The molecular basis of the non-thyroidal illness syndrome

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Abstract

The 'sick euthyroid syndrome' or 'non-thyroidal illness syndrome' (NTIS) occurs in a large proportion of hospitalized patients and comprises a variety of alterations in the hypothalamus–pituitary–thyroid (HPT) axis that are observed during illness. One of the hallmarks of NTIS is decreased thyroid hormone (TH) serum concentrations, often viewed as an adaptive mechanism to save energy. Downregulation of hypophysiotropic TRH neurons in the paraventricular nucleus of the hypothalamus and of TSH production in the pituitary gland points to disturbed negative feedback regulation during illness. In addition to these alterations in the central component of the HPT axis, changes in TH metabolism occur in a variety of TH target tissues during NTIS, dependent on the timing, nature and severity of the illness. Cytokines, released during illness, are known to affect a variety of genes involved in TH metabolism and are therefore considered a major determinant of NTIS. The availability of *in vivo* and *in vitro* models for NTIS has elucidated part of the mechanisms involved in the sometimes paradoxical changes in the HPT axis and TH responsive tissues. However, the pathogenesis of NTIS is still incompletely understood. This review focusses on the molecular mechanisms involved in the tissue changes in TH metabolism and discusses the gaps that still require further research.

Key Words
- nonthyroidal illness
- thyroid hormone transporters
- thyroid hormone receptors
- deiodinases

Journal of Endocrinology (2015) **225**, R67–R81

Journal of Endocrinology

Introduction

Illness results in profound changes in thyroid hormone (TH) metabolism called the 'sick euthyroid syndrome' or 'nonthyroidal illness syndrome' (NTIS). NTIS is characterized by decreased serum triiodothyronine (T_3) and thyroxine (T_4) concentrations, increased serum reverse T_3 (rT_3) concentrations and unaltered or inappropriately low serum thyroid-stimulating hormone (TSH), indicating profoundly altered negative feedback in the pituitary and hypothalamus (Docter *et al.* 1993). The alterations in the central part of the hypothalamus–pituitary–thyroid (HPT) axis are combined with reduced production of T_3 and impaired clearance of rT_3 by the liver, and with specific changes in peripheral TH metabolism in major T_3 target organs. Muscle and adipose tissue show additional and differential changes in TH metabolism. The role of the thyroid gland has been largely neglected with regard to illness induced alterations in TH metabolism for many years, but *in vitro* studies showed that genes involved in the production and release of T_4 and T_3 are severely affected by high concentrations of pro-inflammatory cytokines (Bartalena *et al.* 1998). In addition, acute inflammation in mice reduced thyroidal TSH-receptor expression preceded by an acute increase in interleukin 1 beta (IL1β) expression (Boelen *et al.* 2004*a*). Thus, the

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DOI: 10.1530/JOE-15-0133

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thyroid gland itself is clearly involved in the pathogenesis of NTIS. The ultimate effects of the observed changes in local TH metabolism on tissue function during illness are currently unknown. However, the common view is that while changes observed during the acute phase of illness are beneficial they may become deleterious during prolonged critical illness, making the stage and severity of illness a major determinant of NTIS.

Cytokines have been implicated in the development of NTIS for more than two decades. IL6 was found to be negatively correlated with serum T_3 concentrations in hospitalized patients (Boelen *et al*. 1993). In mice, administration of bacterial endotoxin or lipopolysaccharide (LPS) results in an acute increase of serum IL6 and tumor necrosis factor alpha (TNFα) concentrations (Boelen *et al*. 1995). A causal role for IL6 in the development of NTIS in mice was shown since IL6 knock out mice show a less pronounced drop in serum T_3 during illness (Boelen *et al*. 1996). However, acute injection of cytokines failed to induce NTIS like features, except for interferon gamma (IFNγ) which reduces serum T_3 and T_4 (Boelen *et al*. 1995). Chronic infusions with IL1 and IL6 on the other hand mimick certain symptoms such as decreased serum T_4 and T_3 and decreased thyrotropin-releasing hormone (TRH) expression in the hypothalamus in mice (van Haasteren *et al*. 1994), while chronic IL1β infusions mimicks certain aspects of NTIS in the rat (Hermus *et al*. 1992).

Mechanisms involved in the pathogenesis of NTIS have predominantly been studied by using a variety of *in vivo* and *in vitro* models. Several NTIS rodent models have been described i.e. acute illness, induced by administration of a sublethal dose of LPS (Boelen *et al*. 2004*a*, Fekete *et al*. 2004); chronic inflammation, induced by injection of turpentine in the hind limb ultimately resulting in the formation of an abscess (Chopra *et al*. 1987, Boelen *et al*. 2006); bacterial sepsis, induced by inoculation of *Streptococcus pneumoniae* or i.p. injection with *Escherichia coli* (Knapp *et al*. 2003, Boelen *et al*. 2008) and prolonged critical illness in rabbits induced by burn injury (Weekers *et al*. 2002). The similarity between these models is the decrease in serum TH concentrations, although the time course, severity and inflammatory response are variable. The availability of transgenic mice provided the possibility to study the specific contribution of genes involved in TH metabolism in the context of NTIS. The role of specific molecular factors involved in the altered TH metabolism has been studied extensively *in vitro* by using a variety of cell lines that were stimulated with LPS or pro-inflammatory cytokines with and without specific inhibitors. In this review, we discuss changes in TH regulation and metabolism during NTIS, and the molecular mechanisms involved.

Illness induced alterations in hypothalamic TRH expression

The combination of low serum TH and an inappropriately low TSH response suggests central down-regulation of the HPT axis. This is supported by the observation that TRH gene expression in the paraventricular nucleus (PVN) of the hypothalamus was decreased in post mortem hypothalamic tissue of patients who died after prolonged illness as compared with patients with acute cardiac arrest. Moreover, TRH mRNA expression in the PVN correlates positively with pre-mortem serum TSH and T_3 levels (Fliers *et al*. 1997). In addition, several animal studies show that hypothalamic TRH expression also decreases after acute inflammation (Kakucska *et al*. 1994), chronic inflammation (Boelen *et al*. 2006) and prolonged critical illness in rabbits (Mebis *et al*. 2009). However, the underlying mechanisms are incompletely understood. Local T_3 bioavailability in the hypothalamus might play a role as $TR\beta^{0/0}$ mice display an impaired illness induced TRH decrease and TRβ signalling is important for the feedback regulation of T_3 on TRH neurons. However, the role of circulating TH is probably limited as alterations in the hypothalamus that are supposed to be involved in the illness induced TRH decrease precede the decrease in circulating TH levels (Fekete *et al*. 2005). A striking observation that has been linked to the illness induced TRH decrease is a marked increase in type 2 deiodinase (D2/*Dio2*) mRNA expression both in tanycytes, specialised cells lining the wall of the third ventricle (de Vries *et al*. 2014*a*) and in the hypothalamus of a variety of rodent and rabbit NTIS models (Boelen *et al*. 2004*a*, 2006, Fekete *et al*. 2004, Mebis *et al*. 2009). D2 is the main T_3 producing enzyme in the brain and involved in the regulation of local TH availability. In an *in vitro* coculture system, increased D2 expression in glial cells results in an increase of T_3 responsive gene expression in cocultured neurons, indicating that increased T_3 production by D2 in tanycytes could influence adjacent neurons in a paracrine fashion (Freitas *et al*. 2010). The observation that $TR\beta^{0/0}$ mice do not show a hypothalamic TRH decrease supports the role for local T_3 in the suppression of TRH secretion (Boelen *et al*. 2009*a*). The mechanisms involved in the illness induced increase in *Dio2* mRNA expression are discussed in the following section. In addition, both IL1β and corticosterone are known to affect *Trh* expression directly

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and could also contribute to the TRH decrease upon inflammation (Kakucska *et al*. 1994, 1995). TRH is also decreased during starvation suggesting that part of the observed TRH decrease during illness might be a result of the diminished food intake associated with illness. However, in a mouse model for chronic inflammation, diminished food intake does not play a role in the observed *Trh* decrease (Boelen *et al*. 2006).

Illness induced alterations in pituitary TSHβ expression

One of the characteristics of NTIS is the absence of an appropriate TSH response in the face of low serum T_4 and T_3 concentrations. Low TSH serum concentrations and decreased *Tshβ* mRNA expression in the pituitary have been described in a wide variety of animal models (Boelen *et al*. 2004*a*, 2006, Fekete *et al*. 2004, Mebis *et al*. 2009). The mechanism involved is still unclear although we showed that the illness induced decrease of *Tshβ* expression depends on functional thyroid hormone receptor (TR) signaling, since $TR\beta^{0/0}$ mice show a blunted *Tshβ* decrease upon LPS stimulation compared to their WT counterparts (Boelen *et al*. 2009*a*). The diminished food intake that is associated with chronic inflammation is only partly responsible for the observed *Tshβ* decrease (Boelen *et al*. 2006).

The pituitary expresses both D1/*Dio1* and D2 (Alkemade *et al*. 2006). The D2 mediated conversion of T_4 to T_3 has been thought to be important for the feedback of TH on TSH, since D2 knock out mice show a disturbed negative feedback (Schneider *et al*. 2001). As the LPS induced suppression of TRH in the hypothalamic PVN is associated with an increase of *Dio2* expression in the mediobasal hypothalamus (Boelen *et al*. 2004*a*, Fekete *et al*. 2004), it was speculated that the LPS induced decrease in *Tshβ* expression might also be dependent on increased D2 activity in the pituitary. Surprisingly, the response of *Dio2* expression in the pituitary after LPS appeared to be dependent on the species, strain and type of illness studied; both increased and decreased *Dio2* expression have been observed (Boelen *et al*. 2004*a*, 2006, 2009*a*, Fekete *et al*. 2004). Furthermore, administration of LPS to rats results in an increased pituitary D2 activity after 12 and 24 h, which is dependent on the fall in TH concentrations, in contrast to the hypothalamic D2 increase (Fekete *et al*. 2005). Further studies using pituitary specific D2 knock out mice are necessary to investigate the exact role of D2 in the LPS induced alterations in TH metabolism in the pituitary.

In addition to *Dio2*, the expression of *Dio1* in the pituitary is increased during inflammation (Boelen *et al*. 2004*a*, 2009*a*). This change is mediated by the increase in cytokines during the acute phase response, since animals deficient for IL12 and IL18 do not show the LPS induced increase (Boelen *et al*. 2004*b*,*c*). If the D1 increase in the pituitary gland serves a purpose with regard to the *Tshβ* decrease is unknown at present. Alternatively, the *Tshβ* decrease might be dependent on the changes in *Dio2* expression in the mediobasal hypothalamus, which could affect the pituitary either via suppression in *Trh* expression or theoretically via an increase in T_3 transported from the hypothalamus to the pituitary via the portal capillaries (Fekete & Lechan 2007).

In vitro studies using primary cultures of pituitary cells show that cytokines have a pronounced effect on pituitary release of TSHβ. Both IL1β and TNFα decrease basal TSHβ release independently of T_3 uptake and action in the pituitary cells (Harel *et al*. 1995, Wassen *et al*. 1996). Interestingly, acute energy deprivation has no effect on TSHβ release from pituitary cells in culture, consistent with the *in vivo* studies discussed above showing that the TSHβ decrease during chronic inflammation is only partly explained by decreased food intake (Boelen *et al*. 2006).

The effect of cytokines on TH synthesis

Several components of the TH synthesis pathway are downregulated by cytokines directly on the level of the thyrocyte, ultimately leading to decreased secretion of T_4 and T_3 (Bartalena *et al*. 1998).

Supraphysiological concentrations of the pro-inflammatory cytokines IL1α and IL1β inhibit the TSH-induced thyroglobulin (Tg) mRNA expression and Tg release in human cultured thyrocytes via suppression of cAMP (Rasmussen *et al*. 1988, 1994, Yamashita *et al*. 1989). IL1α and IL1β also decrease ^{125}I incorporation and T_4 and T_3 secretion from human thyrocytes in the presence of TSH (Sato *et al*. 1990). Thyroid peroxidase (TPO) mRNA expression and protein content, important for the oxidation of iodide to iodine, is also directly affected by IL1 in human thyrocytes and rat thyroid FTRL-5 cells (Asakawa *et al*. 1996, Gerard *et al*. 2006). Moreover, IL1β impairs basal and TSH-stimulated uptake of iodide by the natrium/iodide symporter (NIS) in porcine thyroid follicles (Nolte *et al*. 1994). The role of IL6 is less well established: one study showed that IL6 inhibits the TSH- and cAMP-induced increase in TPO mRNA expression and T_3 secretion in thyrocytes obtained from Graves' disease patients (Tominaga *et al*. 1991), while IL6 has

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only a minor effect on cultured human thyroid cells (Rasmussen *et al*. 1991).

IFNγ is a cytokine that is mainly involved in anti-viral and anti-bacterial responses and is produced by natural killer and T-cells. INFγ has a variety of effects on human thyrocytes in culture; it inhibits TSH- induced TH and Tg secretion (Nagayama *et al*. 1987, Kung *et al*. 1992) as well as Tg mRNA expression (Sato *et al*. 1990), TSH-induced TPO expression (Ashizawa *et al*. 1989) and the TSH- and cAMP-induced upregulation of TSH receptors on the thyrocyte (Nishikawa *et al*. 1993). IFNγ also inhibits the TSH-induced increase in NIS expression in rat FTRL-5 cells resulting in diminished iodide uptake (Ajjan *et al*. 1998). Interestingly, overexpression of IFNγ in thyroid cells in a transgenic mouse leads to primary hypothyroidism mainly due to a big decrease in NIS mRNA and protein expression (Caturegli *et al*. 2000).

TNFα plays an important role in the acute phase response and is known to inhibit the TSH-induced cAMP response and Tg production (Deuss *et al*. 1992) and release (Poth *et al*. 1991, Rasmussen *et al*. 1994) in cultured thyrocytes. TNFα also inhibits NIS expression in rat FTRL-5 cells (Ajjan *et al*. 1998).

Finally, cytokines are able to inhibit D1 expression and activity in the rat thyrocyte and FRTL-5 cells (Pekary *et al*. 1994, Hashimoto *et al*. 1995, Tang *et al*. 1995). Taken together, these studies clearly show that cytokines, either alone or synergistically, are able to downregulate various components of the TH synthesis pathway in the thyroid, ultimately leading to decreased secretion of T_4 and T_3 (Fig. 1).

Illness induced alteration in TH transport

Cellular entry of TH is necessary before intracellular conversion of TH by deiodinating enzymes and binding to the nuclear TR can take place. Two categories of TH transporters have been described i.e. the organic anion transporters and the amino acid transporters. The organic anion transporting polypeptide family consists of a variety of homologous proteins of which OATP1C1 is expressed in brain capillaries and in astrocytes where it is involved in the uptake of T_4 across the blood–brain barrier (Sugiyama *et al*. 2003). Well-known amino acid transporters of solute carrier (SLC) group are MCT8 and MCT10. MCT8 transports both T_4 and T_3 and is expressed in many tissues including liver, kidney and in various brain areas including cortical regions, striatum, cerebellum and hypothalamus (Alkemade *et al*. 2005, Heuer *et al*. 2005, Visser *et al*. 2011). MCT10 preferentially transports T_3 instead of T_4 and is expressed in kidney, liver and muscle (Visser *et al*. 2011). Once transported into the cell, THs can be metabolized by outer or inner ring deiodination through the iodothyronine deiodinases.

In a rabbit model for prolonged critical illness, hypothalamic *Oatp1c1* and *Mct10* expression was upregulated, while *Mct8* expression was unaltered (Mebis *et al*. 2009). The functional consequences of these changes were unclear. In mice that received a turpentine injection in the hindlimb, leading to the formation of a sterile abscess, *Mct8* as well as D3 (discussed in the following section) was found to be expressed in infiltrating neutrophils (Boelen *et al*. 2005). The rabbit and mouse studies show that MCT8 does respond to a variety of illnesses, but more extensive studies, including functional studies, will be needed to address this topic in more detail.

TH production and degradation by deiodinases

THs can be produced and degraded by iodothyronine deiodinating enzymes, so-called deiodinases. These enzymes belong to a selenocysteine containing enzyme family and comprise three types: D1, D2 and D3 (Kohrle 2000). D1 and D2 are T_3 producing enzymes while D3 inactivates T_4 and T_3. The expression and activity levels of all three deiodinases are affected during illness. The basic expression levels of the different deiodinases differ; some organs express predominantly D2 and D3 while other organs showed a limited expression of D2 or D3 but do express D1. The combination of the deiodinases expressed in a cell together or in the same tissue determine the availability of T_3 and thereby cellular and tissue function.

Type 1 deiodinase

The role of D1 in the pathogenesis of NTIS has been extensively studied as D1 is thought to be involved in the production of serum T_3 (decreased during illness) via outer ring deiodination and in the clearance of rT_3 (rT_3 concentrations are increased during illness in humans) via inner ring deiodination. D1 is localized in the plasma membrane, and expressed in liver, kidney, thyroid and pituitary. It is positively regulated by T_3 (Toyoda *et al*. 1995, Jakobs *et al*. 1997). Illness induces a marked decrease in liver D1 mRNA expression and activity in critically ill patients (Peeters *et al*. 2003, 2005) and in a variety of NTIS animal models (Boelen *et al*. 1995, 2004*a*, 2005, 2008, Debaveye *et al*. 2005).

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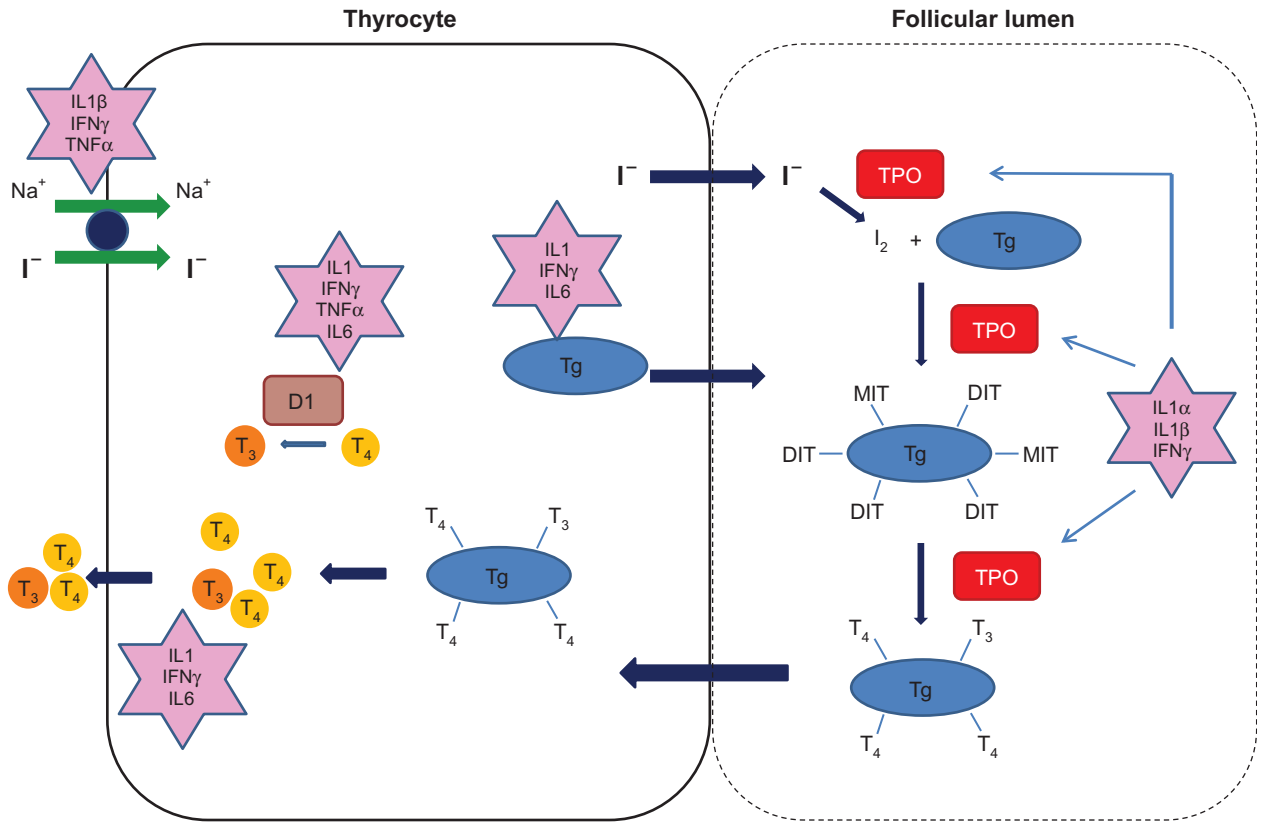

Figure 1

Cytokines have direct inhibitory effects on components of the thyroid hormone synthesis pathway in the thyrocyte. Cytokines diminish the uptake of iodide by the natrium/iodide symporter (NIS). Thyroglobulin (Tg) is synthesized within the follicular cells and is transported into the follicular lumen. The transcription of Tg is inhibited by cytokines. In the lumen, thyroid peroxidase (TPO) is a key enzyme in the formation of TH. It oxidizes I^- to I_2 and subsequently organifies the I_2 by linking it to the tyrosin residues on the Tg protein forming mono-iodotyrosine (MIT) and di-iodotyrosine (DIT). TPO subsequently combines MIT and DIT to form triiodothyronine (T_3) or two DIT residues to form thyroxine (T_4). TPO expression and function is inhibited by cytokines. After endocytosis into the follicular cell, Tg is broken down thereby releasing T_4 and T_3. Additional T_3 is formed by deiodination of T_4 by type 1 deiodinase (D1) which is also inhibited by cytokines.

The *Dio1* gene is activated via a TR/RXR heterodimer which indicates that decreased *Dio1* expression may result from reduced TR or/and reduced RXR expression. T_3 positively regulates the expression of *Dio1* via TRβ mediated binding to TH responsive elements in the *Dio1* promoter and functional TRβ signaling is therefore essential for basal expression of *Dio1* (Amma *et al*. 2001). Liver TRβ expression is downregulated during acute inflammation in mice (Beigneux *et al*. 2003, Boelen *et al*. 2004*a*). *In vitro* studies suggest a major role for cytokines, as IL1β decreases TRβ mRNA expression in a human hepatoma cell line (HepG2; Kwakkel *et al*. 2006). Furthermore, TNFα, IL1 and IL6 decrease the binding capacity of T_3 to the TR (Jakobs *et al*. 1997). An important intracellular signalling pathway for cytokines is the nuclear factor-kappa B (NF-κB) pathway. Nagaya *et al*. (2000) show that TNFα impairs the T_3 dependent induction of *Dio1* expression in HEPG2 cells via interference of NF-κB with TR function. There is, however, no evidence for a direct interaction between the TR and NF-κB which suggests a common cofactor by NF-κB and the TR to play a role (Nagaya *et al*. 2000).

Although it was assumed that mainly the TRβ was involved in the illness induced D1 repression in the liver, studies in $TR\beta^{0/0}$ and $TR\alpha^{0/0}$ mice show that while the LPS induced D1 decrease is still present in the $TR\beta^{0/0}$ mice, this response is attenuated in the $TR\alpha^{0/0}$ mice (Kwakkel *et al*. 2008, 2010). In addition, the IL1β induced decrease in TRβ mRNA expression in HepG2 cells is solely dependent on NF-κB signaling, while the decreases in *Dio1* and TRα are dependent on both NF-κB and activator protein-1 (AP-1) signaling (Kwakkel *et al*. 2006, 2007). This suggests that

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diminished expression of the TRβ by itself is not the only factor in the illness induced liver *Dio1* decrease.

An very elegant alternative mechanism for TRβ-mediated repression of liver D1 during acute inflammation has been proposed by Yu *et al.*, who showed both *in vivo* and *in vitro* that adding exogenous co-activator steroid receptor co-activator-1 (SRC-1) attenuates the illness induced liver D1 decrease (Yu & Koenig 2000, 2006). These studies indicate that competition for limiting amounts of SRC-1, which is a shared coactivator for TR and inflammatory signaling pathways, is one of the mechanisms involved in the illness induced D1 decrease. Indeed, restoration of liver *Dio1* expression by exogenous SRC-1 prevents the fall in serum TH levels after LPS (Yu & Koenig 2000, 2006).

After LPS administration, hepatic RXRα protein rapidly migrates to the cytoplasma where it can be degraded. This process is mediated by the inflammatory pathway JNK (Beigneux *et al.* 2000). However, the IL1β induced decrease of liver *Dio1* mRNA is not prevented by inhibition of JNK alone (Kwakkel *et al.* 2006), which makes it unlikely that RXR is solely responsible for the illness induced decrease in liver *Dio1*.

An additional possibility is that decreased amounts of a specific co-factor glutathione (GSH), required for D1 catalytic activity (Goswami & Rosenberg 1987) may play a role in the illness induced decrease of liver D1 activity. D1 activity in intact liver cells can be suppressed by IL6 and the addition of *N*-acetyl-cysteine, an antioxidant that restores intracellular GSH levels, prevents the IL6-induced suppression of D1 (Wajner *et al.* 2011, Fig. 2).

Although these studies provide mechanisms behind the illness induced D1 decrease in the liver, the importance of this decrease for the development of NTIS is questioned by studies in D1/D2 knock out mice, showing similar responses to LPS administration with regard to changes in serum T_4 and T_3 compared to WT littermates (St Germain *et al.* 2009). Although it is unknown at present whether a lack of D1 affects the illness induced liver T_3 concentrations, it has been shown in critically ill rabbits that the suppression of liver D1 activity was correlated with decreased hepatic T_3 concentrations (Debaveye *et al.* 2008).

Type 2 deiodinase

D2 is localized in the endoplasmic reticulum and deiodinates T_4 into the biologically active T_3. D2 is the main enzyme involved in the production of tissue T_3 and is therefore heavily involved in local TH metabolism. D2 is negatively regulated by TH, both pre- and post-transcriptionally, as T_3 down regulates *Dio2* mRNA expression (Burmeister *et al.* 1997), while T_4 as well as rT_3 (both substrates for D2) affect D2 activity via increasing D2 ubiquitination and subsequent proteasomal degradation (Sagar *et al.* 2007).

Many studies have focused on the role of D2 in the central part of HPT axis as the setpoint of the central HPT axis that is altered during illness. The unresponsiveness of the HPT axis to low serum TH levels has been suggested to be mediated by increased production of T_3 via elevated D2 activity in tanycytes (Fekete *et al.* 2004) as mice lacking the TRβ do not show an illness induced hypothalamic *Trh* decrease (Boelen *et al.* 2009*a*). In addition, global D2 knock out mice do not show a suppression of *Trh* upon LPS stimulation (Freitas *et al.* 2010).

The inflammation induced D2 upregulation in the hypothalamus was found to be independent of the fall in serum TH concentrations, in contrast to D2 expression in other brain areas like the cortex and in the pituitary (Fekete *et al.* 2005). A role for inflammatory cytokines was suggested as LPS administration results in a rapid increase of pro-inflammatory cytokines including TNFα, IL1 and IL6. The *Dio2* promoter contains NF-κB responsive elements and is thus sensitive to inflammatory signal transduction pathways (Fekete *et al.* 2004, Zeold *et al.* 2006). NF-κB is therefore highlighted as a possible mediator of the inflammation induced increase in *Dio2* expression in the hypothalamus.

In vitro, NF-κB is able to induce *Dio2* expression in mesothelioma cells endogenously expressing D2 (Zeold *et al.* 2006). In a primary culture of rat astrocytes and human glioma cells, LPS induces *Dio2* mRNA expression via the NF-κB and MAPK pathways (Lamirand *et al.* 2011). However, the significance of these findings with regard to NTIS are debatable, since the changes in *Dio2* expression occur relatively late in astrocytes compared to tanycytes. Stimulation of primary tanycytes with LPS also results in an increase of *Dio2* expression. This effect can be completely blocked when the transcriptional activity of the NF-κB pathway is inhibited (de Vries *et al.* 2014*a*) indicating an important role for NF-κB in the relevant cell type. These results will have to be replicated *in vivo*, since a study by Sanchez *et al.* (2010) showed that Iκ-Bα, a marker for NF-κB activation, is expressed secondary to the rise in *Dio2* in tanycytes after LPS administration in rats.

During fasting, a rise in D2 activity in the hypothalamus is also observed, however the magnitude of this response is marginal compared to the increase in D2 activity during inflammation. Furthermore, the

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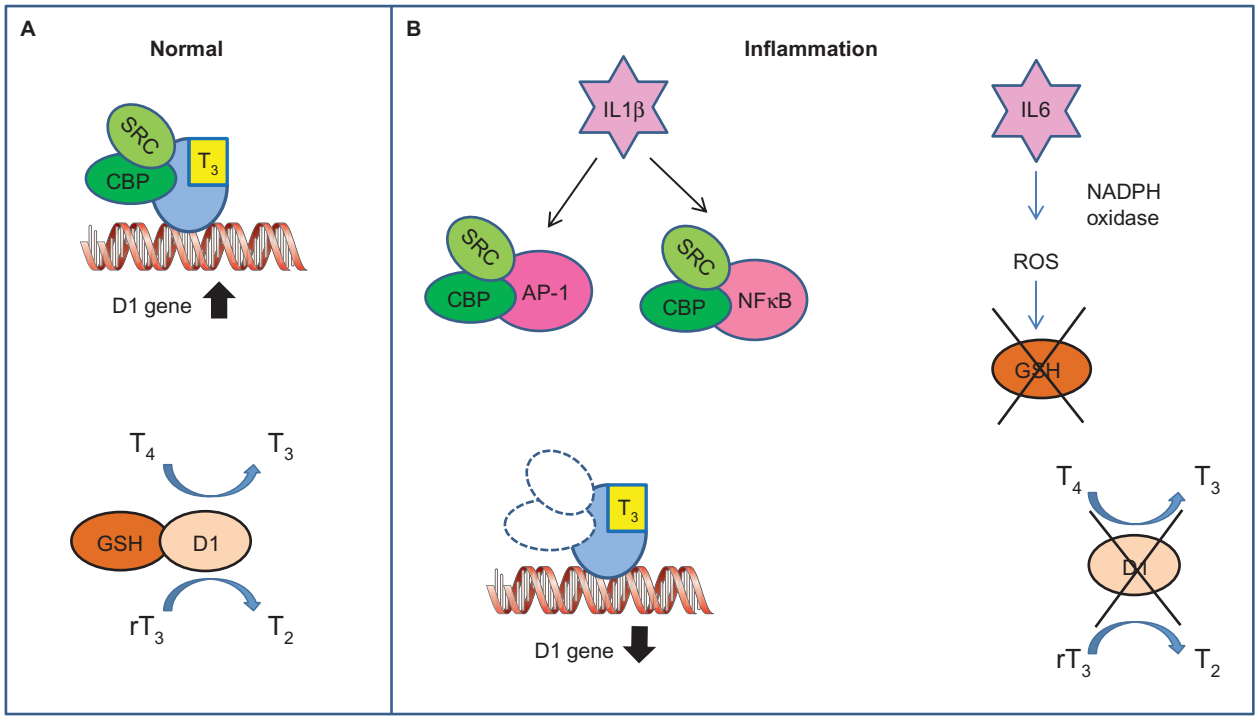

Figure 2
Schematic representation of the mechanisms involved in the inflammation-induced inhibition of type 1 deiodinase (D1) expression and activity. (A) Under physiological conditions, thyroid hormone receptor (TR) mediated gene transcription needs the presence of co-factors such as steroid receptor co-activator (SRC). D1 is dependent on cofactors such as glutathione (GSH). (B) During inflammation, competition for co-factors by cytokine induced pathways such as activator protein-1 (AP-1) and/or nuclear factor-kappa B (NF-κB) leads to less TR mediated transcription of the *Dio1* gene. Cytokines are also able to produce reactive oxygen species via the NADPH oxidase pathway which depletes the available GSH thereby diminishing D1 activity.

mechanisms behind the fasting induced increase in D2 are different and dependent on leptin, corticosterone and changes in neuropeptide expression (Diano *et al.* 1998).

D2 is expressed in skeletal muscle (Bianco & Kim 2006) and is thought to be involved in the peripheral production of T_3 under basal circumstances (Maia *et al.* 2005). *Dio2* expression in skeletal muscle increases in intensive-care unit patients (Mebis *et al.* 2007), in several NTIS animal models of acute (Kwakkel *et al.* 2008) and chronic inflammation (Kwakkel *et al.* 2009), while in septic patients and mice muscle *Dio2* expression decreases (Rodriguez-Perez *et al.* 2008, Kwakkel *et al.* 2009). The increased *Dio2* expression during chronic inflammation is likely due to enhanced CREB signalling (Kwakkel *et al.* 2009), while the decrease during sepsis might be mediated by decreased food intake since 62 h of fasting decreased muscle *Dio2* expression in healthy volunteers (Heemstra *et al.* 2009) (see Fig. 3).

Like inflammation, hypothyroidism increases D2 activity in the hindlimb muscle of mice (Marsili *et al.* 2010). The increased production of T_3 in muscle by D2 plays an important role during myogenesis, muscle regeneration and differentiation, and is mediated via the forkhead box O3 (FoxO3) pathway (Dentice *et al.* 2010, Marsili *et al.* 2011). Fox transcription factors are a class of transcription factors that bind to forkhead regulatory elements in the DNA and regulate a variety of cell functions (Accili & Arden 2004). Whether the FoxO3 pathway also plays a role in the inflammation induced D2 increase remains questionable at this stage.

D2 is also expressed in the lung, although the significance in the healthy adult lung is unknown (Escobar-Morreale *et al.* 1997, Ohba *et al.* 2001). During LPS induced lung injury (caused by intranasal LPS administration) and ventilator-induced lung injury (VILI) in mice, the expression of D2 in the lung is increased (Ma *et al.* 2011). In addition, D2 protein expression is increased in human microvascular endothelial cells that are subjected to cyclic stretch (Ma *et al.* 2011). The increase in D2 expression and the subsequent rise in local T_3 concentrations might be an adaptive and protective mechanisms of the lung to prevent lung damage during inflammation, since knocking down D2 *in vivo* aggravates lung injury after VILI

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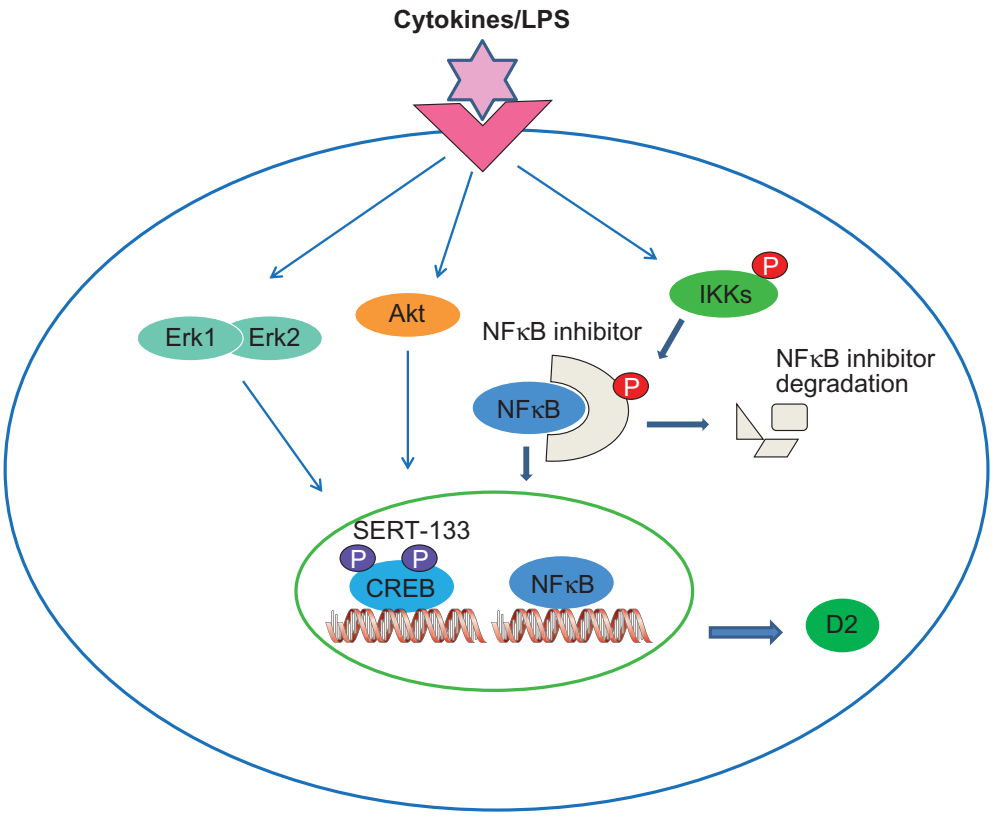

Figure 3
Schematic overview of the activation of type 2 deiodinase (*Dio2*) gene transcription by cytokines. Cytokines or LPS bind to their respective receptors. This leads to activation of IkB kinase (IKK), a kinase that phosphorylates the NF-κB inhibitor IkB. This is followed by degradation of the NF-κB inhibitor and translocation of NF-κB to the nucleus, where it activates *Dio2* gene transcription. Cytokines also activate protein kinase B (Akt) and Erk signaling pathways via binding to cytokine receptors which subsequently results in phosphorylation of cAMP responsive element binding protein (CREB), thereby activating *Dio2* transcription.

(Barca-Mayo *et al*. 2011, Ma *et al*. 2011). VILI leads to local increases of TNFα, IL6 and IL1β, again suggesting the involvement of cytokines in the upregulation of *Dio2* (Barca-Mayo *et al*. 2011) via NF-κB activation (Lentsch *et al*. 1998, Leeper-Woodford & Detmer 1999). Indeed, inhibiting NF-κB activation protects mice from LPS induced acute lung injury (Wang *et al*. 2013).

Interestingly, TH metabolism is also tightly linked with the innate immune system. Increased expression of *Dio2* is found in resident macrophages in the liver upon chronic and acute inflammation. However, this is not mediated by NF-κB and the mechanisms involved are unknown to date (Kwakkel *et al*. 2014).

D2 is homeostatically regulated by a post transcriptional mechanism involving ubiquitination mediated conformational changes and subsequent proteosomal degradation, explaining its short half-life compared to the other deiodinases. This mechanism was first described by Gereben *et al*. (2000) and was shown to be induced by the major substrate of D2, T_4. Ubiquitination of D2 by the ubiquitin conjugating enzymes UBC6 and UBC7 is mediated via WSB-1 (a D2 specific E3 ubiguitin ligase adaptor subunit) which changes the conformation of the D2 dimer and thus its catalytic activity (Sagar *et al*. 2007). D2 can be reactivated by de-ubiquitination by the de-ubiquitinating enzyme USP-33 (Curcio-Morelli *et al*. 2003). In tanycytes, both WSB-1 and USP-33 are co-expressed with D2 (Fekete *et al*. 2007). Recent studies, however, show that T_4 induced ubiquitination in tanycytes is minimal, probably to ensure the sensitivity of the TRH producing neurons in the PVN to fluctuations in serum TH concentrations (Werneck de Castro *et al*. 2015). In line with these findings, there is no evidence that ubiquitination is involved in the regulation of D2 during inflammation. Also in muscle, where D2 expression and activity is increased upon inflammation, WSB-1 and

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USP-33 expression is not correlated with the increased D2 activity during chronic inflammation and sepsis (Kwakkel *et al.* 2009).

Type 3 deiodinase

D3 is localized in the plasma membrane and can be viewed as the major TH inactivating enzyme, as it catalyzes inner-ring deiodination of both T_4 and T_3, exclusively resulting in the production of biologically inactive rT_3 and rT_2 (Kohrle 2000). D3 is highly expressed in the placenta during fetal development, thereby protecting the fetus from an overexposure of T_3 (Darras *et al.* 1999). In the adult organism, D3 is expressed in neurons in the brain, the liver and in parts of the innate immune system, although physiological levels are very low (Gereben *et al.* 2008).

Illness influences D3 expression and activity in the liver, but the results from animal studies vary. While during acute and chronic inflammation and during sepsis liver *Dio3* mRNA expression and activity levels are decreased (Boelen *et al.* 2005, 2008), hepatic D3 expression and activity are increased in rabbits with prolonged critical illness (Debaveye *et al.* 2005). Slightly increased D3 activity is also observed in the livers of severely ill patients (Peeters *et al.* 2003).

During prolonged critical illness, decreased food intake might be an important factor in regulating liver deiodinases. Fasting for 36 h or a 50% reduction in food intake for 3 weeks results in pronounced increase of D3 expression and activity in the liver (de Vries *et al.* 2014*b*). As prolonged illness is associated with persistently diminished food intake, the differences in D3 activity between the several illness models might be explained by the dominant role of reduced food intake. One of the hormones sensitive to food intake is leptin. Acute and chronic inflammation increase serum leptin via IL1β (Faggioni *et al.* 1998) while prolonged critical illness decrease serum leptin levels. The drop in leptin is known to be important for the increase in D3 activity during fasting in mice (Boelen *et al.* 2012) and might thus also be important for the regulation of D3 during illness.

Illness induces changes in muscle D3 expression that depend on the type and timing of the illness. While acute inflammation decreases muscle D3 (Kwakkel *et al.* 2010), bacterial sepsis does not affect D3 and chronic inflammation even increases D3 expression (Kwakkel *et al.* 2009). In critically ill patients, muscle D3 is also increased (Peeters *et al.* 2003). These changes seem to be independent on inflammatory pathways since neither sepsis nor chronic inflammation induces phosphorylation of the NF-κB and ERK pathways (Kwakkel *et al.* 2009). In proliferating myoblasts, D3 functions as a survival factor by decreasing TH concentrations and suppressing TH induced FoxO3 mediated gene expression (Dentice *et al.* 2014). In contrast, during muscle cell differentiation, inhibition of D3 gene expression is mediated by histone H3 demethylating enzyme (LSD-1) that relieved activation marks on the D3 promoter and at the same time activates D2 expression by removing the repressive marks on the D2 promoter in a reciprocal fashion (Ambrosio *et al.* 2013). Whether these epigenetic modifications of deiodinase gene expression are also important during inflammation remains to be investigated.

In cardiomyocytes, D3 expression is low under physiological conditions. Myocardial infarction and pressure induce hypertrophy in rats lead to an upregulation of D3 activity (Wassen *et al.* 2002, Olivares *et al.* 2007). It was postulated that the increase in D3 in peripheral organs might be regulated by hypoxia due to decreased tissue perfusion during illness (Peeters *et al.* 2003), and this assumption is supported by the observation that both D3 and hypoxia-inducible factor 1 alpha (HIF1α) are upregulated in the hypertrophic heart. Furthermore, HIF1α appeared to regulate D3 expression in a variety of cell lines under hypoxic conditions (Simonides *et al.* 2008). HIF1α activity is regulated by prolyl hydroxylases (PHD's) that prime HIF1α for degradation (Aragones *et al.* 2009). Both oxygen and 2-oxoglutarate (2-OG) are necessary cofactors for PHD's and therefore involved in HIF1α regulation. Under hypoxic conditions, HIF1α stabilizes and translocates to the nucleus, dimerizes with HIF1β and activates *Dio3* gene transcription (Simonides *et al.* 2008). However, decreased concentrations of 2-OG might also play a role in the stabilization of HIF1α as diminished food intake, frequently observed during illness, could result in decreased concentrations of 2-OG due to glucagon and increased gluconeogenic flux (Ochs 1984). In addition, during inflammation NF-κB also directly enhances HIF1α gene transcription, thereby increasing total HIF1α availability (Oliver *et al.* 2009, Fig. 4).

It was recently shown that the upregulation of D3 during myocardial infarction is also associated with increased expression of a specific set of microRNA's that might enhance the proliferative capacity of the cardiomyocytes (Janssen *et al.* 2013).

In addition to the organs and tissues mentioned, D3 is also expressed by infiltrating polymorphonuclear leukocytes upon the induction of a sterile abscess by turpentine injection in the hindlimb (Boelen *et al.* 2005). In addition,

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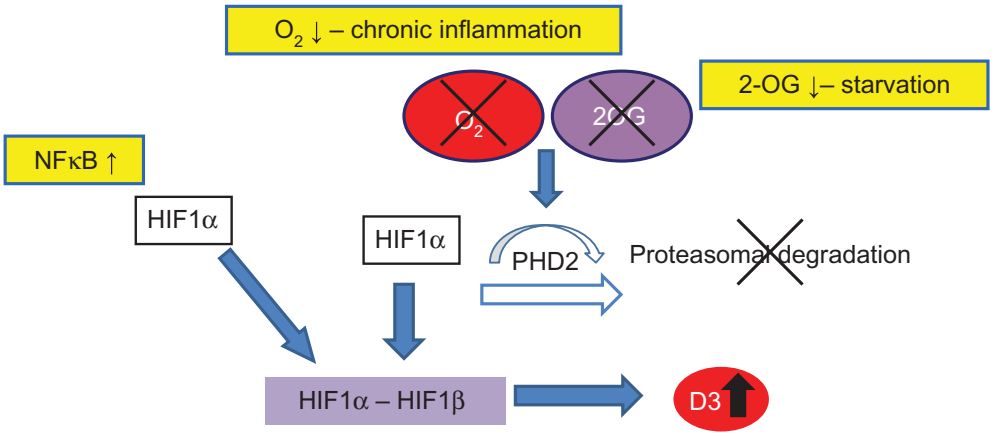

Figure 4
Schematic representation of mechanisms supposed to be involved in D3 regulation during illness. HIF1α is a protein that is regulated post-transcriptionally by proteasomal degradation. When oxygen and 2-oxoglutarate (2-OG) are present, HIF1α is hydroxylated by a class of enzymes called prolyl hydroxylases (PHD's) which makes HIF1α prone to degradation. When oxygen or 2-OG are low during Illness (due to decreased tissue perfusion or reduced food intake respectively), PHD's do not hydroxylate HIF1α, resulting in its stabilization and translocation to the nucleus where it dimerizes with constitutively expressed HIF1β and activates gene transcription. Upon inflammation, NF-κB is also able to induce HIF1α transcription which could contribute to D3 regulation.

peritonitis induced by *E. coli* and pneumonia induced by *S. pneumoniae* stimulates D3 expression in infiltrating granulocytes in the liver and lungs respectively (Boelen *et al.* 2008). Granulocytes are part of the innate immune system and have intracellular bacterial killing mechanisms such as the myeloperoxidase (MPO) system (Klebanoff 2005). It is hypothesized that following bacterial infection, the increased activity of D3 provides the MPO system with I^- that is released when the deiodination of T_3 and T_4 takes place to ensure an effective microbial killing machinery (Boelen *et al.* 2008). However, the mechanisms involved in the increase in D3 activity in activated neutrophils are currently unknown.

Although previously assumed otherwise, increased tissue D3 activity is not involved in the illness induced alterations in serum TH concentrations, since D3 knock out and WT mice showed similarly decreased serum TH concentrations during inflammation (Boelen *et al.* 2009*b*).

TH production and degradation by alternative pathways

TH are also metabolized in peripheral tissues via alternative pathways. Many of these processes take place in the liver. T_3 and T_4 can be conjungated to a sulphate group at the phenolic hydroxyl group, producing sulphated T_3 (T_3S) and sulphated T_4 (T_4S). T_3S has no affinity for the TR, while sulfated TH is prone to degradation by D1 (Mol & Visser 1985, Visser *et al.* 1998). Sulfation is mediated by sulfotransferases (Sults), a family of enzymes that sulfate both endogenous and exogenous substances, and is also dependent of the availability of specific cofactors (3′-phosphoadenosine-5′-phosphosulfate) and the availability of inorganic sulfate (Kaptein *et al.* 1997). Not much is known about the activity of Sults during illness. In serum of patients who died in the ICU, the T_4S concentrations are significantly elevated, but this is due to a decrease in clearance by D1 and not to increased Sult activity (Peeters *et al.* 2005). Furthermore, changes in sulfate availability during illness and diminished food intake could also play a role. In addition to sulfation, TH can be glucuronidated by UDP-glucuronosyltransferases (UGTs; Taurog *et al.* 1952). T_4, and to a lesser extent T_3, are substrates of a variety of UGT iso-enzymes. Glucuronidation facilitates the excretion of TH via the bile and feces (Tukey & Strassburg 2001). No alterations have been described in glucuronidation during critical illness *per se*, but methodological issues include increased glucuronidation due to the administration of drugs (Visser 1994) which will further decrease T_4 concentrations in ill patients.

A way of TH metabolism that is less well studied is ether link cleavage (ECL). This involves the breaking of the ether bridge in between the two tyrosines, yielding diiodotyrosine as a main product. This reaction is catalyzed by peroxidases, such as MPO that is present in leukocytes. *In vitro*, exposure to zymosan (a compound of yeast that induces phagocytosis) increased breakdown

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of T_4 and T_3 by ECL in leukocytes (Burger *et al*. 1983), indicating that this mechanism, besides deiodination, might be important for the bacterial killing machinery in the leukocyte. The role of ECL in TH metabolism under physiological conditions is thought to be limited, since only 5% of total body clearance of TH is mediated via ELC (Faber *et al*. 1989). However, it has been suggested that the serum concentration of DIT, a product of ELC, increase after surgery and during sepsis (Gramm *et al*. 1989, Meinhold *et al*. 1991), indicating that in specific pathophysiological conditions, ECL might attribute to TH clearance.

Concluding remarks

Several mechanisms are known to be involved in the illness induced alterations in the HPT axis and TH target tissues:

i) The illness induced suppression of TRH in the PVN is hypothesized to be mediated by increased T_3 production via increased D2 expression in tanycytes. Studies using specific inhibitors reported a causal role for NF-κB in the upregulation of D2. However, no conclusive data is available whether the induction of D2 observed in illness results in increased local T_3 concentrations.

ii) Whether the decreased thyroidal secretion during illness is due to central suppression of the HPT axis or to a direct inhibitory effect of cytokines on the thyroid gland is still unclear. *In vitro* studies showed that a variety of pro-inflammatory cytokines are able to inhibit crucial steps involved in TH production, from iodide uptake to TH secretion.

iii) The D1 decrease in liver during illness is likely due to suppressed TR signalling, possibly mediated by NF-κB, AP-1 and competition for common cofactors. Whether the suppression of liver D1 is causal for the illness induced decrease in serum T_3 is uncertain.

iv) Changes in D2 and D3 are observed in muscle, innate immune cells, adipose tissue and lung (D2) during illness. Inflammatory pathways might play a role, although NF-κB is not involved in the D2 increase in muscle and macrophages. Activation of the CREB pathway may be involved in the regulation of D2 in muscle.

More studies will be necessary to further define the underlying mechanisms and more importantly, to investigate the functional consequences of the changes in TH metabolism for cellular function. Ultimately, thorough knowledge of the pathogenesis and role of NTIS in critical illness may help to improve clinical outcome through targeted interventions in TH metabolism.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 4 May 2015
Accepted 13 May 2015
Accepted Preprint published online 13 May 2015

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-15-0133

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