increases during human pregnancy (Glinoer, 1997). Are the plasma TH-binding proteins of fish also altered when there are different demands on the thyroid system? There are few available data. During parr-smolt transformation there are major changes in the thyroid function (Dickhoff et al., 1982; Specker et al., 2000), but these were unaccompanied by any change in T4 binding characteristics (Boeuf et al., 1989). However, TH administration increased plasma TTR in sea bream (Morgado et al., 2007). Treatment of immature rainbow trout with estradiol increased the capacity of the low-affinity and high-capacity plasma T3-binding site, suggesting an increase in buffering/storage of plasma T3 associated with ovarian maturation (Cyr and Eales, 1989).

In conclusion, due largely to TBG and and to a lesser extent TTR, the human plasma free T4 level is well buffered against dietary T4 intake, allowing temporary storage of ingested T4 in the slowly metabolized plasma T4 pool, thereby sparing thyroidal T4 secretion. The human plasma free T3 level is buffered less well but natural dietary T3 sources are likely much lower than those for T4 and with less potential impact. Properties of trout plasma TH-binding proteins differ markedly from those for humans, contributing to rapid turnover of a small plasma T4 pool and a larger plasma T3 pool that turns over more slowly. This relatively small and 'poorly buffered' plasma T4 pool, would be highly susceptible to disruption due to unregulated uptake of dietary T4. In contrast, the often larger and better buffered plasma T3 pool would be more resistant to a comparable challenge. Transthyretin would contribute to T3 buffering but T3 exchanges with tissues could also occur.

7. Exchanges of TH with tissues

There may be rapid- or slow-exchanging TH tissue pools. For trout, two significant T3 rapid-exchange tissues are liver (Sefkow et al., 1996) and erythrocytes (McLeese et al., 1998). For trout erythrocytes, 50% of maximal T3 influx or efflux occurs *in vitro* at 30–40 s while for T4 this occurs at 30 min. Thus erythrocytes have the potential to act as a major buffer for trout plasma T3 but not for plasma T4. In contrast, skeletal muscle is likely a slow-exchange tissue for T3; its T3 level is low but with its large mass the muscle represents ~80% of T3 for all trout tissues (Fok et al., 1990).

In considering the efficacy of T3-exchanging tissues and other T3 homeostatic mechanisms in offsetting a dietary T3 challenge, it is critical to distinguish between responses to *experimental* dietary T3 challenges, where plasma T3 is increased considerably, and the likely much lower *natural* dietary T3 challenges due to prey ingestion. In the latter scenario, GIT DIO3 activity, T3 exchange with liver, autoregulatory hepatic DIO3 T3 activity, enterohepatic T3 uptake, buffering by TTR, T3 rapid exchange with erythrocytes and slow T3 exchange with a large muscle pool may suffice to maintain the teleost plasma free and total T3 levels within normal limits.

8. Thyroid secretion of TH through the brain-pituitary axis

Although the particular mechanisms may differ, thyroid secretion in both higher vertebrates (McNabb, 1992; Norris and Carr, 2013) and teleosts (Jones et al., 2013; MacKenzie et al., 2009) is regulated through the hypothalamo-hypophyseal-thyroid axis by TSH secretion. Plasma free T4 has a negative feedback action on this axis to regulate the teleost plasma level of free T4 at a particular set-point (Jones et al., 2017). In humans this feedback allows ingested T4 to contribute to the plasma T4 pool while simultaneously reducing thyroidal T4 secretion and thereby conserving T4 and iodine. In theory, this 'thyrostat' could also contribute to the observed stability in trout plasma T4 following T4 ingestion. However, for such a feedback to operate, sufficient T4 must reach the systemic circulation from the intestine to provide a signal to the hypothalamo-hypophyseal axis. Negligible plasma levels of ^{125}I-T4 were found up to 24 h after ^{125}I-T4 delivery via an anal cannula directly into the lumen of the trout intestine (Whitaker and Eales, 1993). Thus it is unlikely that hypothalamo-hypophyseal negative feedback is involved in trout in preserving the plasma T4 level following T4 ingestion – at least at the T4 dose used.

The setting of the thyrostat is not fixed but, depending on physiologic state, can change to adjust plasma T4 levels. In adult humans under normal conditions (no pregnancy Glinoer, 1997) thyrostat adjustments may be minimal. Plasma T4 levels fall within a narrow range, consistent with the primary thyroid role in regulating basal metabolic rate and homeothermy. In marked contrast, the thyrostat of heterothermic teleosts seems particularly prone to short-term adjustments, as shown by rapid (sometimes hourly) marked elevations in plasma T4. Their transient nature, may be explained in part by relatively poor T4 buffering by plasma proteins and by negligible T4 exchange with erythrocytes.

These acute short-term changes in plasma T4 include pronounced

diel cycles in many taxonomically-diverse teleost species: goldfish (Noeske and Spieler, 1983; Spieler and Noeske, 1979; Spieler and Noeske, 1981; Spieler and Noeske, 1984), rainbow trout (Bouchard and Leatherland, 1992; Cook and Eales, 1987; Eales et al., 1981; Osborn et al., 1978), suckers (Stacey et al., 1984), brook trout (Audet and Claireaux, 1992; McCormick and Naiman, 1984; White and Henderson, 1977), Atlantic salmon (Rydervik et al., 1984); sea bass and sea bream (Pavlidis et al., 2006) and channel catfish (Loter et al., 2007). Feeding also causes an acute elevation in plasma T4 (Flood and Eales, 1983; MacKenzie et al., 1998). A particularly pronounced diel cycle occurs in red drum which show a bimodal and free-running cycle independent of food intake and photoperiod (Leiner and Mackenzie, 2001, 2003; Leiner et al., 2001). Significantly, there were relatively small and inconsistent changes in plasma T3 for many of the above studies.

The fish thyroid system is also highly responsive to stressors and stress-related hormones (Geven, 2009; Geven et al., 2006; Peter, 2011; Walpita et al., 2007). Some of these responses can be rapid. Intraperitoneal injection of isotonic saline or blood removal under anesthesia caused a temporary (within 2 hr) increase in plasma T4 (but not T3) in rainbow trout (Brown et al., 1977). A similar acute response occurred in anesthetized and cannulated rainbow trout infused with glucose, suggesting that a rise in plasma glucose may be responsible (Himick and Eales, 1990a). Indeed, feeding caused a rise in plasma glucose and also an acute increase in trout plasma T4 (Himick and Eales, 1990b). Catecholamine injection acutely increased trout plasma T4 (Eales et al., 1986). In smolting Atlantic salmon physical disturbance (tank cleaning) increased plasma T4 by 4 h (Specker et al., 2000). The above examples show that the teleost plasma T4 level can undergo marked short-term transient changes, responding rapidly to a variety of stimuli and that stress factors may be important. This suggests that T4 may have short-term effects. These have received negligible attention in fish but there is mounting evidence for rapid non-genomic T4 actions in mammalian systems (Davis et al., 2016).

In conclusion, the human hypothalamic-hypophyseal thyrostat contributes to plasma T4 stability, consistent with the thyroid role in basal metabolic rate regulation and homeothermy. It also conserves the thyroid T4 store by relaxing TSH release and thyroidal T4 secretion following T4 ingestion. In teleosts it is unlikely that T4 negative feedback of TSH release explains unchanged plasma T4 levels following experimental dietary T4 challenges. However, short-term thyrostat adjustments involving altered TSH release may contribute to the naturally-occurring acute and typically transient changes in plasma T4 characteristic of heterothermic teleosts and due to stressors, diel cycles, feeding or other factors. Short-term and presumably non-genomic actions of T4 have been shown in mammalian systems and may also occur in teleosts. Consequently it would be advantageous for teleosts to degrade or excrete otherwise unregulated ingested T4 prior to its access to the systemic circulation. In contrast, natural dietary T3 challenges, likely much lower than those for T4, may be degraded or buffered in several ways and without reliance on major T3 deiodination by the GIT.

9. Iodine acquisition and metabolism

The metabolism of TH is inseparable from that of iodine which in the inorganic state exists mainly as iodide (I^-). Its availability varies considerably with environment, being relatively abundant in seawater (Hickman, 1959; Ito and Hirokawa, 2009), lower and geographically variable in freshwater (NERC, 2000) and potentially limiting in many land environments (Yun and Doux, 2009). What bearing might this have on TH homeostasis in fish and humans and particularly following dietary TH challenges?

The fish thyroid evolved from the protochordate endostyle (Barrington, 1962; Salvatore, 1969) in the I^--rich ocean. Marine teleosts drink seawater (Conte, 1969) ensuring an adequate intestinal I^- supply, supplemented by I^- in food and possible I^- uptake via other surfaces (Moren et al., 2008). Freshwater teleosts drink negligibly and so food and gill uptake are the potential iodine sources. Several studies support gill uptake (Geven, 2009; Geven et al., 2007; Gregory and Eales, 1975) and thyroidally-controlled gill I^- transport was proposed (Leloup, 1970), but a gill sodium/iodide symporter has yet to be established. Gill I^- uptake alone should satisfy most thyroid demands as gills are irrigated with a high water flow (Geven, 2009). Indeed, plasma I^- levels increased two-fold in 40-day fasted brook trout and were lower in non-exercised than exercised individuals experiencing greater gill water flow (Higgs and Eales, 1971). Nevertheless, iodine-deficiency can develop in freshwater teleosts (Marine and Lenhart, 1910; Radulescu et al., 1968) and in a classical ground-breaking study, Marine (Marine, 1914) successfully corrected severe goiters in hatchery brook trout by changing to a sea-food diet rich in iodine. Thus dietary iodine can contribute to trout iodine balance in freshwater, but usually to a lesser extent than ambient sources (Gregory and Eales, 1975; Hunt and Eales, 1979).

Plasma I^- levels in freshwater teleosts cover a wide range (0.5–2244 μg/100 ml) with some of the highest levels in laboratory-held brook trout (Gregory and Eales, 1975). Such spectacular levels are unexpected in a species so notoriously susceptible to iodine-deficiency goiter when held in captivity (Marine, 1914; Radulescu et al., 1968). However, these extreme plasma I^- levels were due to two factors. Firstly, their commercial diet was rich in whole-herring meal and hence iodine, and secondly, brook trout possess a plasma protein that reversibly binds I^- (Gregory and Eales, 1975). This may allow plasma storage of considerable I^- without inducing the thyroid-inhibiting Wolff-Chaikoff effect found in humans (Eales et al., 1986; Taurog, 2000; Wolff, 1969). A plasma I^--binding protein occurs in several freshwater Clupeiformes and Mugiliformes (Hickman, 1962; Huang and Hickman, 1968; Leloup, 1970; Leloup and Fontaine, 1960). Other adaptations with the potential to enhance I^- capture and storage exist in freshwater teleosts. Cyprinids and several other taxa develop heterotopic thyroid follicles outside the basibranchial region in vascular tissues such as the head kidney (Baker, 1958; Chavin, 1956). While this can relate to a functional interdependence of thyroidal and interrenal tissue (Geven et al., 2009), it also extends iodine storage outside the basibranchial region where there is limited space for thyroid follicle proliferation without compromising gill function or development of overt goiters (Moccia et al., 1981). Another teleost, the burbot, *Lota lota*, a freshwater representative of the marine Gadidae, stores iodine in the skin (Wiggs, 1971). Thus several freshwater teleosts have adaptations favouring iodine storage. Under what conditions might they be relevant? The long upstream spawning migrations of some anadromous salmonids may provide the best example. They eat little during a long spawning run and may traverse inland environments low in iodine. Furthermore, females transfer considerable amounts of TH to developing ova (Blanton and Specker, 2007; Brown et al., 2014; Lam, 1994; Tagawa et al., 1990) and the offspring may rely on this parental iodine storage to complete their early development in iodine-impoverished environments.

The human thyroid also had a marine origin but with an intervening long terrestrial ancestry, diverging from the line leading to fish in the Ordovician about 485 million years ago (Benton, 2005). With the loss of gills any branchial source of I^- disappeared and I^- had to be acquired from ingested water or food. However, the loss of gills and reorganization of the gular region also liberated the evolving thyroid from its sub-branchial confines and allowed it to increase greatly in size. Thus the human thyroid in the euthyroid state weighs about 15–20 g (a giant compared to other endocrine tissues) and has scope for expansion to many hundreds of grams in endemic goiters (Larsen et al., 1998). The normal thyroid contains 90% of the body's total pool of iodine and 30% of the thyroid mass is thyroglobulin, representing a 2–3 month supply of TH (Holt and Peery, 2008). Thus, in contrast to fish, the thyroid of humans is a major physically-expandable iodine reservoir, storing iodine partly as thyroglobulin-incorporated iodothyronines but even more extensively as iodotyrosines (Dunn et al.,

2000). Consequently for humans there would be no selective advantage in storing iodine extrathyroidally in plasma or other tissue sites. Indeed, human I^- levels in plasma and extracellular fluid are extremely low (1–1.5 μg/100 ml (Larsen et al., 1998) compared to those reported above for some freshwater fish.

Humans can also conserve iodine by utilizing dietary and intestinal T4 to spare endogenous TH synthesis. This is enabled by i) the extreme buffering of the physiologically-relevant plasma free T4 level by TBG, allowing 'storage' of dietary-acquired T4 in plasma, ii) the relaxation of the thyrostat regulating T4 secretion and iii) the enterohepatic T4 cycle which temporarily removes (stores) a biliary-discharged or ingested T4 excess that can be later reclaimed. Thus in contrast to fish there would be no advantage, and indeed a disadvantage, in deiodinating T4 entering the GIT. It would be of interest to know how much T4 is in the diet of modern-day humans and its direct contribution to human thyroid economy. Of even greater interest would be the extent of T4 ingestion in ancestral prehistoric hominoids where culinary practice might not have led to the careful exclusion of thyroid tissue prior to dinner. Furthermore, inadvertent ingestion of thyroid tissue would also include the TH precursors, monoiodotyrosine and diiodotyrosine, particularly abundant in thyroglobulin (Dunn et al., 2000). Their enzymatic deiodination in digesta would liberate iodide. Iodotyrosine deiodination is well established for thyroidal tissue (Kobayashi et al., 1966; Matsuzaki et al., 1968; Querido et al., 1956) but also occurs extrathyroidally (Faberova and Knopp, 1971; Maayan, 1966) and may have a wide phyletic distribution (Phatarphekar et al., 2014). It is expressed in the GIT of metamorphosing *Xenopus* (Fujimoto et al., 2012). To what extent is it routinely active in the GIT?

In conclusion, based on a standardized body weight, both humans and fish (salmonids) have generally comparable thyroid T4 secretion rates and hence iodine requirements. Despite this similarity, iodine conservation emerges as a significant factor underlying the marked difference in their ability to directly utilize ingested T4. Humans, colonizing terrestrial environments, often naturally low in iodine, have evolved several mechanisms enabling efficient iodine acquisition, storage and metabolism. These include enterohepatic cycling of biliary-excreted TH and temporary plasma storage by TBG of any ingested T4. Both spare thyroidal T4 secretion and hence iodine but depend on efficient T4 absorption from the GIT. In contrast, most freshwater teleosts acquire adequate I^- partly from ingestion but mainly from branchial uptake and there would be no advantage in absorbing T4 as an I^- source from the GIT. Indeed it could be highly disadvantageous due to its interference with the rapid and transient natural changes in plasma T4 characteristic of teleosts. Thus T4 may also act as a vitamin (vitamone) for humans - but not for fish.

10. Perspective

The goal of this otherwise unlikely comparison of TH homeostasis and iodine metabolism between humans and teleost fish was to determine 'why' they differ so strikingly in uptake of ingested T4, but not T3. To answer 'why' it is helpful to distinguish between the proximate (mechanistic) factors and ultimate (selective advantage) factors (Mayr, 1963). For humans the primary ultimate factor is preserving the relatively constant plasma free T4 level consistent with basal metabolic rate regulation but dependent on an often limited iodine supply. Thus a key proximate factor enabling iodine conservation is efficient GIT uptake of either ingested or biliary-recycled T4 or T3. In contrast, iodine conservation in teleosts is generally not an issue and the primary ultimate factor may be protection of their natural acute fluctuations in plasma T4 from exogenous T4. Several proximate factors ensure this protection but prominent are mechanisms blocking T4 uptake from the GIT to the systemic blood. For T3, however, the likely much lower natural dietary challenges may be offset by other mechanisms not reliant on major blockage of T3 uptake from the GIT.

Can one apply these 'models' to other vertebrates? There are likely limitations, even for mammals and fish. For example, TBG, which plays a prominent role in human T4 metabolism, is not expressed in all mammals, occurring mainly in primates and large herbivores including the cow, horse, goat, water buffalo and sheep but is absent in the cat and rabbit (Kaneko, 2008; Larsson et al., 1985). Indeed, the laboratory rat, a common human model, lacks significant TBG (Larsson et al., 1985), though it may be expressed in neonatal and ageing individuals (Savu et al., 1991). Furthermore, not all mammals, such as the predatory cat (Hays et al., 1992), may have the efficient GIT T4 uptake of humans. With regard to fish, most data discussed in this review were obtained for teleosts (mainly salmonids) during their extended pre-adult growth phase in freshwater. However, this phase is preceded by one where the thyroid has an established role in development and metamorphosis (Blanton and Specker, 2007; Isorna et al., 2009; Power et al., 2008), and where TH metabolism could differ. Secondly, the growth phase is followed by reproduction with changes in thyroidal status due to thyroid interactions with sex-related hormones (Cyr and Eales, 1996; Habibi et al., 2012) and changes in iodine metabolism associated with TH concentration in eggs (Blanton and Specker, 2007; Brown et al., 2014; Lam, 1994; Tagawa et al., 1990). Thirdly, most salmonids undergo parr-smolt transformation, a 'metamorphosis' with established thyroid involvement (Dickhoff et al., 1982; Specker et al., 2000). Finally, following parr-smolt transformation there is downstream salmonid migration to the ocean, with changes in osmoregulation, iodine availability and diet and which may affect TH and iodine metabolism.

In conclusion, the holistic analysis attempted in this review may help to explain differences in TH and iodine metabolism between humans and certain teleost fish. However, it may have limitations depending on the changing roles that TH may play at different stages in the life cycle of fish and other vertebrates and on their transitions between environments that may vary in iodine availability.

11. Future research

Several arguments presented in this review involve the metabolism of TH by the GIT for which there are few data for fish or other vertebrates. Key questions relate to the mechanism of T4 or T3 uptake from the GIT, the types of deiodination pathways involved, their location in the GIT and their role in either protecting plasma TH levels from dietary TH challenges or regulating TH availability to GIT TH receptors.

Since natural ingested TH challenges will vary with diet, comparisons of GIT TH metabolism between carnivores/piscivores and herbivores/omnivores would be informative. With regard to fish, a comparison among cichlids could be fruitful. Their extensive adaptive radiation into numerous niches has involved major changes in diet and possibly thyroid function.

Plasma T4 levels and dynamics vary greatly between humans and teleosts and the significance of the rapidly changing plasma T4 levels observed in taxonomically-diverse teleosts is currently an enigma. It suggests short-term T4 actions (non-genomic) on target sites but contributing temporary changes in plasma T4 clearance cannot be excluded.

Finally, there is a rapidly expanding literature on the effects of ecocontaminants on fish thyroid function (Blanton and Specker, 2007; Brown et al., 2004; Schnitzler et al., 2012). Testing commonly involves administering the potential contaminant by injection or via the ambient water and then following thyroid function in metabolically active tissues such as liver or kidney. However, for contaminants where the natural route of entry might be via the digestive tract (eg passed down the food chain or taken up by benthic feeders), the GIT tissues will be the first the contaminant encounters. In these instances investigation of altered TH metabolism by the GIT could be worthwhile.

12. Conclusions

- What are the proximate and ultimate factors underlying the difference between humans that efficiently absorb T4 from the digestive tract and teleost fish that lack this ability?
- Humans depend on stable plasma free T4 levels, consistent with T4 regulation of basal metabolic rate and enabled by plasma T4-binding globulin which buffers a large plasma T4 reservoir. This buffering and stability, in combination with efficient T4 absorption from the gastrointestinal tract, deiodination of sulfate-T4 conjugates and T4 enterohepatic cycling, allows ingested T4 to contribute to the plasma T4 pool and to conservation of iodine, the supply of which may be limiting in many terrestrial environments.
- In contrast, teleost plasma T4 levels can show short-term (hourly) changes due to diel rhythms and responses to several acute variables including feeding and stressors. These acute plasma T4 changes are possible due to the small plasma pool of relatively poorly buffered T4, which would therefore be highly susceptible to disruption by unregulated T4 ingestion.
- Protection of these dynamic changes in plasma T4 from ingested T4, a potentially significant source in piscivorous teleosts eating the T4-rich thyroids of their prey, may be achieved by hepatic T4 deiodination, biliary excretion of both sulfate and glucuronide conjugates and an intestinal constitutional DTT-inhibited complete T4 deiodination that is ineffective for T3 and thereby allows T3 absorption.
- Iodide appears readily available to most teleosts due to branchial uptake. However, dietary iodine and iodide liberated by intestinal and hepatic T4 deiodination may also contribute to iodine conservation and benefit certain freshwater teleosts in low-iodine environments.
- Although *experimental* dietary T3 challenges raise teleost plasma T3 levels, the *natural* T3 intake may be far less. This would allow plasma free T3 regulation by hepatic deiodination, conjugation, biliary excretion and binding to plasma proteins, with further buffering by exchanges with erythrocyte and skeletal muscle compartments and thus without recourse to major intestinal deiodination.
- Despite i) the potential importance of the gastrointestinal tract in systemic TH regulation, ii) the clinical relevance of oral TH therapy, iii) the thyroid evolution from the protochordate endostyle and iv) the availability of appropriate molecular tools, there is surprisingly little recent information for any vertebrate on intestinal TH transporters, deiodinases or receptors, which could be compromised directly by ingested contaminants

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