Reawakened interest in type III iodothyronine deiodinase in critical illness and injury

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SUMMARY

Thyroid hormones influence gene expression in virtually all vertebrate tissues. Precise regulation of the active endogenous ligand, 3,5,3′-triiodothyronine (T_3), is achieved by the sequential removal of iodine moieties from the thyroid hormone molecule. Type III iodothyronine deiodinase (D3) is the major inactivating enzyme terminating the action of T_3 and preventing activation of the prohormone, thyroxine (T_4). Recent studies have revealed the induction of high D3 activity in diverse animal models of tissue injury including starvation, cryolesion, cardiac hypertrophy, infarction, and chronic inflammation. By analyzing serum and tissues taken from hospitalized patients at the time of death, investigators have also documented the robust induction of D3 activity in several human tissues that normally have none, including the liver and skeletal muscle, and shown clinically relevant consequences to systemic thyroid status. These studies reveal a novel role of D3 in the tissue response to injury and in the derangement of thyroid hormone homeostasis commonly observed during critical illness.

Keywords

critical illness; D3; deiodinase; euthyroid sick syndrome; low-T_3 syndrome

INTRODUCTION

The endogenous thyroid hormones thyroxine (T_4) and 3,5,3′-triiodothyronine (T_3) are iodinated compounds that regulate gene expression in virtually all vertebrate tissues. Thyroid hormone signaling results from the binding of thyroid hormone to thyroid hormone receptors, which interact with specific genes to stimulate or repress their expression.[1,2] This signaling pathway is sensitive to changes in serum thyroid hormone concentrations such as those observed during hypothyroidism or hyperthyroidism, but also to local regulatory mechanisms such as thyroid hormone transport, activation and inactivation.

Although all cells are exposed to essentially the same circulating concentrations of thyroid hormone, only certain cells express iodothyronine deiodinases, which are enzymes that

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modulate local thyroid hormone signaling by the removal of specific iodine moieties from T_4 or T_3. Type I and type II iodothyronine deiodinases (D1 and D2) activate T_4 to T_3, whereas type III iodothyronine deiodinase (D3) is the main inactivator of both T_4 and T_3.[3,4] D3 is exquisitely responsive to thyroid hormone in adult tissues and its transcriptional stimulation is usually coordinated with a reciprocal ubiquitin-mediated suppression of D2— the critical activating deiodinase for thyroid hormones—constituting a powerful homeostatic mechanism in healthy individuals.[5,6]

Given the relevance of deiodinases in normal physiology, it is not surprising that abnormalities in deiodination are important in numerous clinical settings. The best-known example of such a setting is a pattern of deranged thyroid hormone homeostasis referred to as the low-T_3 syndrome (also known as the euthyroid sick syndrome or nonthyroidal illness).[7] The changes in low-T_3 syndrome vary from patient to patient, but usually include low serum levels of T_3 and high levels of the inactive metabolite reverse T_3 (rT_3). Life-threatening trauma and critical illness are associated with the low-T_3 syndrome. Serum T_3 levels fall in proportion to the severity of illness and, in critically ill patients, this is followed by a decrease in serum T_4 and serum TSH levels. The low-T_3 syndrome is common, with an incidence of up to 75% in hospitalized patients,[8] but its clinical significance (whether it represent a pathologic state or an adaptive compensation to illness) is still debated amongst experts.[9]

It has been accepted that the fall in serum T_3 level is due to central hypothyroidism (suppression of the normal hypothalamic–pituitary–thyroid axis) as well as decreased activation of T_4 to T_3. Recently, a previously unrecognized role of D3 in the low-T_3 syndrome has been suggested. By analyzing serum and tissues obtained from hospitalized patients around the time of death, investigators have documented the robust stimulation of D3 in various tissues, including liver and skeletal muscle, and shown a correlation with the derangement of thyroid homeostatsis.[10–12]

This observation revealed that D3-mediated thyroid hormone inactivation was a previously unrecognized contributor to the low-T_3 syndrome (Figure 1). Further supporting this concept, a number of animal studies have shown high D3 expression in diverse models of tissue injury including starvation,[13] cryolesion,[14] cardiac hypertrophy,[15] infarction,[16] and chronic inflammation.[17] The molecular mechanisms responsible for stimulation of D3 expression in benign and malignant[18] disease states and the physiologic consequences of D3-mediated local hypothyroidism to the microenvironment of injured tissues remain to be defined. Here we describe the molecular and cellular biology of D3 and the ontogeny of its expression. Then we detail the role of deiodinases in the low-T_3 syndrome, in particular the induction of D3 in various tissues after injury or illness. Finally, we discuss the mechanisms whereby D3 might affect levels of active thyroid hormones.

MOLECULAR AND CELLULAR BIOLOGY OF D3

The D3 gene, located on chromosome 14q32 (*DIO3*) in the human or chromosome 12F1 (*Dio3*) in the mouse,[19,20] is unique amongst the deiodinases in being an imprinted gene (i.e. only the paternal or maternal allele is expressed, not both).[21] Like most other imprinted genes, *Dio3* is assembled in a cluster of genes that share a common regulatory element. This delta-like 1 homolog (*Dlk1*)–*Dio3* imprinted gene cluster contains three paternally expressed protein-coding genes—*Dlk1*, retrotransposon-like 1 (*Rtl1*), and *Dio3*—as well as multiple noncoding RNA genes expressed from the maternally in herited chromosome.[5] For both *Rtl1* and *Dio3*, there are genes transcribed in the antisense orientation. The transcript (antiPeg11) that is transcribed in the antisense direction to *Rtl1* is processed into micro-RNA molecules that regulate *Rtl1 in trans* via RNA-induced silencing complex (RISC)-mediated cleavage of

Rtl1 mRNA.[22,23] The function, if any, of *Dio3OS*—the gene transcribed antisense to *Dio3*—remains to be elucidated.

D3 is a protein of about 33 kDa that is anchored to the plasma membrane through a single transmembrane segment, which connects via a small hinge to a globular domain.[5] A striking feature of this domain is the presence of a 'thioredoxin fold', defined by the βαβ (i.e. an α-helix between two β-sheets) and ββα motifs, that characterizes the members of the thioredoxin-fold family of proteins, which serve a wide variety of functions. The D3 active center is a pocket within the globular domain defined by a βαβ motif and a highly conserved intervening element that is also found in α-L-iduronidase, a lysosomal enzyme. In this pocket is the rare amino acid selenocysteine, critical for the nucleophilic attack that takes place during the deiodination reaction.[24] The D3 holoenzyme exists as a homodimer with two in dependent active centers; both counterparts are kept together through interacting surfaces at the transmembrane and globular domains, which is critical for preserving catalytic activity.[25]

Like many other proteins anchored in the plasma membrane, D3 is internalized and becomes part of the endosomal vesicles.[26] These predominantly clathrin-coated vesicles are also capable of recycling internalized D3 back to the cell surface. Newly synthesized D3 thus migrates to the plasma membrane and becomes part of the pool recycling between the plasma membrane and the early endosomes. The signal or signals controlling D3 partition between these two pools are not known. Although immuno cytochemistry studies indicate that the D3 globular domain is in the extracellular space,[26] other studies indicate that catalysis is an intra cellular event because co-expression of the thyroid hormone transporter MCT8 (monocarboxylate transporter 8) increases D3-mediated deiodination.[27] These findings could be explained by the active center being cytosolic, but may alternatively reflect that D3 catalysis takes place inside endosomal vesicles with MCT8 being necessary for T_3 entry into such vesicles.

ONTOGENY OF D3 EXPRESSION

D3 is highly and dynamically expressed in the uteroplacental unit and in numerous embryonic tissues.[6] This D3 activity limits the transfer of maternal thyroid hormones to the fetal circulation,[28] shielding developing fetal structures from the temporally inappropriate action of maternal thyroid hormone and permitting the local regulation of thyroid hormone signaling by the coordinated expression of D2 and D3. The critical role of this D3 expression in development was first demonstrated in studies of *Xenopus laevis* metamorphosis,[29,30] but recent studies of mice with targeted deletion of the *Dio3* gene confirm that D3 is also important for mammalian development. Such D3-knockout mice, lacking D3 activity, manifest a complex phenotype that includes partial embryonic lethality, impaired reproductive function, growth retardation,[31] and perinatal thyrotoxicosis that is followed by prolonged abnormalities of the hypothalamic–pituitary–thyroid axis.[32]

Although tracer kinetic studies in humans show that D3 inactivates approximately 80% of daily thyroid hormone production,[33,34] D3 activity has been identified in only a few adult tissues; thus the anatomic pool of D3 activity in mature tissues has yet to be defined. In healthy adults, high D3 activity has been documented only in the uterus and placenta, with lower expression in the brain,[35] pituitary gland, adrenal gland, and skin.[6,36,37]

Re-activation of high D3 expression has, however, been documented in several tumors, including gliomas,[38] fibrous tumors,[39] and vascular anomalies.[6,40,41] Rare patients with both large tumor burden and high, specific D3 activity can develop 'consumptive hypothyroidism', a condition in which thyroid hormones are catabolized at rates that are faster than the thyroid gland can secrete.[6] Although we do not understand the functional

consequences of D3 expression in all tumors, it has recently been shown that D3 activity induced via the hedgehog signaling pathway—which includes the protein Sonic hedgehog—in basal cell carcinomas promotes the proliferation of malignant cells by blocking the differentiating action of circulating T_3.[18]

It has recently been discovered that, in addition to neoplasia, critical illness can also re-ignite strong D3 expression in adult tissues.[11,12] This discovery has led to the interesting hypothesis that D3 contributes to the derangement of thyroid homeostasis in the low-T_3 syndrome.

THE ROLE OF D3 IN THE LOW-T_3 SYNDROME

Systemic illness[8] and stress[42,43] alter thyroid hormone homeostasis and lead to a fall in serum T_3 levels. Most research into the low-T_3 syndrome has focused on decreased thyroid hormone production, especially central changes of the hypothalamic–pituitary–thyroid axis that reduce TSH secretion and/or bioactivity. In hospitalized patients, these effects are compounded by the administration of medications such as glucocorticoids and dopamine, which further suppress thyroid secretion.[8] In addition, iodine, which is present in certain types of radiologic contrasts[44] and topical antiseptics,[45] can also acutely reduce thyroid hormone secretion. The clinical significance of such iodine exposure to the low-T_3 syndrome in the adult population is unclear, but rare patient subpopulations such as premature neonates may be especially susceptible to the antithyroid effects of iodide excess.[4]

Although decreased glandular secretion is a major component of the low-T_3 syndrome, peripheral changes in thyroid hormone metabolism are another important contributor. Liver D1 levels fall during critical illness, and this has been proposed as an explanation for decreased T_4 activation in the low-T_3 syndrome.[7] Transcription factors and cytokines such as nuclear factor κB,[46] interleukin 1 (IL-1), or IL-6,[47] which are associated with inflammatory responses, block the induction of D1 by T_3 in cultured hepatocytes.

Similarly, both hepatic D1 activity and serum T_3 levels fall *in vivo* in mice after endotoxin administration, and recent data implicate cytokine-induced defects in thyroid hormone receptor coactivators such as steroid receptor coactivator 1 as the mechanism.[48] Such decreases in D1 activity also occur in humans during critical illness, as revealed by decreased hepatic D1 activity in post-mortem studies.[11] Skeletal muscle D2 activity in similar patient populations is stable or increased,[10,49] indicating that, despite the important role of D2 in normal T_3 homeostasis,[50–52] its downregulation is not a significant contributor to the low-T_3 syndrome.

Although this reduction in D1-mediated outer-ring deiodination is well studied and has long been accepted as a contributor to the low-T_3 syndrome, it is important to stress that the etiology of low-T_3 syndrome is multifactorial and that decreased outer-ring deiodination, although critical, may not lower serum T_3 levels alone without impaired glandular secretion. This theory is supported by the finding of normal serum T_3 concentrations in D1- knockout mice, D2-knockout mice, and even mice with combined deficiencies of both D1 and D2.[53,54] Adding further to this complexity, other studies support the idea that an increase in thyroid hormone inactivation contributes to the etiology of low-T_3 syndrome. This hypothesis is illustrated by one study of patients in a medical intensive care unit; serum T_4 levels normalized with intravenous administration of levothyroxine, but serum T_3 levels remained low and serum rT_3 levels rose,[55] suggesting a shift in peripheral deiodination from substrate activation (D1-mediated or D2-mediated outerring deiodination) to substrate inactivation (D3-mediated inner-ring deiodination).

Because D3 is normally undetectable in most adult tissues, there was little reason to suspect that it influenced thyroid status outside of pregnancy until the pathophysiology of consumptive hypothyroidism showed that D3-catalyzed thyroid hormone inactivation could alter systemic thyroid status, even in individuals with normal and stimulated hypothalamic–pituitary–thyroid axes.[6,40] This finding suggested that D3 re-activation could contribute to other low-T_3 states, especially in settings like critical illness where thyroid secretion is suppressed.

This hypothesis was quickly supported by investigators who documented the induction of D3 mRNA and activity in liver and skeletal muscle in patients hospitalized in intensive care units.[11,12] In healthy individuals, D3 is un detectable in these same tissues, and so this was the first example of D3 re-activation in normal human adult tissues. Importantly, liver-specific D3 activity was inversely proportional to the serum T_3:rT_3 ratio, and muscle-specific D3 activity correlated positively with the serum rT_3:T_4 ratio, supporting the idea that this D3 induction contributes to the low-T_3 syndrome.

An active area of study is investigating which specific disease states lead to D3 re-activation. A number of recent studies in animals show that high D3 expression can be re-activated in diverse tissues as a general response to injury. In chickens, starvation increases liver D3 levels more than threefold within 24 hours of caloric restriction, and this increase is associated with a decrease in plasma T_3 levels.[13] D3 is undetectable in the intact sciatic nerve of adult rats, but is rapidly induced after injury by cryolesion or transection.[14] Isolated cultured fibroblasts or Schwann cells from this nerve-injury model show robust induction of D3 mRNA after treatment with 12-0-tetradecanoylphorbol-13-acetate; this activates protein kinase C, implicating this pathway in D3 induction.

In addition, cardiac D3 induction has been documented in two distinct rat models of heart failure—right ventricular hypertrophy induced by pulmonary hypertension[15] and myocardial infarction induced by left coronary-artery ligation.[16] This cardiac D3 expression is restricted only to the hypertrophic or infarcted myocardium, and post-infarction D3 activity is associated with a decrease in serum T_3 levels. Turpentine injection models chronic local inflammation, and injection into the mouse hindlimb is followed by a marked increase in D3 activity in the muscle and subcutis around the resultant abscess; this is accompanied by increased expression of IL-1β and IL-6β mRNA.[17]

The above studies demonstrate that D3 can be re-activated in various benign cell types in response to diverse mechanisms of injury including starvation, cryolesion, cardiac hypertrophy, infarction, and inflammation. This evidence suggests that multiple factors are capable of inducing postnatal D3 expression and, consistent with this theory, several mediators of angiogenesis and the tissue-injury response—including epidermal growth factor, platelet-derived growth factor, insulin-like growth factor I, and the basic and acidic fibro-blast growth factors—are potent stimulators of *Dio3* transcription *in vitro*.[56–58]

Experiments with pharmacologic inhibitors indicate that several of these factors stimulate D3 via protein kinase C and two branches of the mitogen-activated protein kinase (MAPK) system: the branch activated by mitogens via MAPK1 (also known as extracellular signal-regulated kinase 2 or ERK); and the branch activated by stress via MAPK12 (also known as stress-activated protein kinase 3 or MAP kinase p38 γ).[57,59] Two other pleiotropic signaling systems that mediate both developmental events and inflammation—one involving transforming growth factor β and SMAD-family proteins[59] and one involving Sonic hedgehog[18]—have recently been shown to induce transcription of the *DIO3* gene.

LOCAL REGULATION OF THYROID HORMONE SIGNALING

A remarkable concept derived from understanding the deiodinase pathways is that these enzymes can affect intracellular thyroid hormone signaling independently of changes in circulating levels of thyroid hormones.[3] For example, an increase in D2 activity is known to accelerate T_3 production in brown adipocytes, which is key for the adaptive thermogenesis mediated by these cells.[60,61] On the other hand, re-activation of D3 disrupts local thyroid hormone signaling, which in the case of cardiac hypertrophy leads to a gene-expression profile typical of hypothyroidism.[15,62] It is therefore conceivable that D3 re-activation during illness and localized disruption of thyroid hormone signaling is much more frequent than previously thought, probably during even mild illness, when systemic serum T_3 levels are not yet affected.

Although the cellular mechanisms underlying the local control of thyroid hormone signaling by deiodinases are poorly understood, the subcellular localization of D2 and D3 could certainly have a role. D2 is a protein that is resident in the endoplasmic reticulum—a compartment that is extensively connected with the nuclear envelope—and thus D2-generated T_3 does not rapidly exit the cell, but rather enters the cell nucleus and only after several hours equilibrates with serum T_3.[63] On the other hand, the location of D3 in the plasma membrane is appropriate in order to stop thyroid hormone from gaining access to the cell nucleus, which contains thyroid hormone receptors.[26]

In most situations the actions of D2 and D3 are integrated and thus promote tight control of thyroid hormone action.[4] In fact, the hedgehog family has been recently identified as a major player in determining thyroid hormone signaling through coordinated effects mediated via D2 and D3. For example, in the developing growth plate of chickens, signaling via the hedgehog pathway inhibits D2-mediated T_3 production by inducing WSB-1 (WD repeat and SOCS box-containing protein 1)—a ubiquitin ligase that inactivates D2 by transiently disrupting its dimeric conformation.[64,65] At the same time, hedgehog signaling stimulates *DIO3*, which will inactivate thyroid hormone and further decrease thyroid hormone action. The stimulation of *DIO3* by Gli proteins, which are downstream messengers of the hedgehog cascade, has recently been characterized in keratinocytes from both normal skin and basal cell carcinomas, the most common human malignancy.[18] How much of the hedgehog signaling pathway's effect is mediated by the deiodination of thyroid hormone remains to be elucidated.

CONCLUSIONS

From a broad perspective, the recent recognition of the re-activation of D3 during illness adds to a growing body of work that indicates a fascinating role of deiodination in embryonic development, thyroid hormone homeostasis, and now human disease. Studies in patients support the provocative concept that D3 re-activation contributes to the low-T_3 syndrome, and the availability of a D3-knockout mouse strain[31] provides the opportunity to determine how much D3 contributes.

Additional studies are required to identify the molecular mechanisms that regulate re-activation (and cessation) of D3 during illness and the functional consequence of D3-mediated local hypothyroidism to injured tissues. Given the established ability of D2 to amplify local thyroid hormone signaling in tissues such as the pituitary gland,[66] brain[67] and brown fat,[61] an opposite but complementary physiologic role of D3 to mediate cell-specific hypothyroidism can be foreseen. Although unproven, given the established importance of thyroid hormone as a regulator of metabolic rate, one might speculate a benefit of local D3

re-activation in injured tissues through its inhibition of T_3-stimulated energy expenditure during catabolic stress.

REVIEW CRITERIA

We searched for original articles focusing on D3 and nonthyroidal illness in MEDLINE and PubMed published between 1952 and 2007. The search terms we used were "D3", "Dio3", "type 3 deiodinase", "deiodinase", "deiodination", "nonthyroidal illness", "euthyroid sick syndrome", and "low T3 syndrome". All papers identified were English-language full-text papers. We also searched the reference lists of identified articles for further papers.

KEY POINTS

- The low-T_3 syndrome is multifactorial, with evidence that decreased glandular secretion, decreased T_4 activation, and increased thyroid hormone inactivation all contribute

- Type III iodothyronine deiodinase (D3) is normally undetectable in mature tissues, but its expression is re-activated in diverse cell types in response to injury

- D3 re-activation during illness is associated with a fall in serum T_3 levels

- Additional studies are required to identify the molecular mechanisms that regulate the re-activation of D3 during illness and the functional consequence of D3-mediated local hypothyroidism to injured tissues

Acknowledgments

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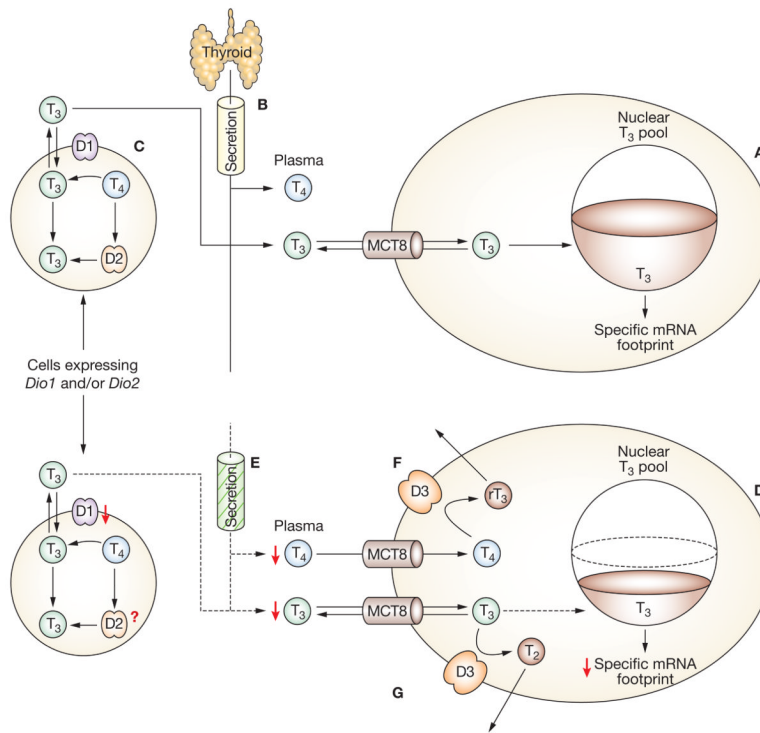
Figure 1.
Changes in thyroid hormone homeostasis during illness. (**A**) In euthyroid individuals, thyroid hormone signaling in peripheral tissues is determined by the available nuclear T_3 pool; "footprint" indicates the set of genes that are affected by thyroid hormone. The nuclear pool is normally maintained through (**B**) the regulation of glandular secretion and (**C**) the conversion of T_4 into T_3 by tissues containing D1 and D2. (**D**) During illness and the low-T_3 syndrome, the nuclear T_3 pool is decreased because of (**E**) decreased glandular secretion (the word "Secretion" has been hatched and lines from it dotted to indicate this), decreased conversion of T_4 into T_3 (indicated by the red arrow next to D1), and (**F,G**) the inactivation of T_4 and T_3 by re-activated D3. The red question mark indicates uncertainty regarding the role of D2 in illness. Some processes are shown in a simplified manner for the sake of clarity: the smaller circles on the left represent cells expressing D1 and/or D2; T_4 is shown inside these simplified cells with the understanding that it originates from the plasma. Abbreviations: D1, type I iodothyronine deiodinase; D2, type II iodothyronine deiodinase; D3, type III iodothyronine deiodinase; *Dio1*, D1 gene; *Dio2*, D2 gene; MCT8, monocarboxylate transporter 8; rT$_3$, reverse T_3; T_2, 3,5-diiodothyronine.