

Illness-induced changes in thyroid hormone metabolism: focus on the tissue level

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ABSTRACT

During illness changes in thyroid hormone metabolism occur, collectively known as the non-thyroidal illness syndrome (NTIS). NTIS is characterised by low serum thyroid hormone levels without the expected rise in serum thyroid-stimulating hormone, indicating a major change in thyroid hormone feedback regulation. Recent studies have made clear that during NTIS differential changes in thyroid hormone metabolism occur in various tissues, the net effect of which may be either activation or inhibition of thyroid hormone action. In this review we discuss systemic and local changes in thyroid hormone metabolism during illness, highlighting their physiological implications in terms of disease course.

KEYWORDS

Deiodinase, inflammation, non-thyroidal illness syndrome, thyroid hormone

THYROID HORMONE METABOLISM

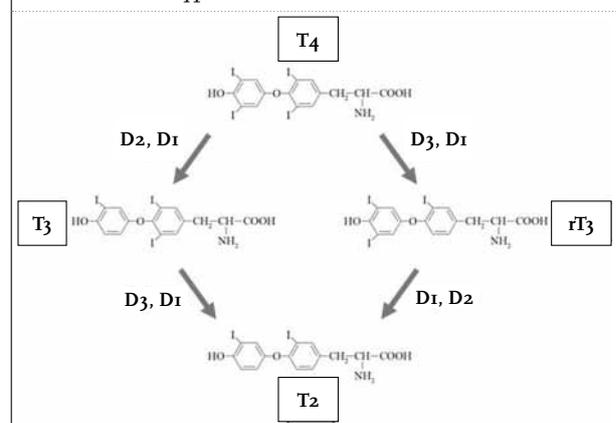
Thyroid hormones play a key role in energy homeostasis in adult life. The setpoint for thyroid hormone production and secretion by the thyroid gland is regulated by the hypothalamic neuropeptide thyrotropin-releasing hormone (TRH), determining the balance between serum thyroid-stimulating hormone (TSH) and thyroid hormone (TH) concentrations.¹ The major form of TH produced by the thyroid is the inactive prohormone thyroxine (T_4).² T_4 can be converted into the biologically active tri-iodothyronine (T_3) by the removal of an iodide by the selenoenzyme family of iodothyronine deiodinases, which have a tissue-specific distribution. There are three deiodinases, i.e., type 1 (D1), type 2 (D2) and type 3 (D3).³ Both the inner (phenolic)

ring and the outer (tyrosyl) ring of T_4 can be deiodinated, ultimately leading to the formation of 3,3'-di-iodothyronine (T_2) (figure 1).

NON-THYROIDAL ILLNESS SYNDROME

During illness many aspects of thyroid hormone metabolism change, collectively known as the non-thyroidal illness syndrome (NTIS). The hallmark of NTIS is decreased serum thyroid hormone levels without an increase in TSH and TRH expression, indicating the absence of negative feedback regulation. This may represent a useful adaptation of the body to counteract excessive catabolism observed during illness and can be viewed as a part of the acute phase response.⁴ However, especially during prolonged critical illness in the ICU setting NTIS may be maladaptive.⁵

Figure 1. Overview of the deiodination of thyroxine (T_4) into tri-iodothyronine (T_3), reverse tri-iodothyronine (rT_3) and di-iodothyronine (T_2), showing the role of the various deiodinase subtypes



In the last decade several rodent models of NTIS have been established to unravel the mechanisms behind NTIS. For instance, acute inflammation can be induced in rats and mice by the administration of the bacterial endotoxin lipopolysaccharide (LPS), resulting in decreased serum T_3 , T_4 and TSH within 24 hours.^{6,7} Chronic inflammation can be induced by a turpentine injection in the hindlimb of mice inducing a local sterile abscess and a decrease in serum T_3 and T_4 within two days.⁸ Finally, *S. pneumoniae* infection, inducing severe bronchopneumonia and septicaemia in rats, reduces serum T_3 and T_4 significantly in relation to the extent of bacterial outgrowth in the lung and spleen.⁹ An animal model of prolonged critical illness was developed in Leuven, using parenterally fed rabbits with a burn injury, displaying decreased serum T_3 and a tendency to decreased serum T_4 .¹⁰ Recent work has shown that illness-induced alterations in serum T_4 , T_3 and TSH levels are accompanied by significant and highly diverse changes in deiodinase expressions in a variety of tissues and organs of patients and experimental animals.

ILLNESS-INDUCED CHANGES IN DEIODINASE EXPRESSION

The changes in central hypothalamic thyroid hormone metabolism reported during illness are remarkably similar in all animal models studied. Generally, D2 expression increases^{6,11-14} while D3 expression decreases.¹⁵ The net result is probably increased local bioavailability of T_3 , which may help to prevent the activation of hypophysiotropic TRH neurons in the hypothalamus and to persistently suppress the hypothalamic-pituitary-thyroid axis at the central level.¹⁶⁻¹⁸ In contrast to hypothalamic D2, pituitary D2 expression varies during illness, depending on the genetic background as well as type of illness.^{6,12,15}

In the liver of all NTIS models D1 decreases, while liver D3 varies depending on the type of illness.^{8-10,19,20} This discrepancy is currently under investigation and might be explained by differences in feeding status.

In muscle, D2 expression decreases while D3 increases in septic patients and in mice infected with *S. pneumoniae*.^{21,22} In contrast, muscle D2 expression appeared to be increased in post-mortem muscle biopsies of prolonged critically ill patients²³ and in muscle of mice with acute inflammation, the latter in association with decreased D3.²⁰ Finally, in mice with local chronic inflammation, both muscle D2 and D3 increase simultaneously.²² In sum, changes in pituitary, liver and muscle deiodinase expression are dependent on type and severity of illness and possibly also on species/genetic background studied. Infiltrating granulocytes in the turpentine-induced abscess showed a marked induction of D3.⁸ This phenomenon was subsequently confirmed in animal models of bacterial pneumonia and peritonitis.⁹

SYSTEMIC CONSEQUENCES OF CHANGED DEIODINASE EXPRESSION

Yu and Koenig showed in an LPS model that restoration of liver D1 expression by exogenous administration of the steroid receptor co-activator (SRC)-1 prevents the development of low serum T_3 , pointing to liver D1 as the key contributor to decreased serum T_3 levels in rodents.²⁴ In contrast, during prolonged illness the decrease in liver D1 appeared to result from decreased T_3 levels, as infusion of T_4 and T_3 abolished the liver D1 decrease.²⁵ Our group reported that the decrease in serum T_3 preceded the LPS-induced decrease in liver D1, but we observed the reverse order using a slightly higher dose of LPS.^{6,26}

The possible role of D2 in the lowering of serum TH levels during NTIS is controversial as well. Although decreased D2 expression in skeletal muscle has been proposed to contribute to decreased serum TH, most studies reported increased muscle D2 while serum TH levels decreased.^{22,23,26}

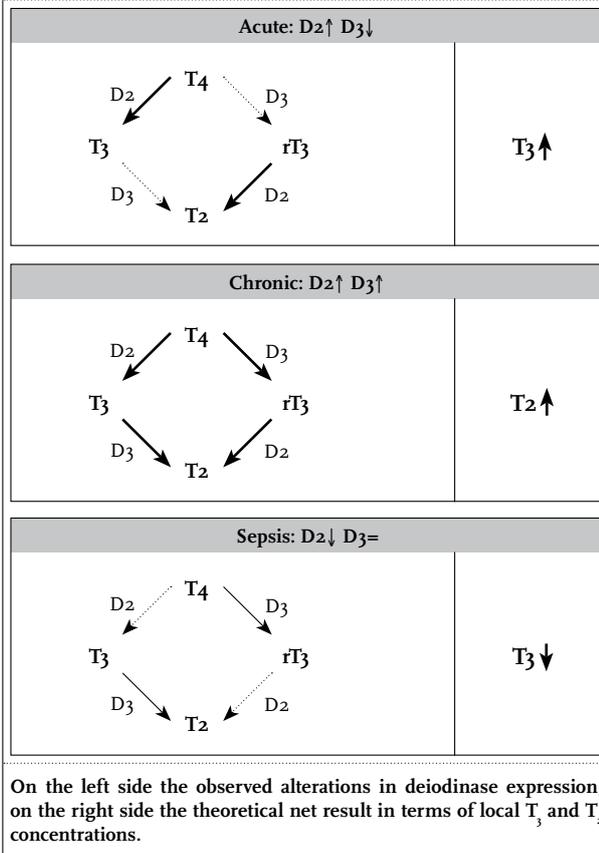
Finally, D3 induction has been considered a possible contributor to decreased serum T_3 and increased r T_3 levels during prolonged critical illness in humans.¹⁹ However, animal studies do not support this as abundant local D3 expression in our chronic inflammation model is not sufficient to decrease serum T_3 levels⁸ and mice devoid of D3 show a similar decrease of serum TH levels during bacterial pneumonia compared with wild-type mice.¹³

Consumptive hypothyroidism has been described in massive infantile haemangiomas, which is likely due to the high expression of D3 in haemangioma cells.²⁷ Since the expression level of D3 in haemangioma cells is much higher than in liver during illness, this intriguing disease entity does not present strong support for a role of D3 in decreasing serum T_3 levels during NTIS. Animal studies do not point to a clear-cut role for D1, D2 and D3 in illness-induced alterations in serum thyroid hormone concentrations during illness. However, it should be kept in mind that the contribution of the thyroid gland to serum T_3 production differs between humans and rodents (~20% in humans vs ~50% in rodents), leaving open the possibility of a more prominent role for the deiodinases in humans compared with rodents. Moreover, deiodinase knock-out mice display normal serum T_3 levels indicating that a decrease in peripheral T_3 production by deiodinases during illness cannot be solely responsible for the decrease in serum T_3 observed during illness.

LOCAL CONSEQUENCES OF CHANGED DEIODINASE EXPRESSION

It is now clear that the illness-induced decrease of serum T_3 and T_4 is associated with heterogeneous changes in

Figure 2. Schematic representation of the differential alterations in muscle deiodinase expression in mouse models of illness: acute inflammation (LPS administration, upper panel), chronic inflammation (turpentine induced abscess, middle panel) and severe bacterial infection and sepsis (*S.pneumoniae* infection, lower panel)



peripheral thyroid hormone metabolism. In addition, the peripheral changes are not the key determinants of decreased serum T₃ and T₄ levels. These observations suggested an alternative role of deiodinase changes during illness. It seems obvious that tissue deiodinase activities are important determinants of local T₃ generation. This was most clearly demonstrated in the hypothalamus, where increased D₂ and decreased D₃ activities result in decreased local T₃ availability and, thereby, suppression of TRH expression in the paraventricular nucleus.^{16,17} This paracrine loop was recently supported by an elegant *in vitro* study.²⁸

In liver, the changes in deiodinase expression during NTIS might result in net decreased hepatic T₃ concentrations. This may be beneficial as food intake usually decreases dramatically during illness and many T₃-regulated genes in the liver are involved in energy metabolism. However, there are no experimental studies to date to support this notion. Muscle deiodinase expression also changes profoundly, depending on the type and severity of illness. The

differential regulation of muscle D₂ and D₃ expression are likely to result in different outcomes in terms of T₃ and T₂ muscle concentrations in the different mouse models of illness. This is depicted schematically in figure 2. Both T₃ and T₂ are known to regulate muscle metabolic state.^{29,30} It is, therefore, tempting to speculate that differential regulation of deiodinase expression contributes to alterations in muscle metabolic state during the different stages of disease. During sepsis, mitochondrial dysfunction is frequently observed.³¹ As both T₃ and T₂ are important in mitochondrial biogenesis and activity,^{29,30} a tissue-specific shortage of T₃ and/or T₂ may contribute to sepsis-induced mitochondrial dysfunction. Furthermore, as thyroid hormone is an important regulator of type and contractibility of muscle fibres,³² changes in muscle deiodinase expression might contribute to critical illness myopathy (CIM), which is frequently observed in ICU patients.³³

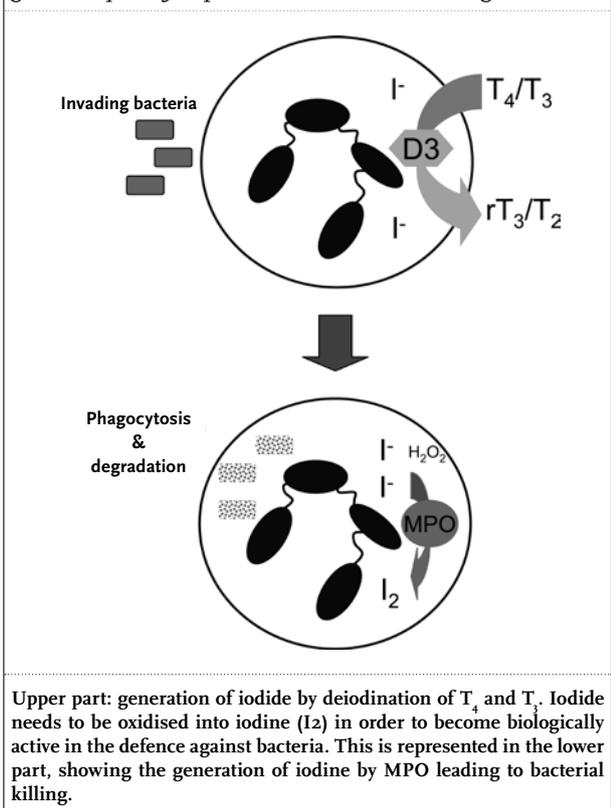
BACTERIAL KILLING

The possible function of D₃ expression in activated granulocytes is intriguing. TH plays a role in differentiation and proliferation of cells with high T₃ inducing cell differentiation and low T₃ inducing cell proliferation. Granulocytes are short-living, fully differentiated cells that migrate to the site of infection and do not proliferate, which may argue against a role for D₃ induction in differentiation or proliferation of activated granulocytes. Studies from the 1960s already suggested a role for thyroid hormone in the bacterial killing capacity of leukocytes. One of the major antibacterial mechanisms is the myeloperoxidase system, which exerts its antimicrobial effect in combination with hydrogen peroxide (H₂O₂) and a halide such as iodide. Thyroid hormones are an important source of iodide, and it was shown in 1964 that leukocytes take up and deiodinate T₄, thereby generating inorganic iodide.³⁴ In combination with the recent demonstration of D₃ induction in infiltrating leukocytes during infection, it is tempting to speculate that D₃ induction helps to generate iodide as part of the innate immune response (figure 3). Studies in *S. pneumoniae*-infected D₃KO mice indeed showed a defective bacterial clearance compared with wild-type mice, which supports this hypothesis.¹³

CONCLUDING REMARKS

Current knowledge has completely altered the concept of NTIS. In the classic view, NTIS is a syndrome with low plasma TH concentrations as its key phenomenon. Recent studies, however, have clearly shown that NTIS represents a profound and differential change in thyroid

Figure 3. Proposed model of the contribution of granulocyte D3 expression to bacterial killing



hormone physiology at the organ level in terms of local TH metabolism. Changes in tissue deiodinase expression should be interpreted in the context of type of illness and of the organ/tissue studied. Finally, the granulocyte is proposed as a novel and important cell type involved in NTIS during bacterial infection.

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