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Regulation of Type 1 Iodothyronine Deiodinase in Health and Disease

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The major physiologic function of type 1 iodothyronine deiodinase (D1) is to produce triiodothyronine (T_3) for the plasma. D1 activity is regulated by numerous factors, perhaps the most important of which in human pathophysiology is T_3. T_3 induces D1 expression, contributing to the T_3 excess commonly found in hyperthyroidism. Cytokines, nutritional status, sex steroids, and other factors also regulate D1 activity, although different organs often show different responses. Numerous homeostatic mechanisms can counterbalance isolated changes in D1 expression, such as the genetically decreased expression in C3H/He mice. Two relatively commonly used drugs, propylthiouracil and amiodarone, inhibit D1, which can have substantial effects on circulating thyroid hormone levels. Overall, many factors interact in complex ways to establish D1 levels, contributing to the circulating concentrations of thyroxine (T_4) and T_3.

Introduction

THE MAJOR PHYSIOLOGIC function of type 1 iodothyronine deiodinase (D1) is to produce triiodothyronine (T_3) for the plasma. However, other sources (D2 and direct thyroidal secretion) also contribute to the circulating T_3. In humans, it has not been possible to quantify the percentage of plasma T_3 specifically attributable to D1. D1 is expressed primarily in the liver, kidney, thyroid and pituitary. It also is expressed at low levels in numerous other tissues, such as (in the rat) intestine, placenta, lactating mammary gland and central nervous system. In contrast to the rat, humans do not express D1 in the central nervous system.

D1 Ontogeny

D1 expression during ontogeny has been investigated in several species. Although the developmental patterns of expression have been described, the mechanisms that control expression during development remain to be elucidated. In the developing chick, hepatic D1 activity is low at embryologic day 15 (E15) and gradually increases thereafter until hatching (1–3). D1 mRNA levels did not show a consistent pattern in one study (1), so the basis for the increase in D1 activity over time is not clear. It is interesting to note that plasma T_3 levels increase only modestly during the early stages of the D1 increase, probably due to a simultaneous increase in D3 and/or because of D1-catalyzed inner ring deiodination.

In the rat, liver and kidney D1 mRNA and enzyme activity are low at E19–20 but rise gradually from postnatal day 1 (P1) to P10, increasing further at adulthood (4). The pattern for intestine D1 is similar, except that expression drops dramatically after P10. Pituitary and thyroid D1 increase gradually from P12 to adulthood.

In humans, D1 ontogeny has been studied only in liver (5). Using postmortem tissues from fetuses of 20 weeks' gestation, preterm infants of 27–32 weeks' gestation and term infants who survived up to 39 weeks postnatally, D1 activity did not show a clear dependence on age. D1 activity in these postmortem samples was approximately 25% of that measured in presumably healthy adult transplant donor livers. The necessity of studying postmortem tissues from sick fetuses and infants limits the conclusions, but the relatively prominent fetal hepatic D1 activity contrasts with fetal rat liver yet is similar to ontogeny in chick liver. Also similar to the chick, human fetal serum T_3 is low despite the clear expression of D1. These same human fetal livers robustly expressed D3 (in contrast to adult liver), which presumably helps prevent the accumulation of circulating T_3.

Regulation of D1 by T_3

Thyroid hormone induces transcription of the human, rat and mouse D1 (*Dio1*) genes (6,7), although this regulation is not universal because it is absent in the house musk shrew (8). In humans, therefore, one would expect hyperthyroidism to induce D1, increasing relative T_3 production. Indeed, hyperthyroidism is commonly associated with a greater elevation in T_3 than T_4, and D1 activity was elevated approximately threefold in a group of seven Graves' disease thyroid glands compared to five normal thyroids (9). Furthermore, plasma

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T_3 levels appear to be decreased by the D1 inhibitor propylthiouracil (PTU) more substantially in hyperthyroid patients than in normal individuals, suggesting that D1 makes a larger contribution to circulating T_3 in hyperthyroidism than in the euthyroid state (discussed in Bianco et al. [10]).

The human *Dio1* promoter contains two functional T_3 response elements (TREs) (11). The more distal TRE has the classic structure of an AGGTCA-like direct repeat separated by a 4-bp spacer. As expected, this TRE binds well to heterodimers of retinoid X receptors (RXRs) and T_3 receptors (TRs). The proximal TRE is quite unusual and has the structure of a direct repeat separated by 10 bp. The binding sites are octamers (YYRGGTCA) rather than hexamers, and this TRE binds TR monomers and homodimers, but does not bind RXR-TR heterodimers. It is the first example of a naturally occurring TRE that appears to function independently of RXR. Although the rat and mouse *Dio1* genes also are induced by T_3, the TREs have yet to be identified.

There are two TR genes (*Thra* and *Thrb*), and the major functional receptors derived from these genes are denoted TRα_1 and TRβ_1. Liver expresses substantially more TRβ_1 than TRα_1. As is found for many hepatic proteins, the expression of TRβ_1 is not uniform, but is zonated. In rodents, TRβ_1 expression is highest close to the central veins, and D1 expression probably is highest in the same regions (12). T_3 induction of hepatic and renal D1 is severely blunted in TRβ_1-null mice, but is normal in TRα_1-null mice (13). Mice that are null for both TRs have no detectable hepatic D1, demonstrating an ancillary role for TRα_1 in the regulation of *Dio1* and indicating that TRs (TRβ_1 or TRα_1) are required for the basal expression of hepatic D1.

Thyroid D1

In addition to being induced by T_3, thyroid gland D1 activity is induced by thyrotropin (TSH) (14–16) and cyclic adenosine monophosphate (cAMP) (17), the major mediator of TSH signaling. The rat thyroid cell line FRTL5 often is used as a model system for studying thyrocyte biology. In FRTL5 cells, TSH and T_3 also increased D1 mRNA (17). Similar to the effect of TSH, immunoglobulin G from patients with Graves' disease induced D1 (18). If this effect occurs in humans with Graves' disease, it could contribute to the relatively large elevation in serum T_3. The mechanism of the TSH and cAMP effect is unknown, but it does require new protein synthesis and is somewhat slower than the response to T_3, suggesting that it may be indirect. The T_3 response is a direct transcriptional effect, although as noted above, TREs have yet to be identified in the rat and mouse *Dio1* genes.

Effects of Drugs on D1 Activity

Two clinically important drugs have substantial effects on D1 activity. Although propylthiouracil (PTU) is used to treat hyperthyroidism primarily because it inhibits thyroid peroxidase, at high doses PTU also inhibits D1 activity (19). Methimazole does not have a similar effect, making PTU the preferred drug in thyroid storm. PTU is thought to inhibit D1 by complexing with the D1 active site selenocysteine via an S-Se bond (20).

Administration of the antiarrhythmia drug amiodarone leads to a predictable series of changes in serum thyroid hormone levels (21). Acutely, T_3 falls and reverse triiodothyronine (rT_3) rises, followed by increases in T_4 and TSH. Eventually, a new steady state is achieved in which the T_4 is increased (sometimes above the assay reference range) and the TSH and T_3 are normal. These changes are at least partially accounted for by inhibition of D1 activity (22). Despite the clear-cut *in vivo* inhibition of D1, it is difficult to demonstrate inhibition by adding amiodarone to *in vitro* enzyme assays (23). In part this may reflect technical difficulties due to the limited solubility of amiodarone. However, amiodarone derivatives do inhibit D1 activity *in vitro* (23), suggesting that the *in vivo* effects may be caused by amiodarone metabolites. Inhibition by amiodarone derivatives appears to be competitive with the substrate T_4.

The Nonthyroidal Illness Syndrome

The nonthyroidal illness syndrome (NTIS), also known as the sick euthyroid syndrome or low T_3 syndrome, is a complex whole body response to virtually any serious illness (24). Although the validity of free hormone measurements in the NTIS has been questioned (25), it is generally felt that a low circulating free T_3 is the hallmark of the syndrome (26). rT_3 is elevated, and the TSH and free T_4 usually are normal. In more severely ill patients the TSH is subnormal, and the free T_4 also can be low in extremely ill individuals. If a patient overcomes the illness, all of these changes resolve. In fact, the TSH may transiently rise above the reference range during the recovery phase. It is commonly speculated that the NTIS is an evolutionary adaptation to illness, as tissue hypothyroidism would conserve energy. However, whether the NTIS remains adaptive in the modern day era of intensive care unit medicine is unclear. Most endocrinologists do not treat the NTIS, although well-reasoned arguments for treating the most severe cases have been put forth (27). Clinical studies have failed to demonstrate a benefit to thyroid hormone therapy in the NTIS (28,29), but the very small number of patients studied makes it seem unlikely that a true benefit would have been identified, especially if only certain subgroups of patients are potential responders.

Many different changes in thyroid hormone economy contribute to the NTIS. That TSH is normal in the setting of a low free T_3 indicates that the hypothalamic-pituitary axis has an altered response to circulating thyroid hormone. The decrease in serum T_3 primarily reflects a decrease in peripheral deiodination of T_4, but as discussed below, the basis for the decreased T_4 to T_3 conversion is uncertain and is likely multifactorial.

Animals models of illness are associated with decreases in hepatic D1 (30,31). Various cytokines have been administered to humans (32) or animals (31) in an attempt to reproduce the NTIS. Although changes similar to the NTIS including a decreased serum T_3 are commonly observed, the syndrome has yet to be precisely mimicked. Thus, it is felt that cytokines contribute to the NTIS but cannot fully explain it, or that the syndrome is mediated by complex cytokine combinations that have yet to be tested experimentally.

Because a decrease in hepatic D1 is clearly associated with animal models of NTIS, the effects of cytokines on hepatocyte D1 have been studied in cell culture. Using the human hepatoma cell line HepG2, tumor necrosis factor (TNF)-α was observed to inhibit the T_3 induction of D1, and this was mediated by induction of NF-κB (33). In principle, such an effect would decrease T_3 production, which would further reduce the induction of D1 by T_3, thus setting off a down-

ward spiral. Another study, using primary cultures of rat hepatocytes, demonstrated that interleukin (IL)-1 and IL-6 block the T_3 induction of D1, and that this effect appears to be mediated by a functional deficiency in a TR coactivator protein known as steroid receptor coactivator-1 (34).

Interestingly, the effects of cytokines on pituitary D1 appear to be in the opposite direction (35). In primary cultures of rat pituitary cells, IL-1 stimulated D1 1.8-fold, and IL-6 and TNF-α caused similar changes but they failed to achieve statistical significance. A single injection of lipopolysaccharide into adult male rats led to a transient 1.5-fold elevation of anterior pituitary D1, although hepatic D1 decreased as expected. If similar inductions occur in human pituitary thyrotrophs in the NTIS, this could contribute to the failure of circulating TSH to rise in the face of a low circulating T_3 level.

Deiodinase levels also have been studied in one large series of humans with the NTIS, in which liver and skeletal muscle biopsies were obtained from more than 50 deceased patients from the intensive care unit (36). The tissue samples were obtained on average approximately 20–25 minutes after death. D2 activity was undetectable in all of the samples. D1 enzyme activity was detectable in all livers, and D3 was detectable in many liver and muscle samples (D3 was not detectable in healthy human liver or skeletal muscle). Hepatic D1 was lowest in patients who died of cardiovascular collapse, intermediate in patients who died of multiorgan failure, and highest in patients who died acutely of severe brain damage (in those patients D1 activity was stated to be similar to that in normal liver). Although only correlations can be drawn from this study, it does suggest the potential for decreased hepatic D1 as a contributing factor to the NTIS.

However, because in humans it has not been possible to determine the contributions of D1 and D2 to circulating T_3, it is not possible to determine whether inhibition of D1, D2, or both is most important in the NTIS. In addition, the unexpected induction of D3 in the above study suggests that as a possible contributing factor. Further complicating the situation, there is evidence for decreased T_4 uptake into tissues during human fasting (37), which is associated with thyroid hormone changes similar to those observed in the NTIS. Obviously, decreased cellular uptake of T_4 also could lead to decreased T_3 production. Thus, additional research is needed to resolve the mechanism of low T_3 in the NTIS, as well as to address whether the syndrome should ever be treated (and if so, how).

Mammary Gland D1

Lactation induces deiodinase expression in the mammary gland, which is speculated to contribute to milk T_3 content. In the rat, D1 is expressed, but in cows and pigs, D2 is expressed. Rat mammary gland D1 mRNA contains a shortened 3′ untranslated region (38), but whether this is physiologically significant is unknown. Studies in the rat indicate that suckling induces mammary gland D1 mRNA and enzyme activity through a mechanism involving β-adrenergic stimulation, and that expression is confined to alveolar epithelial cells (39). Prolactin also increased D1 enzyme activity, but mRNA levels did not change.

Sex Steroid Regulation of D1

Hepatic D1 mRNA and enzyme activity are higher in male rats than in female rats, although there are no differences in kidney D1 (40,41). Castration reduced hepatic D1 in male rats and testosterone therapy overcame this reduction, both at the mRNA and enzyme activity levels (42). In one study (42) but not in another (40), ovariectomy of rats reduced liver D1 activity and this basal level was stimulated by estrogen therapy but reduced further by progesterone (42). Progesterone also blocked the estrogen induction. The mechanisms involved are unknown. More modest but qualitatively similar changes were observed in pituitary D1.

Regulation of Hepatic D1 by Circadian Rhythms and Feeding Behavior

As noted previously, TRβ_1 and D1 are preferentially expressed in the pericentral zones in rat liver. TRβ_1 expression varies in a diurnal manner, with highest expression at the beginning of the dark period (7:30 PM) and lowest expression in the middle of the light period (1:30 PM) (12). The maximum difference is modest, approximately 30% more TRβ_1 at 7:30 PM, but this might be physiologically relevant as both D1 and another T_3-responsive hepatocyte gene, glutamine synthase, tended to show a diurnal variation in expression with peak levels at night.

Liver D1 also is regulated by feeding behavior (43). When rats are trained to have food access restricted to only 2 or 3 hours per day, they begin to anticipate food availability as evidenced by increased locomotion and water drinking. In rats maintained on such a restricted feeding schedule (feeding from 12:00 PM to 2:00 PM daily), D1 activity was low both before (8:00 AM) and during (11:00 AM) anticipatory activity, but increased threefold to fourfold after eating (4:00 PM). Despite this substantial change in D1 enzyme activity, D1 mRNA was constant. This is different than the well documented decrease in rat liver D1 associated with fasting in two ways. Fasting causes a decrease in D1 mRNA as well as enzyme activity. In addition, the level of D1 activity was actually lower during anticipatory activity than following a 24-hour fast in rats otherwise fed ad libitum. As an aside, it should be noted that the fasted rat is a poor model for fasting humans.

D1 Deficiency

Because the role of D1 is to supply plasma T_3, one might expect D1 deficiency to result in a low T_3 concentration. There are no documented cases of D1 deficiency in humans, and D1 null animals have not been generated. However, the mouse strain C3H/He has 5-10 fold reduced D1 expression relative to most other strains, such as C57BL/6 (44,45). Remarkably, total and free T_3 levels are normal in C3H/He mice. This normal free T_3 is generated at the expense of twice normal circulating free T_4 levels, thus illustrating the power of thyroid axis homeostasis. Perhaps surprisingly, the normal free T_3 and elevated free T_4 occur with no detectable change in circulating TSH. This reequilibrated state likely is a consequence of several counterbalancing forces. Assuming mice are similar to rats, then direct thyroidal secretion accounts for approximately 40% of circulating T_3 (versus 20% in humans), and D1 accounts for approximately half of the remainder. While the fractional conversion of T_4 to T_3 by D1 would be reduced in C3H/He mice, the higher free T_4 level would increase the net flux through this system. D1 also can degrade T_4 via inner ring

deiodination, and presumably this activity would be decreased in C3H mice, helping to maintain the elevated free T_4. The fact that TSH is not decreased in response to the high free T_4/normal free T_3 state perhaps reflects decreased pituitary D2 (T_4 stimulates proteosomal degradation of D2), which would lead to reduced pituitary T_3. Overall, these multiple factors enforce euthyroidism in the C3H/He mouse. The results suggest that partial D1 deficiency in humans, should it exist, might be well compensated and difficult to detect.

The underlying reason for decreased D1 expression in C3H/He mice has been carefully investigated. The enzyme itself is normal, but expression at the mRNA and protein levels is reduced. The defect maps to the *Dio1* gene itself, and appears to be accounted for at least in part by a 21 bp insertion in the promoter region that includes five CTG repeats (46). The 21-bp insertion correlates with decreased promoter activity, but the mechanism is not known.

D1 Activity and Circulating Thyroid Hormone Levels in Selenium Deficiency

Because D1 is a selenoprotein, one would predict that selenium deficiency would decrease D1 enzyme activity. In fact, selenium deficiency in rats was shown to decrease hepatic and renal D1 activity before the enzyme was cloned and demonstrated to contain selenocysteine (47–49). However, organs such as the thyroid and pituitary are much more resistant to dietary selenium deficiency than is the liver, so the effects of selenium deprivation depend on the organ being studied. Selenium deficient rats have an elevated T_4, a very slightly reduced T_3 and a normal TSH (47,48). At least in terms of the T_4 and TSH, these findings are similar to what is observed in the partially D1-deficient C3H/He mouse (44). However, it should be recognized that selenium deficiency could influence thyroid hormone levels by mechanisms independent of D1. For example, selenium deficiency could impair D2 or D3 activity. In addition, even though the thyroid is relatively resistant to selenium deficiency, decreased activity of the selenoenzyme glutathione peroxidase in the thyroid might increase peroxide levels, which could enhance iodine organification in the short term or be cytotoxic in the long term.

In humans, it would be difficult to find cases of pure, isolated selenium deficiency. Nevertheless, selenium deficient humans tend to have mildly elevated serum T_4 levels (50–53). Interestingly, in an area of Zaire with both iodine and selenium deficiency, selenium supplementation was associated with a decrease in serum T_4 and, in subjects with cretinism, an elevation in TSH (i.e., worsening hypothyroidism) [54,55]. One possible explanation is that selenium deficiency reduced D1-catalyzed inner ring deiodination of thyroid hormones, thus protecting against hypothyroidism.

D1 Activity in Diabetes Mellitus

Experimental diabetes mellitus in rats caused a 50%–60% decrease in hepatic and kidney D1, as well as decreases in serum T_3 and T_4 (56). Insulin treatment resulted in a slow increase in D1 mRNA, with an increase first noted at 72 hours and normalization after 1 week. In contrast, glucagon administration appears to reduce D1 activity (57).

D1 in Pituitary Tumors

Because D1 is expressed in the normal anterior pituitary, it might be anticipated that human pituitary tumors also could express this enzyme. One study has reported the measurement of deiodinase activity in 43 pituitary adenomas and three normal pituitaries, all removed surgically (58). The adenomas included 18 nonfunctioning tumors, 7 TSH-secreting tumors, 5 growth hormone (GH) secreting tumors, 1 combined TSH and GH-secreting tumor, 8 prolactinomas and 4 adrenocorticotropic hormone (ACTH)-secreting tumors. Although there was a large variation in D1 activity within tumor types, the highest activities were seen in the thyrotroph and lactotroph adenomas. Approximately half of these tumors had D1 activities several-fold greater than any of the three normal pituitaries. Many of the tumors also expressed D2.

Summary and Conclusions

Type 1 deiodinase activates thyroxine via outer ring deiodination and also has the ability to inactivate thyroid hormone via inner ring deiodination. Thus, D1 makes an important contribution to the maintenance of circulating thyroid hormone levels. Although the percent of plasma T_3 that is caused by D1 activity has been quantified in the rat, it has been difficult to make a similar determination in humans. D1 expression is highest in the liver, kidney, thyroid and pituitary, and it also is expressed at low levels in several other organs. T_3 induces D1 expression at the transcriptional level, which contributes to the relative excess of T_3 in hyperthyroidism. Amiodarone (or its metabolites) inhibits D1 activity, potentially creating difficulty in the interpretation of thyroid function tests. The ability of PTU to inhibit D1 is advantageous in the treatment of severe hyperthyroidism. D1 activity is low in the nonthyroidal illness syndrome, where this may contribute to the low T_3 state. D1 activity in other organs, such as the lactating mammary gland, may be physiologically important, although further research is needed to better define the roles of D1 in human health and disease.

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