Deiodinases: implications of the local control of thyroid hormone action

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Deiodinases: implications of the local control of thyroid hormone action

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The deiodinases have not yet been identified, though the clinical implications of several polymorphisms are under investigation (23–27). Understanding the signaling pathways these enzymes are involved with could have therapeutic utility for all of these clinical settings. However, the real excitement in this field stems from the discoveries that deiodinases can participate in both the bile acid and Hedgehog signaling cascades (Figure 4) (28, 29).

Nonstandard abbreviations used: D1, type I iodothyronine deiodinase; Dio3, type III iodothyronine deiodinase; D1KO mice, Dio1-knockout mice; GPBAR1, G protein–coupled bile acid receptor 1; PTU, propylthiouracil; T3, 3,5,3′-triiodothyronine; T4, thyroxine; TR, thyroid hormone receptor; TRH, TSH-releasing hormone; TSH, thyroid-stimulating hormone; UCP-1, uncoupling protein 1; VDY, von Hippel–Lindau protein–interacting deubiquitinating enzyme; WSB-1, WD repeat and SOCS box–containing 1.

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As a result of this linkage, novel roles for these enzymes in the realms of metabolic control and developmental biology have become apparent.

Deiodinases in thyroid homeostasis

Serum T3 levels are relatively constant in healthy subjects, a finding that is not surprising considering that T3 is such a pleiotropic molecule. The deiodinase signaling pathways in peripheral tissues constitute a major determinant of plasma T3 level, since all T3 generated in the cytoplasm eventually exits the cell, unless of course it is metabolized. In fact, extrathyroidal pathways have been estimated to contribute about 80% of T3 produced daily in healthy subjects (30). The D2 pathway, rather than the D1 pathway, is thought to be the major source of extrathyroidal T3 production in humans based on a number of prior clinical studies (31, 32). This conclusion is supported by in vitro modeling data, in which T3 production via either the D1 or D2 pathways in the same cell types was compared at substrate concentrations spanning the hypothyroid to thyrotoxic range (33). In contrast, D1 activity is increased in patients with hyperthyroidism so that this pathway becomes the predominant extrathyroidal source of T3 (34). This D1 predominance lies the rapid fall in serum T3 concentrations that occurs in patients with hyperthyroidism when serum T4 concentrations increase, expression of type III iodothyronine deiodinase (Dio3), which encodes D3, is upregulated, increasing T3 clearance, while expression of Dio2, which encodes D2, is modestly downregulated, decreasing T3 production. Conversely, if serum T3 concentrations were to fall, downregulation of the D3 pathway would decrease the clearance of T3. The homeostatic role of D1 is less intuitive, as Dio1 is T3 responsive (35). Given that D1 can deiodinate the phenolic and tyrosil rings of T4 with equal facility, D1 in effect activates only 1 of every 2 molecules of T4. Thus, D1's homeostatic function may be to siphon T4 away from the D2 pathway, therefore providing some degree of protection against the development of hyperthyroidism when serum T4 concentrations increase (Table 1).

Another D2-mediated regulatory mechanism relevant to T3 homeostasis is covalent attachment to the approximately 8-kDa protein ubiquitin, which inactivates the enzyme (36). Like other ubiquitinated proteins, D2 is degraded in the large protease complexes known as proteasomes (37), but D2 can also be reacti-vated by von Hippel–Lindau protein–interacting deubiquitinating enzymes 1 and 2 (VDU1 and VDU2, respectively) (Figure 3) (38). D2 ubiquitination accelerates in proportion to T4 concentration, creating a feedback loop controlling D2-mediated T3 production (36, 37). Therefore, if serum T4 concentrations fall, activation of the D2 pathway compensates, at least in part, for the lowered substrate concentration by increasing the relative proportion of T4 converted to T3 (Table 1).

Insights from deiodinase-deficient mouse models

Insight as to the importance of the deiodinase-based homeostatic mechanisms for the maintenance of serum T3 concentrations has been gained from studies of genetically modified mice (Table 2) (39). Four mouse models have been described with varying deficiencies in the activating deiodinases: mice with targeted disruption of Dio1 (D1KO mice) (40); mice with targeted disrup-
The review of the Dio2 gene (D2KO mice) (41); C3H mice, which have genetically low levels of D1 (42, 43); and D2KO mice backcrossed into a C3H background (C3H/D2KO mice) (44). Remarkably, each of these animals has a normal serum T3 concentration and an increased serum T4 concentration. Clearly, potent compensatory mechanisms for maintaining serum T3 must exist, but what are they? One component of this response must be that the high serum T4 concentrations provide sufficient substrate to compensate for the partial losses of activating deiodinases. The elevations in serum T4 concentration may result from increased thyroidal secretion and/or decreased clearance, but in either case it is fascinating that the hypothalamic-pituitary-thyroid axis could be wired such that adjustments in serum T4 concentrations are made in order to maintain serum T3 concentrations.

Another likely component of the T3-maintenance response in these animal models could be increased thyroidal T3 secretion due to increased thyroid-stimulating hormone (TSH) levels. TSH is released from thyrotroph cells in the anterior pituitary gland, and its role is to stimulate virtually every aspect of thyroid hormone biosynthesis and secretion. In the absence of TSH, thyroidal activity falls and secondary hypothyroidism ensues. In fact, both the D2KO and C3H/D2KO models feature an elevation in serum TSH concentrations. It must be noted that serum TSH concentrations are normal in C3H and D1KO mice in spite of sizeable elevations in serum T4. In these cases, the D2 pathway may play a more prominent role in the maintenance of serum T3 concentration.

TSH release is under negative feedback regulation by thyroid hormone at the pituitary and hypothalamic levels, the latter involving suppression of TSH-releasing hormone (TRH) from paraventricular neurons. Given that T3 is the active form of thyroid hormone, it is not surprising that a negative feedback relationship exists between plasma T3 and TSH release. However, the fact that TSH release is also suppressed by plasma T4 may seem surprising, given that the latter is thought to be a prohormone (45). Mechanistically, fluctuations in serum T4 are transduced in pituitary thyrotrophs by the D2 pathway (46). The fact that the set point for TSH secretion depends on both serum T3 and T3 generated by D2 in the thyrotrophs can explain why TSH rises during iodine deficiency and mild hypothyroidism, situations in which serum T4 concentrations fall before there is any fall in serum T3 concentrations (14, 47).

Given the importance of thyrotroph D2 in TSH regulation, one would predict that D2KO animals would have an increased set point for TSH secretion, and indeed, serum TSH concentrations are 2 times higher than in normal mice (41). Given that D1 is not expressed in thyrotrophs, the reasons that D1KO mice have normal TSH concentrations in the face of high serum T4 and normal serum T3 concentrations are less clear, since this combination might be expected to suppress TSH release. One hypothesis is that the feedback effect of T4 on TSH release varies depending on serum T4 concentration, becoming less effective as serum T4 concentrations increase (Figure 3). Such a relationship has in fact been demonstrated in cultured wild-type thyro-
trophs, in which D2-mediated T3 production increases approximately 5-fold when free T4 in the medium is elevated from hypothyroid to euthyroid concentrations (from 1 to 20 pM) but only increases approximately 2-fold during the transition into the hyperthyroid range (from 20 to 400 pM) (46). Given that these concentrations of T4 are well below the $K_m$ (T4) for D2, which is approximately 1 nM, the likely explanation for the asymptotic relationship between T4 substrate and T3 production is ubiquitination of D2, which accelerates as serum T4 concentrations increase.

The knowledge gained from these animal models of deiodinase deficiency could ultimately help explain the phenotype of affected individuals in 2 families with inherited mutations in the gene for the selenocysteine insertion sequence–binding protein 2 (SBP-2), a protein important for the synthesis of selenoproteins, including the deiodinases (48). Deficiencies in all 3 deiodinases would be predicted to occur in these subjects, and indeed D2 activity is low in cultured fibroblasts. The functional characterization of these patients with respect to the deiodinases is not complete, and thus it is premature to discuss the mechanisms that underlie their thyroid phenotype. Nevertheless, it is striking that serum TSH concentrations and serum T4 concentrations are both high in affected individuals, reminiscent of the mouse models of activating deiodinase deficiency (48).

**Thyroid hormone homeostasis in illness**

Life-threatening trauma, major surgery, and critical illness are associated with a well-known pattern of decreased pituitary-thyroid function, sometimes referred to as the *low T3 syndrome*. These patients have low serum T3 concentrations, which are inversely related to the severity of their illness, and eventually develop low serum T4 and TSH concentrations (49–51). Whether these changes represent physiologic compensation for the illness or a pathological state is a long-standing controversy (52), but the fact that the changes can occur in a matter of hours indicates a profound alteration of thyroid economy.

**Table 1**

<table>
<thead>
<tr>
<th>Human iodothyronine selenodeiodinases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td><strong>Biochemical properties</strong></td>
</tr>
<tr>
<td>Molecular weight of monomer (Da)</td>
</tr>
<tr>
<td>Preferred substrates (position)</td>
</tr>
<tr>
<td>$K_m$ (apparent) (M)</td>
</tr>
<tr>
<td>Half-life</td>
</tr>
<tr>
<td>Subcellular location</td>
</tr>
<tr>
<td><strong>Susceptibility to inhibitors</strong></td>
</tr>
<tr>
<td>PTU</td>
</tr>
<tr>
<td>Amlodiarone/metabolites</td>
</tr>
<tr>
<td><strong>Tissues with high activity</strong></td>
</tr>
<tr>
<td><strong>Response to elevated T3 and T4</strong></td>
</tr>
<tr>
<td>Transcriptional</td>
</tr>
<tr>
<td>Posttranslational</td>
</tr>
<tr>
<td><strong>Physiological regulation</strong></td>
</tr>
<tr>
<td>Induction</td>
</tr>
<tr>
<td>Repression</td>
</tr>
<tr>
<td><strong>Physiological role</strong></td>
</tr>
<tr>
<td>Clearance of rT3 and T3S</td>
</tr>
<tr>
<td><strong>Role in diseases</strong></td>
</tr>
</tbody>
</table>

Detailed deiodinase properties can be obtained in previously published reviews (4–7, 11). Up and down arrows indicate increases and decreases, respectively; the number of arrows corresponds with the intensity of the change. aFGF, acidic FGF; bFGF, basic FGF; rT3, reverse T3; T3S, triiodothyronine sulfate.
that *Dio1* is a gene highly responsive to T3, and thus the low D1 activities measured in these animals could be an effect of rather than a cause of the low T3 syndrome (54). Furthermore, the D2 pathway rather than the D1 pathway is the predominant source of serum T3 in humans, and so these D1 data may not directly apply in patients. In fact, it has been documented that skeletal muscle samples from critically ill patients obtained within minutes of death do not have D2 activity. Remarkably, these patients exhibited ectopic induction of D3 activity in liver and skeletal muscle samples, suggesting that increased thyroid hormone catabolism may be an additional component of the syndrome (55).

While changes in peripheral deiodination may be necessary for the pathogenesis of the syndrome, they are probably not sufficient to cause it. Given the remarkable capacity of the hypothalamic-pituitary-thyroid axis to compensate for decreases in T3 production in peripheral tissues, as demonstrated in the deiodinase-deficient mice, central hypothyroidism must also be part of the syndrome (56). TSH secretion is decreased in critically ill subjects, and continuous infusion of TRH has been shown to strikingly increase serum T4 and T3 concentrations (57). The molecular determinants of central hypothyroidism in these patients are not well characterized. While dopamine and glucocorticoids play a suppressive role with respect to TSH (58), leptin administration leads to increases in serum TSH, T4, and leptin administration leads to increases in serum TSH, T4, and T3 concentrations in fasting rats (59) and humans (60). Another pathway that could be involved in the suppression of TSH secretion is the NF-kB cascade, which upregulates D2 expression in the medial basal hypothalamus of rats following LPS injection (61, 62), though it remains speculative whether this induction of D2 leads to local thyrotoxicosis and thus decreased TRH secretion. Ultimately, it seems that the low T3 syndrome does involve changes in peripheral deiodination but also requires a form of central hypothyroidism in which the peripheral alterations in thyroid hormone metabolism are not compensated as they would be in healthy subjects or in the mice with deiodinase deficiencies.

**D2 control of energy expenditure**

While deiodinase activities change in homeostatic ways in response to fluctuations in serum concentrations of T3 and T4, these enzymes are also directly regulated via a wide variety of intracellular signals not obviously related to thyroid hormones. The first evidence that primary changes in deiodinase activity elicit downstream effects in response to nonthyroidal signals came from studies of brown adipose tissue in rodents. This tissue is the major site of adaptive thermogenesis in rodents, with heat being generated as a result of the actions of uncoupling protein 1 (UCP-1) (63). Cold-induced thermogenesis in brown adipose tissue has been shown to depend upon the cyclic AMP–mediated acceleration of D2-catalyzed T3 production (64), which in turn leads to the induction of T3-responsive thermogenic genes, including *UCP-1* (Figure 4). In spite of the D2-mediated increase in nuclear T3 levels (65), serum T3 concentrations do not change, indicating that D2 has a tissue-specific metabolic action. Without this action, brown adipose tissue thermogenesis is impaired, and D2KO mice survive in the cold only by shivering, a behavior not normally seen in small mammals (66, 67).

That the action of D2 has relevance for metabolism beyond its role in cold-induced thermogenesis was recently established with the discovery that bile acids can confer resistance to diet-induced obesity in mice via upregulation of D2 expression in brown adipose tissue (29). In this tissue, binding of bile acids to the plasma membrane G protein–coupled bile acid receptor 1 (Gpbar1, also known as Tgr5) triggers an increase in cyclic AMP formation, and, subsequently, D2 expression. In normal mice fed a high-fat diet supplemented with bile acids, oxygen consumption increased and the mice did not gain weight or become as insulin resistant as mice fed the high-fat diet alone. However, this effect is lost in D2KO mice. It is noteworthy that D2 is overexpressed in 2 other rodent models of resistance to diet-induced obesity. *Ucp-1*–knockout mice are paradoxically lean (68) and have ectopic expression of D2 in their white fat while double liver X receptor (LXR) knockout mice...
express D2 ectopically in the liver (69). If the ectopic expression of D2 in these animals results in tissue-specific thyrotoxicosis, as is suggested by gene expression profiling in the case of the LXR double-knockout mice, this would certainly support the concept that the D2 signaling pathway increases energy expenditure.

It has been assumed that the D2 pathway is more important for thermogenesis during infancy than in adulthood, based on the observation that the mass of brown adipose tissue in humans peaks at the time of birth (70–72). However, adults retain enough brown adipocytes such that brown fat mass increases in high catecholamine states, as evidenced in patients with pheochromocytoma (73). These neuroendocrine tumors secrete catecholamines, which drive brown fat growth via increases in adipocyte cyclic AMP production. In fact, even normal adults may have more brown adipose than once thought, as studies utilizing 2-deoxy-2-[F-18]fluoro-d-glucose (FDG) in PET scans have indicated the presence of brown adipose in the neck (74, 75). While histologic correlation for these supraventricular areas of FDG uptake remains to be performed, it has been demonstrated that this uptake can be reduced or eliminated when subjects are studied in a setting where cold stress is eliminated (76).

Another potential site where the bile acid/GPBAR1/D2 pathway may affect energy expenditure in adults is in skeletal muscle, and the pathway has been shown to be operant in human skeletal myocytes in culture (29).

While the link between the D2 pathway and energy expenditure seems clear, it must be remembered that the identities of the T3-responsive genes that most directly lead to increases in energy expenditure remain to be determined. Identifying these critical genes is an important goal since thyroid hormone is one of the few known truly potent stimulators of the metabolic rate; indeed, energy expenditure is several-fold higher in hyperthyroid as compared with hypothyroid patients (77). The cellular mechanisms by which T3 increases energy expenditure are thought to include increased mitochondrial uncoupling, as this effect has been demonstrated in both the skeletal mus-

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**Figure 4**

Pathways regulating D2 expression and thyroid hormone signaling. In D2-expressing cells, such as brown adipocytes, stimulation of D2 expression increases local T3 production, resulting in increased saturation of T3 receptors. This increase can be mediated by norepinephrine (NE) stimulation of β-adrenergic receptors (βARs), such as occurs during cold stimulation, or by bile acid–mediated (BA–mediated) stimulation of GPBAR1 (also known as TGR5). Both of these pathways activate cAMP production and stimulate Dio2 transcription. In brown fat, cAMP also promotes VDU1 expression, amplifying D2 induction via deubiquitination. Other signaling pathways can decrease D2 activity, resulting in relative hypothyroidism. For example, the Hedgehog cascade decreases D2 activity by promoting WSB-1 expression and thus D2 ubiquitination, presumably via the Gli cascade. rT3, reverse T3; SHH, sonic hedgehog.

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**Table 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>D1KO</th>
<th>D2KO</th>
<th>D3KO</th>
<th>C3H</th>
<th>C3H/D2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid function tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum T4 level</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Serum T3 level</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum TSH level</td>
<td>Normal</td>
<td>Increased</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>Euthyroid</td>
<td>Euthyroid</td>
<td>Hypothyroid</td>
<td>Euthyroid</td>
<td>Euthyroid</td>
</tr>
<tr>
<td>Tissue specific</td>
<td>Not reported</td>
<td>Mild cold intolerance, hearing impairment</td>
<td>Central hypothyroidism</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Reproductive capacity</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Table was compiled based on data from previous reports (40, 41, 66, 90, 92).
local of mildly thyrotrophic human volunteers (78) and in hepatocytes of thyrotrophic rats (79). However, in neither case has a clear link to uncoupling proteins been established. Another general mechanism by which T3 has been reported to increase energy expenditure is via acceleration of the turnover of ATP-utilizing enzymes. Several candidate genes have been implicated, including those coding for Na+/K+ ATPase (80, 81) and sarcoplasmic endoplasmic reticulum Ca2+ ATPase (82, 83), among others (84–86).

Local control of thyroid hormone action during development

Thyroid hormone has well-known important developmental functions (87, 88). Serum thyroid hormone concentrations are generally low during development, and the contrast between serum and tissue T3 content afforded by the deiodinases is thus particularly critical for developing structures (39, 87). Signaling via thyroid hormone is tightly regulated both spatially and temporally via the expression pattern of deiodinases. The thyroid hormone-inactivating D3 pathway is highly stimulated during development, with a tissue distribution much broader than that in adults. The expression pattern of D3 limits thyroid hormone signaling locally in developing structures and also systemically by lowering serum T3 concentrations. In some tissues, the timing of D3 expression has been shown to be critical, e.g., T3-induced proliferation of retinal ciliary marginal zone cells in Xenopus laevis occurs preferentially in ventral cells because dorsal cells express D3 (89). This spatial asymmetry allows for proper rotation of the retina during development. Proper D3 expression is also critical for the development of the hypothalamic-pituitary-thyroid axis itself, as evidenced by the observations that mice with targeted disruption of the Dio3 gene (D3KO mice) have central hypothyroidism after having high serum T3 concentrations late in embryonic life and for the first 10 days after birth (90). The regulatory mechanisms underlying the developmental expression of Dio3 remain a subject of active interest; notably, the morphogen TGF-β has been found to be a potent stimulant of Dio3 transcription (91).

The expression of Dio2 is more limited during development. Bursts of D2 activity occur in some tissues, allowing for increased thyroid hormone signaling in both spatially and temporally specific patterns. For example, there is a 3-day peak of Dio2 expression and activity in the cochlea of mice from postnatal days 7–10; if absent, mice are severely hearing impaired (92, 93). Dio2 mRNA is localized to structures that give rise to the bony labyrinth whereas T3 nuclear receptors are limited to the sensory epithelium, suggesting a paracrine pathway of D2-mediated T3 production and action in cochlear development.

The changes in deiodinase activity seen in the developing retina and cochlea are due to changes in Dio2 and Dio3 transcription. In contrast, in the tibial growth plate of developing chickens, the critical regulatory events occur posttranslationally (28). In these animals, ubiquitination of D2, and thus thyroid hormone signaling, is under the control of the Hedgehog signaling cascade. In response to Hedgehog signaling, the D2-specific ubiquitin ligase WD repeat and SOCS box-containing 1 (WSB-1) is induced in perichondrial cells, thus accelerating D2 ubiquitination (Figure 4). The resulting decrease in D2 activity is thought to contribute to the Hedgehog induction of parathyroid hormone-related peptide (PTHrP). The link between D2 activity and PTHrP has been further substantiated by studies showing that pharmacologic acceleration of D2 ubiquitination via non-Hedgehog pathways also results in induction of this peptide (28).

By linking Hedgehog signaling with thyroid hormone action, WSB-1/D2 may play an important, previously unrecognized developmental role in cells or microenvironments where both Hedgehog and T3 have regulatory effects. For example, continuous Hedgehog signaling promotes the proliferation of oligodendrocyte precursor cells (94) whereas T3 favors differentiation of these cells (95, 96). Because astrocytes are known to respond to Hedgehog and to have D2 activity (97, 98), one mechanism for the proliferative effect of Hedgehog could be WSB-1–mediated downregulation of astrocyte T3 production, which would help sustain a microenvironment of relative hypothyroidism. On the other hand, WSB-1 may play a homeostatic role in some settings, for example, in X. laevis intestine during metamorphosis, where D2 is expressed and Hedgehog signaling is induced by T3 (99). In this case, a negative feedback loop could exist where WSB-1–mediated D2 ubiquitination could be induced as a result of D2-catalyzed T4-to-T3 conversion.

Final remarks

From a broad perspective, deiodination of iodothyronines can be seen as an example of a paradigm in which hormones are activated or inactivated in a controlled fashion in specific extraglandular tissues. The deiodinases thus play a role analogous to that of 5α-reductase and P450 aromatase in sex steroid metabolism and of 11β-hydroxysteroid dehydrogenase in glucocorticoid metabolism. The breadth of actions of these enzymes are only now being recognized; compared with the situation with the steroid metabolizing enzymes, for which multiple antagonist drugs are in widespread clinical use, drug development for the control of deiodination is in its infancy.

The therapeutic potential is both obvious and intriguing: if the D2 pathway can be harnessed pharmacologically, the resulting control of energy expenditure may be useful in the treatment of obesity, type 2 diabetes, and the metabolic syndrome.

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