THEMATIC REVIEW

Deiodinases: the balance of thyroid hormone

Type 1 iodothyronine deiodinase in human physiology and disease

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Abstract

Thyroid hormone is essential for the normal function of virtually all tissues. The iodothyronine deiodinases catalyze the removal of an iodine residue from the pro-hormone thyroxine (T_4) molecule, thus producing either the active form triiodothyronine (T_3; activation) or inactive metabolites (reverse T_3; inactivation). Type I deiodinase (D1) catalyzes both reactions. Over the last years, several studies have attempted to understand the mechanisms of D1 function, underlying its effects on normal thyroid hormone metabolism and pathological processes. Although peripheral D1-generated T_3 production contributes to a portion of plasma T_3 in euthyroid state, pathologically increased thyroidal D1 activity seems to be the main cause of the elevated T_3 concentrations observed in hyperthyroid patients. On the other hand, D1-deficient mouse models show that, in the absence of D1, inactive and lesser iodothyronines are excreted in feces with the loss of associated iodine, demonstrating the scavenging function for D1 that might be particularly important in an iodine deficiency setting. Polymorphisms in the *DIO1* gene have been associated with changes in serum thyroid hormone levels, whereas decreased D1 activity has been reported in the nonthyroid illness syndrome and in several human neoplasias. The current review aims at presenting an updated picture of the recent advances made in the biochemical and molecular properties of D1 as well as its role in human physiology.

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Introduction

Thyroid hormones are critical to the development and metabolism of virtually all tissues. Although the human thyroid gland mainly secretes thyroxine (T_4), thyroid hormone actions are mediated by the active hormone, triiodothyronine (T_3). In euthyroid individuals, the conversion of peripheral T_4 to T_3 accounts for 80% of all the T_3 produced. This critical step in thyroid hormone metabolism is catalyzed by two enzymes, the type 1 and type 2 iodothyronine deiodinases (D1 and D2), via outer (5′)-ring deiodination of the pro-hormone T_4. Type 3 iodothyronine deiodinase (D3) catalyzes the inner (5)-ring deiodination of T_4 and T_3, thus inactivating the thyroid hormone action.

In the last decades, several studies have extended our understanding on the mechanisms of D1 function in humans, underlying its effects on normal hormone metabolism and pathological processes. D1 is the only selenodeiodinase that can function as either an outer- (5′) or an inner (5)-ring iodothyronine deiodinase and was the first to be cloned (Berry *et al.* 1991*a*, Mandel *et al.* 1992). D1 is believed to provide a significant portion of the circulating plasma T_3 in euthyroid vertebrates, including humans. Nevertheless, the remarkable preference of D1 for reverse T_3 (rT_3) as the enzymatic outer-ring deiodination substrate, as well as the deiodination of sulfated iodothyronines, argues for its role as a scavenger enzyme to deiodinate inactive iodothyronines, thus clearing these compounds from the circulation and serving, if necessary, to recycle iodine within the organism (Schneider *et al.* 2006). More recently, attention has been turned to the role of D1 in the biosynthesis of thyronamines, a newly identified class of endogenous compounds that appears to antagonize thyroid hormone actions (Scanlan *et al.* 2004).

The genetic background influences serum thyroid hormone profile. Single nucleotide polymorphisms (SNPs) in the deiodinase genes may interfere in the phenotypic expression of these enzymes influencing the levels of thyroid hormone. Indeed, several SNPs have been identified in the *DIO1* gene and associated with changes in circulating thyroid hormone

levels. Of note, it is remarkable that no inherited deficiency or mutation in human deiodinase genes has been reported so far. Pathologically increased thyroidal D1 activity plays a key role in the elevated serum T_3 concentrations observed in hyperthyroid patients. Conversely, impaired D1 activity is likely to contribute to the lower levels of serum T_3 in the nonthyroid illness syndrome. Because thyroid hormone influences the vital balance between cell proliferation and differentiation, deiodinases might also play a role in controlling the intracellular levels of thyroid hormone levels in tumor-igenesis. Decreased *DIO1* expression has been suggested as a marker of the epithelial follicular thyroid cell dedifferentiation, and even though the reasons for that remain speculative, it is striking that lower D1 expression has been described in almost all tumors derived from parenchymal or epithelial tissues.

This review aims at presenting an updated picture of the recent advances of our knowledge regarding the role of deiodinase type 1 as a regulator of thyroid hormone metabolism in human physiology and disease.

Genetic, biochemical, and molecular properties of type 1 deiodinase

The human *DIO1* gene is located in the p32–p33 region on chromosome 1 and consists of four exons (Jakobs *et al.* 1997*a*). The mRNA size is about 2–2·1 kb with a UGA selenocys-teine (Sec) codon in the region encoding the active center (Berry *et al.* 1991*b*). The TGA codon for the incorporation of Sec is located on the second exon (Mandel *et al.* 1992, Jakobs *et al.* 1997*b*). The encoded 27 kDa D1 protein is highly similar in size (26–30 kDa) and sequence among species with a few informative exceptions (Berry *et al.* 1991*a,b*, Mandel *et al.* 1992, Maia *et al.* 1995*a*, Sanders *et al.* 1997). The D1 protein contains a critical Sec residue at position 126 and is exquisitely sensitive to inhibition by propylthiouracil (6-*n*-propyl-2-thiouracil, PTU; Mandel *et al.* 1992). The human *DIO1* gene is under the control of GC-rich SP1 promoters and contains two thyroid hormone response elements (TREs), both contributing to the T_3 responsiveness of the human *DIO1* promoter (Toyoda *et al.* 1995, Zhang *et al.* 1998).

In vertebrates, D1 is mainly expressed in liver and kidney, whereas in adult mammals, the Dio1 transcripts are also identified in thyroid, pituitary gland, intestine, placenta, and gonads (St Germain & Galton 1997, Bates *et al.* 1999, Wagner *et al.* 2008). An interesting study that evaluated the expression profile of all three deiodinases in a wide spectrum of rat tissues showed that D1 is the only deiodinase expressed in liver, kidney, and intestine at all stages of development (Bates *et al.* 1999). Both *D1* mRNA and activity are present at low levels during fetal development and increase at later life stages, suggesting that D1 expression is regulated at least in part at a pretranslational level. The only exception for this expression pattern seems to be the testis, which presents higher levels of D1 activity in neonatal and weanling life (Bates *et al.* 1999, Wagner *et al.* 2008). Data on the ontogeny of the deiodinases

in human fetal tissues are limited. On the basis of high levels of rT_3 and T_3 sulfate (T_3S) observed in the human fetus, low levels of D1 activity are predicted, which progressively increase during the late gestational period and after birth (Santini *et al.* 1999). Indeed, hepatic D1 expression has been detected in the second gestational trimester at similar levels as observed in newborns, being around 20% of that found in adult liver (Huang *et al.* 1988, Richard *et al.* 1998). Of note, D1 is undetectable in human fetal brain tissues (Kester *et al.* 2004).

D1 is a thioredoxin (Trx)-fold integral membrane protein with a single transmembrane segment presented in the N-terminus and several clusters, corresponding to core secondary structures that compose the deiodinase globular domains (Callebaut *et al.* 2003). Studies using confocal microscopy of transiently expressed D1 in the human embryonic kidney cell line (HEK-293) indicate that it is localized in the plasma membrane with a cytosolic catalytic site (Baqui *et al.* 2000). The half-life of D1 protein is >12 h and its inactivation and subsequent degradation is enhanced by substrates such as iopanoic acid or rT_3 but is apparently not
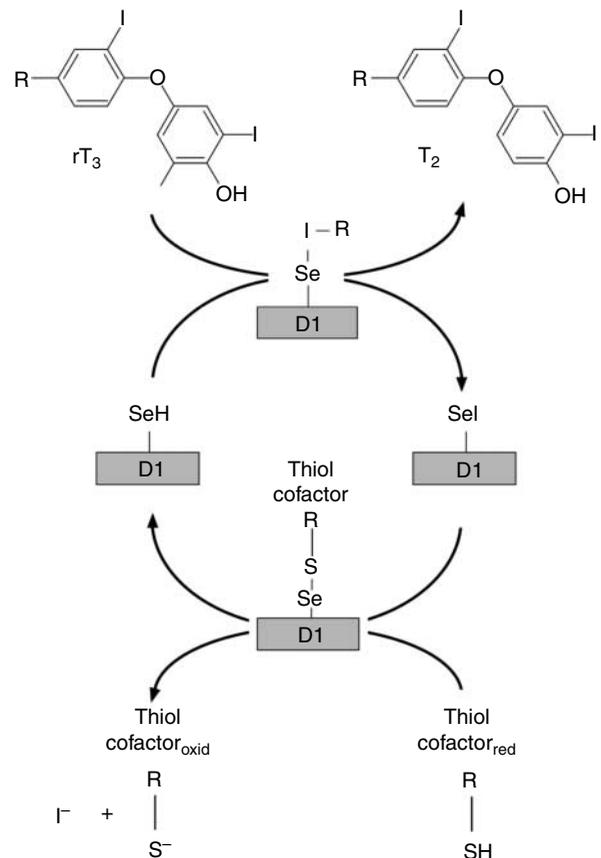

Figure 1 Schematic model of thyroid hormone catalysis by type 1 deiodinase. D1-catalyzed reaction follows ping-pong kinetics with two substrates: the first being an iodothyronine and the second being an as yet unidentified endogenous intracellular thiol cofactor. rT_3, $3,3',5'$-triiodothyronine; T_2, diiodothyronine; D1, deiodinase type 1; Se, selenium; I, iodide.

susceptible to ubiquitination (St Germain 1988, St Germain & Croteau 1989, Gereben *et al.* 2000). It is still unclear whether the inactivated D1 can be reactivated *in vivo*, but continued protein synthesis is probably required for the maintenance of D1 activity. As shown in Fig. 1, D1-catalyzed reaction follows ping-pong kinetics with two substrates: the first being the iodothyronine and the second being an as yet unidentified endogenous intracellular thiol cofactor (Visser *et al.* 1976, 1978, Chopra *et al.* 1978, Leonard & Rosenberg 1980, Berry *et al.* 1991*c*). The catalytic cycle of D1 comprises two half reactions: first, there is transference of I^+ from the substrate to selenolate (Se^-), resulting in an intermediate compound that is immediately reduced by the cofactor generating a selenium iodide (SeI) complex. The proposed mechanism of the enzymatic reaction for the D1 enzyme involves the interaction of the sulfhydryl group of the enzyme cysteine (Cys) residue with the second substrate. In this case, the as yet undefined cofactor would act as a reducing agent releasing iodine from the Sec residue and regenerating the active enzyme (Goswami & Rosenberg 1984, Berry *et al.* 1991*c*, Sun *et al.* 1997). Early studies on the D1-catalyzed reaction suggested that the endogenous cofactor might be glutathione (GSH) or Trx because both were effective in supporting catalysis (Goswami & Rosenberg 1987, St Germain 1988, Sharifi & St Germain 1992). PTU, a potent uncompetitive D1 inhibitor, is thought to react with the SeI intermediate by competing with the thiol cosubstrate to form an essentially irreversible complex (Sharifi & St Germain 1992). On the other hand, gold and iopanoic acid are competitive inhibitors of the D1 deiodination reaction, presumably interacting with the selenium in the active center (Berry *et al.* 1991*c*, Mandel *et al.* 1992). As expected for an enzymatic reaction, the D1-catalyzed deiodination for both the outer and the inner ring of T_4 is influenced by pH (Visser *et al.* 1979, Leonard & Visser 1986).

A remarkable feature of D1 is its higher preference for rT_3 as the enzymatic outer-ring deiodination substrate, as well as the deiodination of sulfated iodothyronines (Otten *et al.* 1983, Visser *et al.* 1988, Toyoda *et al.* 1997). Inner-ring deiodination of T_3S by human and rat D1 is nearly 40 times faster than that from T_3 (Otten *et al.* 1984). The same is observed for T_4S and T_2S. Of interest, T_4 can serve as a substrate for the induced low K_m processes, but, in this case, K_m values were dependent on the artificial cofactor (dithiothreitol, DTT) concentrations (Sharifi & St Germain 1992). Conjugation of the phenolic hydroxyl with sulfate markedly enhances the suitability of the iodothyronine substrates for D1-catalyzed $5'$ deiodination (Otten *et al.* 1983, Mol & Visser 1985). This is reflected in a markedly higher V_{max}/K_m ratio for those substrates. Sulfation of T_3 also clearly enhances the inner-ring deiodination, but the preference of D1 for T_3S is much lower than that for rT_3 or rT_3S. The rate-limiting steps in the sulfation or desulfation of iodothyronines in a given tissue should be kept in mind when trying to predict the effects of D1-catalyzed deiodination.

Table 1 summarizes molecular and biochemical characteristics of the human D1.

Table 1 Molecular and biochemical properties of the human type 1 deiodinase

Parameter	Property	References
Reaction catalyzed	5- or $5'$-deiodination	
Chromosomal location	1p32–p33	Jakobs *et al.* (1997*a*)
Molecular mass	28·3 kDa	Mandel *et al.* (1992)
Subcellular location	Plasma membrane with the catalytic center in the inner surface	Baqui *et al.* (2000)
Substrate preference	$rT_3 > T_2S \gg T_4$ (5′) $T_4S > T_3S > T_3$, T_4 (5)	Otten *et al.* (1983, 1984) and Toyoda *et al.* (1997)
K_m[a]	rT_3 (5′): 0·21 µM T_3 (5): 2·8 µM T_4 (5′): 1·9 µM	Visser *et al.* (1988)
Cofactor	Endogenous: unknown Artificial: dithiothreitol (DTT)	
Tissue distribution	Liver, kidney, thyroid, and pituitary	Mandel *et al.* (1992) and Santini *et al.* (1999)
Inhibitors		
PTU	Uncompetitive inhibition	Berry *et al.* (1991*c*) and Mandel *et al.* (1992)
Gold and iopanoic acid	Competitive inhibition	
Regulatory factors		
Upregulation	T_3	Toyoda *et al.* (1995), Jakobs *et al.* (1997*b*) and Zhang *et al.* (1998)
	TSH	Ishii *et al.* (1983) and Beech *et al.* (1995)
	Retinoic acid	Schreck *et al.* (1994) and Toyoda *et al.* (1995)
	cAMP	Beech *et al.* (1995)
	GH	Jorgensen *et al.* (1989) and Alcantara *et al.* (2006)
Down regulation	Selenium deficiency	Corvilain *et al.* (1993) and Duntas (2010)

[a]5 mM DTT.

Regulation of type 1 iodothyronine deiodinase expression

The expression and activity of D1 are modulated by a variety of hormonal, nutritional, and developmental factors, the most potent being thyroid hormone (Harris *et al.* 1978, Kaplan & Utiger 1978, Maia *et al.* 1995*b*, Koenig 2005). The T_3 effect in rat and mouse *Dio1* gene is due to transcriptional activation and does not require protein synthesis (Berry *et al.* 1990, Maia *et al.* 1995*c*). T_3 also positively regulates the human *DIO1* gene at the transcriptional levels by interaction with two complex TREs located in the promoter region (Toyoda *et al.* 1995, Jakobs *et al.* 1997*b*, Zhang *et al.* 1998). In addition, the human *DIO1* promoter contains thyroid hormone response-retinoic acid (RA) response elements that mediate thyroid hormone receptor (TR)β activation (Schreck *et al.* 1994, Toyoda *et al.* 1995). Interestingly, a recent report indicates that, in mice, the promoter of the *Dio1* gene is also regulated by the hepatocyte nuclear factor 4α (HNF4α; Ohguchi *et al.* 2008). Based on the findings of that study, HNF4α would play a role in thyroid hormone homeostasis by cooperatively regulating the $5'$-deiodination of T_4 with GATA4 and T_3-inducible Krüppel-like transcription factor 9 (KLF9). The authors also suggest that the T_3 regulation of *Dio1* gene is probably due to an indirect mechanism that involves the T_3-dependent stimulation of KLF9 expression (Ohguchi *et al.* 2008).

In addition to thyroid hormones, other physiological compounds modulate D1 expression (Table 1). The administration of GH to euthyroid adults is known to increase the ratio of plasma T_3 to T_4 whereas reducing that of rT_3 to T_4 (Jorgensen *et al.* 1989, Alcantara *et al.* 2006), in a peripheral mechanism that probably involves augmented D1 and/or a reduction in D3 activity (Darras *et al.* 1992, Van der Geyten *et al.* 1999). TSH also induces D1 synthesis in the human thyroid gland, by a mechanism that involves, at least in part, the second messenger cAMP, via a protein synthesis-dependent process (Ishii *et al.* 1983, Pekary *et al.* 1994, Beech *et al.* 1995). Although the mechanism for the stimulation of *Dio1* transcription by cAMP has not been fully elucidated, its effects are additive to that of T_3, resulting in a fivefold stimulation relative to control (Mori *et al.* 1996).

Data on the effects of glucocorticoids on D1 expression are controversial. Although some *in vitro* studies have shown that glucocorticoids induce *D1* mRNA and activity in rat liver, others described no changes in D1 activity (Menjo *et al.* 1993, Van der Geyten *et al.* 2005). Studies using rat liver and kidney cell cultures observed an increase of *D1* mRNA and activity after incubation with dexamethasone (Davies *et al.* 1996*b*). Controversially, studies on a pituitary rat cell line found that dexamethasone alone had no effect on *Dio1* gene expression but did enhance the effect of T_3 (Maia *et al.* 1995*b*). On the other hand, the administration of dexamethasone to euthyroid adult males increased the circulating rT_3 and rT_3/T_4 ratios, which could be a result of the augmented production of rT_3 instead of decreased clearance (LoPresti *et al.* 1989).

Deiodinases are selenoproteins and, thus, susceptible to selenium deficiency. The effect of selenium deficiency on the synthesis of intracellular selenoproteins is apparently tissue dependent, being more pronounced in liver, skeletal muscle, and heart (Meinhold *et al.* 1992, Bermano *et al.* 1995, Bates *et al.* 2000). In rats, selenium deficiency decreases D1 activity in liver and kidney by a mechanism that involves protein translation, secondary to a blockage in the Sec incorporation (Beckett *et al.* 1987, DePalo *et al.* 1994). The administration of T_3 did not affect D1 activity in the selenium-deficient rats, whereas selenium-fed controls had a twofold increase in enzyme activity. Mice with excessive iodine intake presented a decreased selenium concentration in urine and liver and reduced renal and hepatic *D1* mRNA and activity levels (Yang *et al.* 2006). The selenium supplementation corrected these alterations. In humans, selenium deficiency is observed in subjects receiving diets with restricted protein content, such as those given for phenylketonuria, and also in elderly patients (Kauf *et al.* 1994, Calomme *et al.* 1995, Lombeck *et al.* 1996, Jochum *et al.* 1997). Seleno-deficient individuals have mildly elevated serum T_4 and T_4 to T_3 ratios, but normal TSH. Indeed, the deficiency of this essential micronutrient has been implicated in the pathogenesis of myxedematous endemic cretinism, prevalent in African endemic goiters, and associated to a thyroid 'exhaustion' atrophy occurring near birth. This might result from the low resistance of a fragile tissue to enhanced H_2O_2 generation under intense thyroid stimulation by high TSH levels (Goyens *et al.* 1987, Vanderpas *et al.* 1990, Duntas 2010). Of note, deterioration of thyroid function was observed after selenium administration to iodine-deficient people in an African region of endemic goiter, suggesting that the reduction in D1 activity during selenium deficiency can protect against iodine deficiency, presumably by reducing the deiodination of T_4, T_3, or T_3S (Contempre *et al.* 1991, 1992).

Role of D1 deiodinase in thyroid hormone activation and inactivation

The functional role of D1 in humans remains a matter of debate. Nearly 80% of peripheral T_3 originates from deiodination of the pro-hormone T_4 by D1 and D2. However, the relative roles of D1 versus D2 in extrathyroidal T_3 production are still controversial. Probably because D1 was the first selenodeiodinase to be identified and because of its subcellular location, it was often assumed that the majority of circulating T_3 was derived from T_4 via D1 activity. Nevertheless, the long-life of D1 protein and T_3 upregulation of D1 activity, just the opposite of what would be expected in a typical feedback loop, raise some questions about this assumption. Moreover, clinical studies have showed a maximum decrease of 25% in serum T_3 in athyreotic, T_4-replaced, euthyroid individuals treated with higher doses of PTU (Geffner *et al.* 1975, Saberi *et al.* 1975). Indeed, subsequent cumulative data on the biochemical and molecular properties of D2 indicate that this enzyme also contributes a significant portion of serum T_3 levels in humans

(Bianco *et al.* 2005, Maia *et al.* 2005). The D1 enzyme seems extremely inefficient in carrying out this reaction when compared with the D2, which has a 700-fold greater catalytic efficiency for $5'$-deiodination of T_4 (Maia *et al.* 2005). First, in contrast with D2-catalyzed reaction that generates 1 mol of T_3 for each T_4 molecule, for each 2 moles of T_4 deiodinated by D1, only 1 mol of T_3 and a second of rT_3 is produced since D1 catalyzes the inner- and outer-ring deiodination of T_4 equally well, as predicted from V_{max}/K_m estimates (Visser *et al.* 1988). This can explain a catalytic efficiency difference of 2, whereas the rest is primarily due to the much slower rate of D1-catalyzed T_4 to T_3 conversion under physiological conditions. This is not easily observed under typical *in vitro* assay conditions because the catalytic activity of this enzyme significantly varies from the artificial DTT generally used to other cofactor candidates such as GSH, as well as with variations of the cofactor concentrations (Goswami & Rosenberg 1987, Goemann *et al.* 2010).

The human D1- or D2-derived T_3 production significantly varies according to the thyroid status. Because *DIO1* expression is positively regulated by thyroid hormone, D1-catalyzed T_4 to T_3 reaction is expected to be decreased in the hypothyroid state (Maia *et al.* 1995c, Kim *et al.* 1998). In contrast, increased D2-catalyzed T_4 to T_3 conversion is anticipated due to the increase in the half-life of D2 protein and *DIO2* transcription secondary to the decreased levels of free T_4 (FT_4) and T_3 (FT_3) respectively (Gereben *et al.* 2000, Bianco *et al.* 2005, Wagner *et al.* 2007). In the opposite direction, D1-catalyzed T_3 production would predominate in the hyperthyroid state (see below). These assumptions are consistent with the predicted increased efficiency of D2-catalyzed T_4 to T_3 conversion as demonstrated in early studies; these studies showed that in hypothyroid patients, the fractional whole-body conversion rate of T_4 to T_3 was 42%, whereas this rate fell to 21% in the same patients made euthyroid by L-T_4 replacement therapy (Inada *et al.* 1975). Sustained elevations in serum T_3/T_4 ratios have also been reported in athyreotic subjects partially withdrawn from T_4 therapy (Lum *et al.* 1984).

In addition to the importance of the D1 and D2 in converting T_4 to T_3 in peripheral tissues, these enzymes are also highly expressed in the thyroid gland (Leonard & Visser 1986, Toyoda *et al.* 1992, Schoenmakers *et al.* 1995, Salvatore *et al.* 1996, Leonard *et al.* 2001). D1 seems to be constitutively expressed in the human thyroid gland, whereas D2 expression varies closely with the degree of thyroid stimulation (Salvatore *et al.* 1996). The thyroidal contribution for overall thyroid hormone economy is estimated on two-thirds from hydrolysis of thyroglobulin and one-third from deiodination (Laurberg *et al.* 2007). Interestingly, perfusion studies demonstrated that dog and human thyroid have a preferential secretion of T_3, favoring a more pronounced D1 activity in this gland (Laurberg 1978, Tegler *et al.* 1982).

The distinct subcellular localization of D1 and D2 might also contribute to its functional roles. D1 is located in the inner surface of the plasma membrane, whereas D2 is in the endoplasmic reticulum (Baqui *et al.* 2000), which could explain the early observations that T_3 generated by D1 rapidly equilibrates with plasma T_3. Moreover, this deiodinase seems to be positioned much better to clear rT_3 and other compounds from the circulation (Toyoda *et al.* 1997). The role of the facilitated deiodination of sulfated iodothyronines might be the recovery of the trace element iodine from inactive hormone metabolites, reutilized for T_4 synthesis (Toyoda *et al.* 1997). On the other hand, D2-derived T_3 production has a greater effect on T_3-dependent gene transcription than that from D1, which indicates that generation of nuclear T_3 is an intrinsic property of the D2 protein (Maia *et al.* 2005).

Important insights into the role of D1 for thyroid hormone metabolism were also obtained from two genetically modified animal models: C3H strains, which present inherited low D1 expression in liver and kidney, and D1KO mice, with targeted disruption of the *Dio1* gene (Berry *et al.* 1993, Schoenmakers *et al.* 1993, Schneider *et al.* 2006). The reduced D1 activity in C3H mice correlates with a CGT repeat insertion into the $5'$-flanking region of the *Dio1* gene that seems to impair C3H promoter potency (Maia *et al.* 1995a). Both the strains have elevated serum total and FT_4 and rT_3 but normal serum-FT_3 and TSH concentrations. The normal FT_3 concentration in these mice could be explained by the fact that, although the fractional conversion of T_4 to T_3 per day would be reduced, the higher FT_4 concentration permits normal daily T_3 production. In addition, serum T_3 levels were significantly higher in C3H than in C57 mice after the same dose of exogenous T_3, suggesting a reduction in T_3 clearance that might contribute to the maintenance of serum T_3 concentrations (Maia *et al.* 1995c). However, the rate of disappearance of T_3 was comparable in euthyroid WT and D1KO mice (Schneider *et al.* 2006). A potential source of serum T_3 in both C3H and D1KO mice is D2-catalyzed T_4 to T_3 conversion. Indeed, it has been shown that, despite the higher serum-FT_4, the levels of D2 activity in brown adipose tissue of C3H mice are comparable to those observed in C57 animals (Wagner *et al.* 2007). The normal serum-FT_3 levels would lead to a euthyroid state in peripheral tissues and can account for the observed euthyroid phenotypes in both phenotypes. Of note, no cases of inherited D1 deficiency in human have been documented so far.

In the last decade, animal models with deficiency of both D1 and D2 enzymes were generated (Christoffolete *et al.* 2007, Galton *et al.* 2009). The C3H–D2KO mouse (targeted disruption of the *Dio2* gene and genetically low D1 expression) has hepatic and renal D1 activities lower than those observed in wild-type mice (C57/BL6) but unexpectedly higher than those of the C3H mice. These mice present euthyroid serum T_3 levels and serum T_4 levels even more augmented than in the C3H. The serum TSH is increased, which could be important to maintain euthyroid serum T_3 concentrations. The double D1/D2KO mice are also able to maintain a normal serum T_3 level and their general health, growth, and reproductive capacity are seemingly

unimpaired (Galton *et al.* 2009). The authors underline the feature that D1 and D2 enzymes might not be essential to the maintenance of normal plasmatic T_3 levels in the rodent as long as the hypothalamic–pituitary–thyroid axis is intact. These alterations, however, might not perfectly reflect those putatively found in humans, because the rat thyroid is responsible for 50% of the circulating T_3, whereas humans depend more on peripheral deiodination, given that only 20% of the T_3 is derived from the thyroid gland.

Iodine is essential for thyroid hormone synthesis, and iodine deficiency leads a series of physiological adaptations in the hypothalamic–pituitary–thyroid axis in an attempt to maintain plasma and tissue T_3 in the normal range. The earliest thyroidal modification is a decrease in 3,5-diiodotyronine, with a consequent decrease in the thyroidal T_4, whereas thyroidal T_3 remains constant (Riesco *et al.* 1976). Indeed, elevated plasma TSH, associated with decreased serum T_4 and a virtually unchanged T_3, are the physiological hallmarks of moderate iodine deficiency as well as of the early phases of primary hypothyroidism. In both situations, however, the extrathyroidal changes are complex and involve a high degree of tissue specificity. It is observed that although D1 and D3 activity is unchanged in marginal iodine deficiency, D2 activity is markedly upregulated in D2-expressing tissues, thus increasing the proportion of T_3 formed locally and mitigating the decreases in tissue T_3 content (Larsen *et al.* 1981, Janssen *et al.* 1994, Schröder–van der Elst *et al.* 1998). Interestingly, however, increase in liver D1 activity has been observed in severe iodine-deficient rats under selenium supplementation (Arthur *et al.* 1991). Of note, studies in the D1KO mouse demonstrated that iodothyronines other than T_4 are the substrates for $5'$-deiodination by D1 enzyme, which releases iodine back into the circulation (Schneider *et al.* 2006). In the absence of D1, inactive and lesser iodothyronines escape deiodination and are excreted in the feces with the potential loss of the associated iodine. This scavenging function of D1 might be particularly important in the iodine deficiency setting (Galton *et al.* 2009).

Recently, attention has been turned to a potential role of D1 in the biosynthesis of thyronamines (3-iodothyronamine, 3-T_1AM, and thyronamine, T_0AM), a newly identified class of endogenous compounds that seem to be isozyme-specific substrates of deiodinases (Scanlan *et al.* 2004, Piehl *et al.* 2008, Scanlan 2009). These molecules are chemical derivatives of thyronines, the principal chemical form of T_4 that appears to antagonize the typical actions of thyroid hormones. It has been shown that the iodothyronamines have V_{max}/K_m values comparable to the corresponding iodothyronine, indicating that they would be as readily deiodinated as iodothyronines by the appropriate deiodinase isoenzyme (Piehl *et al.* 2008). Nevertheless, unlike T_4, T_4AM is not a substrate for D1 or D2 enzymes. Instead, T_4AM is readily deiodinated to $3,3',5'$-triiodothyronamide (rT_3AM) by D3, and rT_3AM can be further deiodinated to ultimately provide T_1AM. Using HepG2 cell lysates or mouse liver membrane fractions, D1 was able to use rT_3AM or $3',5'$-diiodothyronamine

($3',5'$-T_2AM) as substrates and both reactions were sensitive to PTU. On the other hand, T_1AM is the most efficiently processed thyronamine substrate using a sulfotransferase preparation from human liver, and the V_{max}/KM value for T_1AM compares to that of T_3, suggesting that similar to T_3, sulfation of T_1AM may be an important clearance mechanism for regulating free circulating levels (Piehl *et al.* 2008). The physiological role of thyronamines is uncertain, but pharmacological data show that a single-dose T_1AM administration *in vivo* induces intense hypothermia and bradycardia, leading to a hypometabolic state that may confer a potential neuroprotective benefit in cases of ischemic injury (Scanlan *et al.* 2004). Indeed, T_1AM treatment was found to reduce infarct volume by 40% in a middle cerebral artery occlusion stroke model in mice. Interestingly, the degree of neuroprotection afforded by T_1AM was correlated with the magnitude of T_1AM-induced hypothermia (Doyle *et al.* 2007). These findings indicate the existence of an exciting signaling pathway that leads to rapid physiological effects that are opposite to those produced by thyroid hormone excess (Scanlan 2009). Nevertheless, as pointed out by the authors, the precise relationship between T_1AM and thyroid hormone remains poorly understood, and there is currently no direct evidence for *in vivo* thyroid hormone-derived synthesis of thyronamines.

Role of type 1 deiodinase in human disease

DIO1 *polymorphisms*

As stated above, no cases of inherited D1 deficiency have been reported so far and, remarkably, no mutations have been identified in any of the deiodinase enzyme-encoding genes to date. In contrast, however, several genetic variations have been described in *DIO1* and *DIO2* genes, which may influence circulating or intracellular thyroid hormone levels (Peeters *et al.* 2006, Butler *et al.* 2010, Dora *et al.* 2010).

Two SNPs in the human *DIO1* gene, D1a-C/T (variation at the nucleotide position 785 of the D1 cDNA sequence – C785T) and D1b-A/G (variation at the position 1814 – A1814G), have been associated with changes in serum rT_3 levels (Peeters *et al.* 2003*a*). Each *T*-allele of D1a-T (frequency of 34%) was associated with an increase of $\sim$2 ng/dl in plasma rT_3 levels, whereas the less frequent G allele of D1b (10·3%) was associated with lower rT_3/T_4 and higher T_3/rT_3 plasma ratios. In the elderly, carriers of the *D1a-T* allele had higher serum-FT_4 and rT_3, lower T_3, and lower T_3/rT_3, whereas the *D1b-G* allele was associated with higher serum T_3 and T_3/rT_3 (de Jong *et al.* 2007). Consistently with a lower D1 activity for the *DIO1*-785T, a recent study has shown that the administration of T_3 to individuals harboring this variant was associated with enhanced potentiation of the effect of the antidepressant sertraline (Cooper-Kazaz *et al.* 2009). The genetic influence of these polymorphisms in healthy Danish twins has also been addressed and revealed that carriers of the *DIO1*-785T allele had 3·8% higher FT_4 and 14·3% higher rT_3

levels, resulting in a lower T_3/T_4 and T_3/rT_3 ratio and a higher rT_3/T_4 ratio. The D1b-A/G polymorphism, however, was not associated with changes in serum thyroid hormone levels (van der Deure *et al.* 2009). As both SNPs are located in the 3′-UTR, it has been speculated whether the mRNA stability would be compromised or affect mRNA folding, which is necessary for the incorporation of Sec in the catalytic center of the protein (Peeters *et al.* 2003*a*).

The D1a-C/T and D1b-A/G polymorphisms have also been associated with changes in free insulin–like growth factor 1 (IGF1) levels (Peeters *et al.* 2005*a*). Based on the data derived from the four haplotype alleles and corresponding serum thyroid hormone levels in two different populations, the authors assumed that the haplotype D1a-T/D1bA is associated with decreased D1 activity, whereas patients with the haplotype D1a-C/D1bG displays increased D1 levels. The D1a-T/D1bA haplotype was associated with higher levels of free IGF1 levels, which could serve as a tentative mechanism for normalization of D1 activity. Of note, this haplotype showed an allele dose effect on serum T_3 concentrations in elderly men (resulting in lower levels of T_3) but not in the population constituted by healthy blood donors.

Recently, a new polymorphism A/C located in intron 3 of the human *DIO1* gene has been described (Panicker *et al.* 2008). This polymorphism was associated with increased FT_3 and decreased FT_4 and rT_3 levels not only in patients receiving thyroid hormone replacement therapy but also in a large group of healthy individuals. Of interest, in both the groups, the former described that D1a-C/T SNP also leads to variations in T_3, FT_4, and rT_3 levels, although in a less pronounced fashion (Peeters *et al.* 2003*a*, de Jong *et al.* 2007, Panicker *et al.* 2008). The effect of the A/C polymorphism is consistent with the *C*-allele being associated with higher D1 enzymatic activity. Although the mechanism by which this polymorphism affects deiodinase function remains unknown, the authors estimate that it accounts for nearly 2% of genetic variance of FT_4 and 1·5% of FT_3.

Graves's hyperthyroidism and multinodular goiter

It is well established that hyperthyroid patients suffering from Graves' disease or multinodular toxic goiter have a disproportionate increase of serum T_3 as compared with the increase in serum T_4 (Larsen 1972, Nicoloff *et al.* 1972, Woeber 2006). In both diseases, thyroid hormone production is no longer targeted to physiological needs; instead, it is driven by a number of abnormalities. In Graves' disease, the abnormal generation of stimulating antibodies of TSH receptor is implicated (Davies *et al.* 2005, Laurberg *et al.* 2008), whereas in multinodular goiter, a constitutive activation of the thyroid follicular cells occurs (Krohn *et al.* 2005).

Thyroid hormone excess could be a result of either increased thyroidal T_3 production or elevated quantities of T_3 from peripheral T_4 to T_3 conversion. This central question was recently addressed by Laurberg *et al.* (2007) in untreated patients with Graves' disease or multinodular goiter. In agreement with earlier studies (Abuid & Larsen 1974), it was observed that patients treated only with PTU, a specific inhibitor of D1, presented a rapid and sustained fall in serum T_3 levels of ~57%, whereas those treated with a combination of PTU plus potassium iodine or sodium ipodate, which inhibits both D1 and D2 and several processes involved in thyroid hormone production and secretion respectively, present an additional fall of ~20%. Considering that the secretion of intrathyroidal and peripheral T_3 is selectively inhibited by PTU, the authors demonstrated that D1 deiodination has a crucial role in T_3 generation in these diseases. In fact, although thyroidal D1 contributes 6% of daily thyroidal normal T_3 production, this can increase to around 57% in patients with severe hyperthyroidism, suggesting that the major source of serum T_3 in hyperthyroid patients is the thyroid gland as a consequence of increased thyroidal D1 (Fig. 2). The remainder of the thyroidal T_3 production is derived from thyroglobulin, with a nearly doubled T_3 to T_4 ratio, plus fractional T_4 to T_3 conversion in the peripheral tissues. As
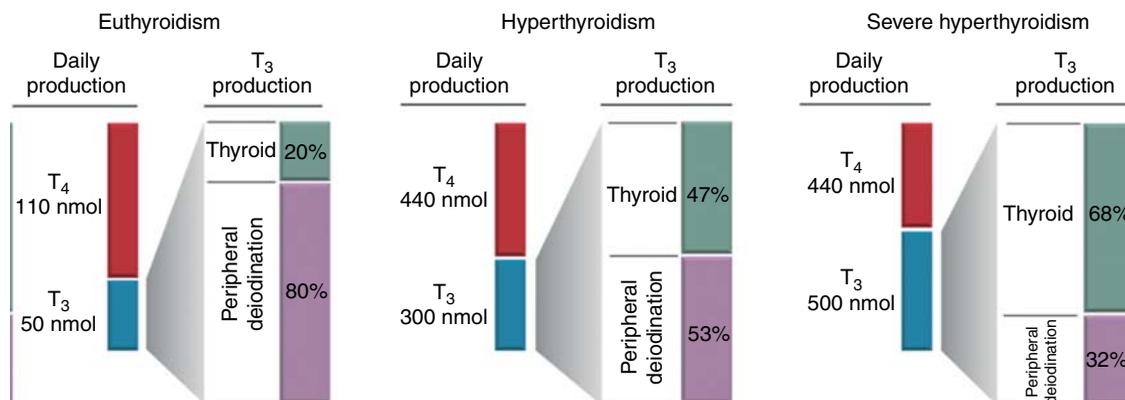
Figure 2 Schematic representation of the estimated sources of T_3 production in euthyroid and hyperthyroid state. The thyroidal contribution to serum T_3 levels increases in parallel with the disease severity, reaching nearly two-thirds of the total T_3 production in severe hyperthyroidism (derived from Laurberg *et al.* 2007).

liver and kidney D1 increases in the presence of excessive thyroid hormone levels, this enzyme is also responsible for the majority of the peripheral T_3 production (Maia *et al.* 2005, Laurberg *et al.* 2007). These observations support the choice of PTU as the preferred thionamide for therapy in severe hyperthyroidism or thyroid storm (Maia 2007). Nevertheless, methimazole is superior to PTU during chronic therapy (Nakamura *et al.* 2007). The reasons are the longer duration of methimazole action that favors better compliance and improves prognosis and the lower frequency of side effects compared with PTU. Moreover, the relatively low doses of PTU used in chronic therapy will not effectively inhibit D1.

The high thyroidal T_3 production might explain the pattern of persistently high serum T_3 with normal or low serum T_4 levels during treatment observed in a minority of patients with T_3-predominant Graves' disease. Recently, D1 and D2 activities were evaluated in samples of thyroid tissue from patients with T_3-predominant Graves' disease pretreated with methimazole before thyroidectomy (Ito *et al.* 2011). Intriguingly, not only an augmented activity of both enzymes but also a correlation between the thyroidal D2 activity and serum FT_3 to FT_4 ratio was observed, even more robust than that of thyroidal D1 activity.

Fasting and nonthyroidal illness syndrome

Fasting and severe illness induce profound changes in the thyroid hormone economy marked by decreases in serum T_3 and T_4 levels without a compensatory rise in the serum TSH level in both animal models and humans (Leonard *et al.* 1991, Nishikawa *et al.* 1998). Indeed, the decrease in the concentration of circulating T_3 relative to that of T_4 and an increase in rT_3 concentrations in fasting humans was one of the earliest indications that the peripheral metabolism of thyroid hormones could be modulated by physiological or physiopathological events (Portnay *et al.* 1974). Nevertheless, the complex physiopathological mechanisms responsible for these systemic changes remain poorly understood (Warner & Beckett 2010). Changes in deiodinases expression have been postulated to play important roles in the altered circulating levels of thyroid hormones in fasting and nonthyroidal illness syndrome (NTIS) (Debaveye *et al.* 2008, Kwakkel *et al.* 2009). Decrease in T_3 production could be explained by decreased levels of D1 and/or D2, whereas the elevation of rT_3 could be due to decreased activity of D1 and the increase in D3 activity, which determines increased hormone degradation (Peeters *et al.* 2003*b*, 2005*b*).

In rodents, fasting induces decrease in liver and pituitary D1 activities. However, it is not established whether this reduction is due to a direct effect of fasting on D1 activity or secondary to the decreased levels of serum thyroid hormones, which is also observed in this situation (St Germain & Galton 1985, O'Mara *et al.* 1993, Aceves *et al.* 2003). Interestingly, it has been demonstrated that leptin, an adipocyte-derived hormone that is diminished in food deprivation, modulates

the $5'$-deiodinases in different tissues depending on the energetic status (Cabanelas *et al.* 2006). Leptin was shown to exert direct peripheral effects on deiodinase activity, positively regulating liver, kidney, and pituitary D1 activity in fed animals (Cabanelas *et al.* 2006).

Results with leptin replacement in fasting, however, have produced contradictory results depending on the tissue analyzed. Some studies failed to demonstrate a decrease in hepatic D1 activity on food-restricted animals in rats treated with i.c.v. leptin injection (Ahima *et al.* 1996, Legradi *et al.* 1997, Cusin *et al.* 2000), whereas others showed that the decrease in thyroid D1 is not restored by leptin replacement. In the latter, the authors suggest that the diminished D1 activity could result from the increased levels of corticosterone observed in these animals (Araujo *et al.* 2009). Conversely, rats with high-fat-induced obesity presented increased D1 activity in the thyroid, liver, and kidney and higher rates of oxygen consumption and energy expenditure, without changes in the thyroid hormone circulating levels (Araujo *et al.* 2010). In starved humans, circulating T_3 concentrations decrease rapidly to about 50% of control and remain low for up to 3 weeks of fasting (Vignati *et al.* 1978, Kaptein *et al.* 1985, Rosenbaum *et al.* 2005). However, the sustained decrease in serum T_4 and T_3 could also be due to increased thyroid hormone inactivation by D3 enzyme, as recently reported in other pathological situations (Olivares *et al.* 2007, Simonides *et al.* 2008).

An entire set of data obtained from critically ill patients demonstrated that patients with more pronounced alterations in serum thyroid parameters have a significantly higher mortality rate and that rT_3 and T_3/rT_3 are prognostic factors for survival (Peeters *et al.* 2005*c*). Critically ill patients showed reduced hepatic D1 activity, which was negatively correlated with T_3 and rT_3 plasma levels. Interestingly, D1 activity in liver was lowest in patients who died of cardiovascular collapse and highest in patients who died of brain damage. Lower D1 activity was also observed in patients with acute renal failure and in those receiving inotropes, compared with those who did not require these treatments (Peeters *et al.* 2003*b*). In contrast, other studies found no differences in D1 activity measured in the subcutaneous adipose tissue in patients in intensive care units, suggesting that thyroid hormone bioavailability might be regulated in a tissue-specific way (Rodriguez-Perez *et al.* 2008).

Cytokines, such as IL1, IL6, TNFα, have been postulated as potential mediators of the alterations in thyroid function that occur during severe illness (Chopra *et al.* 1991, Boelen *et al.* 1993, Pekary *et al.* 1994). Studies in health volunteers demonstrated that a single dose of IL6 caused a transient decrease in serum T_3 and TSH (Torpy *et al.* 1998), changes that are characteristic of the NTIS. In hospitalized patients, there is also an inverse correlation between the serum IL6 and the T_3 concentrations (Boelen *et al.* 1993, 1995, Davies *et al.* 1996*a*). These proinflammatory molecules seem to inhibit the expression and function of D1 in human hepatocarcinoma

cells (HepG2; Jakobs *et al*. 2002), whereas studies on rat hepatocytes have demonstrated that IL1 and IL6 impair the T_3 induction of *D1* mRNA by a mechanism that involves a functional disruption of steroid receptor coactivator 1 (SRC-1)–thyroid hormone receptor interaction caused by competition between IL1 and T_3-stimulated transcriptional events for limiting quantities of SRC-1 (Yu & Koenig 2000, Jakobs *et al*. 2002). The T_3 inhibitory effect of IL1β was salvaged by coexpression of the nuclear SRC-1 but not by cAMP response element binding protein (Yu & Koenig 2006).

The effects of TNFα have been examined in hepatocytes and HepG2 cells with contradictory results. TNFα decreased the T_3-stimulated *D1* mRNA in HepG2 cells (Nagaya *et al*. 2000). In a second study in dispersed rat hepatocytes, IL1β and IL6 blocked the T_3 induction of *D1* mRNA and activity but TNFα had no effect on D1 expression (Yu & Koenig 2000). The contradictory effects observed could be due to differences in the experimental paradigms. Despite this, both studies suggest that a mechanism for acute decrease in D1 expression during illness could be competition for limited amounts of one or more transcription factors that are rate limiting for both cytokine- and T_3-dependent transcriptional events. In has been shown in *in vitro* studies that IL1β stimulates both D1 and D2 expression (Baur *et al*. 2000).

Human neoplasias

The balance between proliferation and differentiation is among the wide variety of biological events influenced by thyroid hormone and recent studies suggest that deiodinase enzymes might play an important role in the control of thyroid hormone metabolism and action during tumorigenesis. Studies focusing on *DIO1* and *DIO2* gene expression in benign and malignant thyroid tumors have demonstrated that D1 and D2 expression are diminished, whereas D3 is increased in tumoral tissue (Arnaldi *et al*. 2005, Meyer *et al*. 2007, Dentice *et al*. 2009).

Changes in D1 expression have been proposed as a marker of the epithelial follicular thyroid cell dedifferentiation (Schreck *et al*. 1994, Kohrle 1997, Meyer *et al*. 2007). Significant decreases in *D1* mRNA and activity levels were demonstrated in samples of papillary thyroid carcinoma (PTC) as compared with adjacent normal thyroid tissues (de Souza Meyer *et al*. 2005). These results were observed in all histological subtypes, especially in the classical form of PTC, as well as in the different clinical stages (Ambroziak *et al*. 2005, Arnaldi *et al*. 2005, de Souza Meyer *et al*. 2005). In contrast to PTC samples, D1 levels were normal or increased in follicular thyroid adenoma, follicular thyroid carcinoma (FTC), and Hürthle cells carcinoma (Arnaldi *et al*. 2005, de Souza Meyer *et al*. 2005). These findings illustrate the distinct D1 expression patterns in PTC and follicular neoplasias, thus suggesting that downregulation of D1 expression is an early event in thyroid cell dedifferentiation toward PTC.

Although earlier studies reported that D1 activity was absent in samples of anaplastic thyroid carcinoma (ATC; Schreck *et al*. 1994), more recent studies reported high levels of *D1* mRNA and activity in sample of a mixed anaplastic and Hürthle cell carcinoma (de Souza Meyer *et al*. 2005). Undifferentiated thyroid carcinomas are the end-stage forms of thyroid cancer and are believed to arise from papillary or follicular carcinomas. Based on the above observation, one could speculate that the lack of expression of this isoenzyme could be a marker of papillary origin.

Changes on D1 regulation were also documented in various thyroid cancer cells. Using cell lines of FTC (FTC-133 and FTC-238), Schreck *et al*. (1994) have demonstrated that D1 loses its responsiveness to TSH and T_3 stimuli, but not to RA, a component that regulates growth rates and differentiation of several cell types. Low basal D1 activity, which is markedly increased by RA, was described in these cell lines but neither basal nor RA-inducible D1 activity is detected in cell lines derived from ATC (HTh 74 and C 643) (Schreck *et al*. 1994, Schmutzler *et al*. 2004). Proliferations of FTC-133 and FTC-238 cells were decreased by all-trans RA. Pretreatment of FTC-133 with RA resulted in a reduced tumor growth in xenotransplantation experiments as compared with untreated control cells (Schmutzler *et al*. 2004). These studies indicate that the coexpression of D1 and RA receptors in differentiated thyroid carcinoma preserves its basal regulatory functions in contrast to less differentiated thyroid neoplasias.

Downregulation of D1 expression was also reported in other human neoplasias. Lower levels of *D1* mRNA were described in samples of renal clear cell carcinoma, the most frequent renal cancer (Pachucki *et al*. 2001). Interestingly, several variants of *DIO1* transcripts were found in this type of neoplasias, all of them underexpressed in tumor tissue as compared with normal renal tissue. These findings suggest a possible role of disturbed expression of splicing factors splicing factor-2/alternative splicing factor (SF2/ASF) and heterogeneous ribonucleoprotein A1 (hnRNPA1) in samples of human renal cancer (Piekielko-Witkowska *et al*. 2009). Low levels of D1 expression were also demonstrated in liver carcinoma when compared with normal tissue (Sabatino *et al*. 2000). In addition, HepG2 cells exhibit high levels of D1 activity, which is stimulated by RA or T_3 (Schreck *et al*. 1994, Toyoda *et al*. 1995). Hemangioma tissue presents nearly undetectable D1 activity compared with healthy liver tissue (Kornasiewicz *et al*. 2010). In addition, decreased D1 activity was described in pulmonary squamous cell cancer, adeno-carcinoma (Wawrzynska *et al*. 2003), and prostate cancer (Dutkiewicz *et al*. 1995).

On other hand, mammary cancer induced in Sprague–Dawley mice with *N*-methyl-*N*-nitrourea had twice as much D1 activity when compared with normal, nonlactating tissue (Macejova *et al*. 2001). Interestingly, D1 levels were higher in 2- to 4-month-old tumors when compared with 6-month-old tumors (Macejova *et al*. 2001), characterizing a loss of D1 expression with tumor progression. Besides, the MCF-7 cells

(an ovarian hormone–dependent cell line derived from mammary cancer) also present D1 regulated by RA, although it does not respond to T_3 or isoproterenol (Garcia–Solis & Aceves 2003). Similar to that observed in other cells lines, no detectable activity of D1 is present in less differentiated mammary cell lines (MDA–MB–231), either in basal conditions or under different treatments (Garcia–Solis & Aceves 2003). Human breast cancer tissue expresses high levels of D1 activity and mRNA, a profile unlike most other human tumors of epithelial origin (Debski *et al.* 2007).

D1 activity is found in normal pituitary as well as human pituitary adenomas. Although a wide variation on D1 activity among the tumor histological subtypes has been reported, the highest activities were seen in the thyrotroph and lactotroph adenomas. Approximately, half of these tumors presented D1 activities several-fold greater than any of the normal pituitary samples (Baur *et al.* 2002, Tannahill *et al.* 2002).

In summary, except for the follicular thyroid lesions and tumors originating in the mammary gland, D1 expression is decreased in the majority of human neoplasias of epithelial origin. Nevertheless, whether it is part or consequence of the neoplastic process still remains to be clarified. A possible explanation for the decreased D1 expression could be loss of physiological response to T_3 due to aberrant expression of TRs or a high frequency of TR mutations, as reported in several human tumors (Cheng *et al.* 2010). One can also speculate that it is a result of the low intracellular T_3 level secondary to D3 overexpression (Dentice *et al.* 2009). Nevertheless, because tumor tissue may represent a more homogeneous population of cells than normal tissue, we cannot rule out that changes in expression could also be secondary to a difference in the cell types, rather than a change in expression level in cancer cell itself.

Conclusion

Since the identification, several decades ago, of the type 1 deiodinase, a considerable amount of research has been carried out in an attempt to extend our knowledge of its molecular and biochemical properties as well as our understanding of its role in human thyroid hormone metabolism. This enzyme is a member of a family of oxidoreductases that contains the rare amino acid Sec in its active site and D1-catalyzed reaction follows ping-pong kinetics with two substrates: the first being the iodothyronine and the second being an endogenous intracellular thiol cofactor. Besides its capacity of outer-ring deiodination, which contributes to daily T_3 production, D1 also catalyzes the iodine removal by inner-ring deiodination inactivating thyroid hormones. Indeed, the remarkable D1 preference for rT_3 as the enzymatic outer-ring deiodination substrate as well as the deiodination of sulfated iodothyronines argues for a major scavenging function of this enzyme, namely the recovery of the trace element iodine from inactive hormone metabolites to be reutilized for thyroid hormone synthesis.

This functional role can be particularly relevant in a setting of iodine deficiency.

A multiplicity of hormonal, nutritional, and developmental factors modulates D1 expression. Thyroid hormone is the most important physiological upregulator of D1 expression, and hypothyroidism is associated with low levels of *D1* mRNA and activity. D1 activity is also susceptible to selenium deficiency, and selenium-deficient individuals have mildly elevated serum T_4 and T_4 to T_3 ratios, but normal TSH.

Besides its role in human physiological control of peripheral thyroid hormone metabolism, alterations in D1 expression and activity have also been described in human diseases. Polymorphisms in *DIO1* gene have been associated with changes on thyroid hormone levels, whereas augmented thyroidal D1-catalyzed T_3 generation seems to play a major role in T_3 overproduction observed in Graves' disease and multinodular goiter. Decreased D1 expression has been implicated in the thyroid hormone changes observed in fasting and NTIS, whereas disturbed expression and regulation of this enzyme is reported in human neoplasias.

Nonetheless, there are still significant gaps in our knowledge of D1 function in human physiology. The endogenous cofactor is as yet unidentified, which may jeopardize conclusions obtained from *in vitro* studies using artificial conditions. The relative role of peripheral D1-catalyzed T_3 production in human euthyroid state or in pathological processes, such as NTIS, is still a matter of debate. D1 expression is decreased in the majority of human tumors of epithelial origin but whether this occurs as an attempt to counter-regulate the proliferate state or contribute to the dedifferentiation process to the neoplasm remains to be determined. Further studies in the exciting field of thyroid hormone metabolism are warranted to unravel these unanswered questions.

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