REVIEW

# The hypothalamus-pituitary-thyroid axis in critical illness

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## ABSTRACT

**The thyroid axis is comprised of thyrotropin-releasing hormone (TRH) at the level of the hypothalamus which stimulates the pituitary to release thyrotropin (TSH). TSH in turn stimulates the thyroid to secrete the pro-hormone thyroxin (T4) and to a lesser extent the receptor active hormone tri-iodothyronine (T3). The majority of circulating T3 is generated by peripheral conversion of T4 by the intracellular iodothyronine deiodinases. Thyroid hormone (TH) is transported over the cell membrane by specific TH transporters such as monocarboxylate transporter 8 (MCT8). After transport and metabolisation in the cell, T3 can interact with nuclear TH receptors and activate or inactivate TH responsive genes.**

**Critically ill patients show uniform disturbances in the hypothalamus-pituitary-thyroid axis. There is clear evidence that circulating and tissue TH levels are low and this is called the low T3 syndrome or non-thyroidal illness syndrome. The clinical importance of the low T3 syndrome is still not very clear because it can either protect against or aggravate the catabolic state. Recently, novel insights were generated into the pathophysiology of the low T3 syndrome. Recent studies in animal models as well as in patients have shown alterations in TH transport and also in deiodinase activity which, together, may suggest an attempt of certain peripheral tissues as well as of the hypothalamus to compensate for low circulating TH levels. Reduced expression of TRH in the hypothalamus appears to play a key role in the prolonged phase of critical illness, although the processes that trigger this upstream disturbance remain unclear.**

## KEYWORDS

Deiodinase, critical illness, hypothalamic TRH, low T3 syndrome, MCT8, TSH

## CRITICAL ILLNESS

Critical illness is a condition in which patients depend on intensive medical support of vital organ functions in order to survive. Interestingly, studies have shown that the acute phase and chronic phase of critical illness are very different in terms of the metabolic and endocrine responses.[1] In the initial phase, these metabolic adaptations result in an increased availability of glucose, free fatty acids and amino acids as substrates for vital organs such as the immune system and the brain.[2,3]

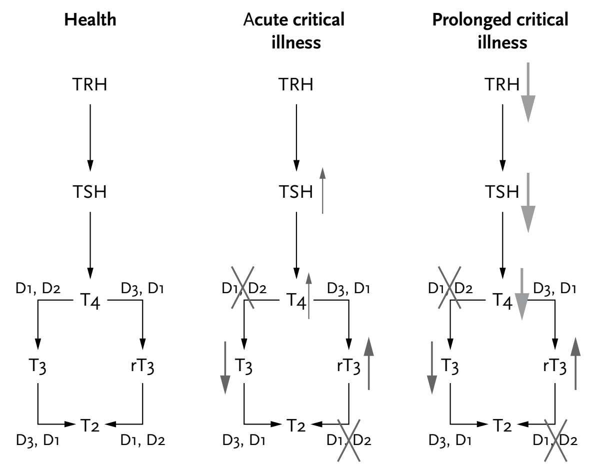
These changes have consistently been considered to be adaptive and beneficial, as they may postpone anabolism and, at the same time, activate the immune response.[4] In prolonged critical illness, a so-called 'wasting syndrome' occurs: despite feeding, protein continues to be lost from vital organs and tissues due to both activated degradation and suppressed synthesis, whereas adipose tissue is preferentially maintained.[5,6] This protein wasting leads to muscle atrophy and weakness, resulting in prolonged dependency on mechanical ventilation. Mortality of prolonged critical illness remains very high, in general exceeding 20%.

In the last decade, many efforts have been made to further understand the neuroendocrine characteristics of critical illness and it has appeared that the acute phase is mainly characterised by an actively secreting anterior pituitary gland and a peripheral inactivation or inactivity of anabolic hormones, whereas prolonged critical illness is hallmarked by reduced neuroendocrine stimulation of target endocrine organs.[7-9] While this has been documented for all hypothalamic-pituitary-dependent axes, the focus of this review will be on the alterations within the thyroid axis.

## LOW T3 SYNDROME

During health, the hypothalamus-pituitary-thyroid (HPT) axis functions as a classical feedback system (*figure 1*). At the level of the hypothalamus, thyrotropin-releasing

**Figure 1.** *Schematic outline of thyroid axis during health, acute critical illness and prolonged critical illness*




hormone (TRH) is released which stimulates the pituitary to secrete thyroid-stimulating hormone (thyrotropin or TSH). TSH in turn drives the thyroid gland to release the prohormone thyroxin (T4) into the circulation. Conversion of T4 in peripheral tissues produces the active hormone 3,5,3'-tri-iodothyronine (T3) and reverse T3 (rT3) which is thought to be metabolically inactive. T4 and T3 in turn exert a negative feedback control on the level of the hypothalamus and the pituitary.

Acute stress, due to sepsis, surgery, myocardial infarction or trauma, causes a drop in circulating T3 levels and a rise in rT3 levels and these changes can already be observed within a few hours after the onset of stress (*figure 1*).[10] Concomitantly, there is a brief rise in circulating levels of T4 and TSH.[11] The changes in the thyroid axis during acute critical illness are so uniformly present in all types of acute illnesses that they have been interpreted as a beneficial and adaptive response that does not warrant intervention.[4,12]

In prolonged critically ill patients circulating T3 levels decrease even further and T4 levels start to decline as well.[8] Despite the low serum T3, and in severe cases also low T4, single-sample TSH levels do not rise but remain within the normal range (*table 1*)[8] suggesting that in the chronic phase of critical illness, patients develop an additional neuroendocrine dysfunction (*figure 1*). It is unlikely that nature has been able to select coping mechanisms for the chronic phase of critical illness. Indeed, survival of this condition has only recently been made possible due to the development of highly technological interventions, making it unlikely that the hormonal responses that co-occur necessarily represent an adaptive response selected by 'nature'. This raises the question whether the low circulating T3 levels are protective in the prolonged phase of critical illness, or rather contribute to the clinical problems and are therefore harmful. To date, however, no studies have shown a benefit in treating patients with thyroid hormone with non-thyroidal illness, including preterm infants and postcardiac surgery patients.[13-19]

Together, these complex alterations that occur within the thyroid axis during critical illness are commonly referred to as the 'euthyroid sick syndrome', 'low T3 syndrome' or 'non-thyroidal illness' (NTI) syndrome,[20] different names indicating the ignorance regarding the exact pathophysiology and on the existence of altered thyroid hormone action as well as the clinical relevance of these changes. In routine clinical care, discrimination between true hypothyroidism and low T3 syndrome or NTI, is difficult but observing the full spectrum of changes in thyroid hormone and TSH levels can help (*table 1*).

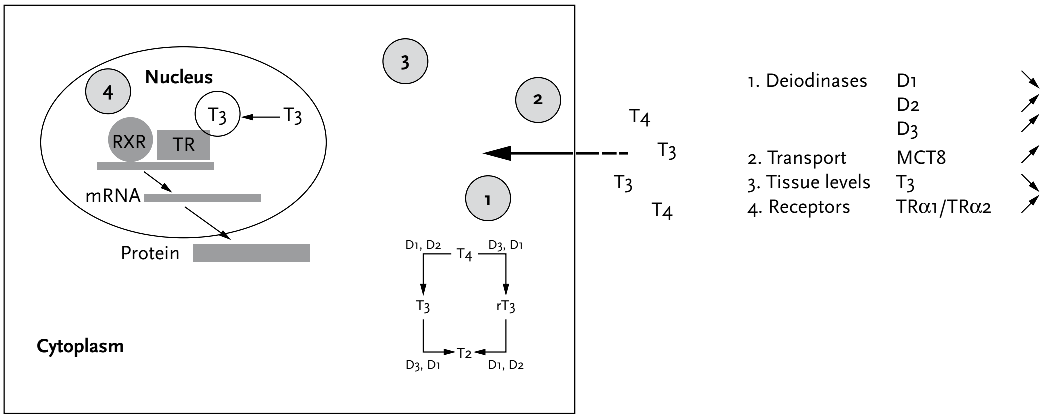
## PERIPHERAL CHANGES WITHIN THE THYROID AXIS DURING CRITICAL ILLNESS

Although thyroid hormone can exert some rapid nongenomic actions, mainly on the heart,[21,22] the major effects are produced by interaction of the active thyroid hormone T3 with nuclear receptors in order to stimulate or inhibit transcription of thyroid hormone responsive genes.[23,24] First, however, thyroid hormone has to be transported over the cell membrane[25] and once inside the cell, it can be metabolised by the iodothyronine deiodinases.[26] Peripheral transport, metabolism and receptor binding of thyroid hormones are all essential steps for normal thyroid hormone action. Changes have been documented in all these steps of thyroid hormone action in the peripheral tissues of critically ill patients (*figure 2*).[26-32] In prolonged

**Table 1.** *Simplified scheme of alterations in thyroid hormone parameters in primary hypothyroidism, central hypothyroidism and non-thyroidal illness*

| | Primary hypothyroidism | Central hypothyroidism | Non-thyroidal illness |
|---|---|---|---|
| T4 | Low | Low | Normal or low |
| T3 | Low or low-normal | Low or low-normal | Low |
| rT3 | Low or normal | Low or normal | Elevated or normal |
| TSH: | | | |
| • Single sample | Elevated | Low or normal | Normal |
| • Pulsatile secretion | Elevated | Low | Low |

**Figure 2.** *Schematic outline of thyroid hormone uptake and metabolism in the cell (left) and overview of the observed peripheral changes in prolonged critical illness (right)*




**TR = thyroid hormone receptor; RXR = retinoid-X receptor; MCT8 = monocarboxylate transporter 8; D1 = type 1 deiodinase; D2 = type 2 deiodinase; D3 = type 3 deiodinase.**

critical illness, these peripheral alterations persist, but a neuroendocrine-induced suppression of thyroidal T4 release, becomes the predominating feature.[1]

### Thyroid hormone deiodination

There are three types of iodothyronine deiodinases (D1 to D3).[26] These enzymes constitute a family of selenoproteins that selectively remove iodide from T4 and its derivatives thereby activating or inactivating these hormones. In general, each enzyme is expressed in a given cell type. D1 is expressed in the thyroid gland, liver, kidney and pituitary and has outer ring deiodination (ORD) activity, hereby contributing to the bioactivation of T4 to T3, but this enzyme also has inner ring deiodination (IRD) activity especially towards sulphated T4 and T3. D1 activity is regulated by T3 at the transcriptional level which results in a stimulation of D1 activity during hyperthyroidism and a decrease in D1 activity during hypothyroidism.[24] D2 is expressed in the brain, thyroid gland, skeletal muscle and anterior pituitary and only has ORD activity. D2 thus converts T4 into the active hormone T3 and rT3 into 3,3'-diiodothyronine (T2). D2 is thought to contribute to circulating T3[33] and is essential for local T3 production, especially in brain and pituitary.[34] D3 only has IRD activity and therefore mediates the degradation of thyroid hormone: it catalyses the conversion of T4 into rT3 and of T3 into T2.[26,35] It is present in brain, skin, various foetal tissues, and in pregnant uterus and placenta where it protects the foetus against excess T3 concentrations, which are detrimental for normal development.[36] It has been named an oncofoetal protein since it has also been found in vascular tumours and malignant cell lines.[32] These D3-expressing tumours cause a massive inactivation of circulating thyroid hormone which leads to a condition called 'consumptive hypothyroidism'.[37]

During critical illness, the changes observed in circulating thyroid hormone parameters, i.e. low T3 and high rT3, suggest that decreased monodeiodination of T4 could be involved.[18,19] This would result in reduced conversion of T4 into active T3 and increased metabolisation of T4 into the inactive metabolite rT3. This was indeed confirmed in a study by Peeters *et al.* who showed that D1 activity is markedly reduced in post-mortem liver samples of critically ill patients as compared with values previously observed in healthy individuals.[20] Furthermore, D1 activity correlated positively with the serum T3/rT3 ratio, the latter being associated with the degree of tissue hypoperfusion preceding death in these patients.[20] Decreased hepatic D1 expression and activity is likely mediated by cytokines as shown in a mouse model of acute illness and in primary cultures of rat hepatocytes.[25-27] Debaveye *et al.* were able to demonstrate in a unique rabbit model of prolonged critical illness that the drop in D1 activity is reversible as it can be reactivated by infusing TRH in critically ill rabbits.[21,28] This treatment restored hepatic D1 activity and brought serum T4 and T3 levels back within normal range.[21] Since D1 is also important for degradation of sulphated iodothyronines, it was hypothesised that sulphated T4 (T4S) could be increased in critically ill patients who have a diminished D1 activity. The concentrations of sulphated iodothyronines in serum are normally low[38,39] and indeed, in one study, increased circulating concentrations of T4S were measured in critically ill patients as compared with healthy references.[40] A negative correlation was found between serum T4S levels and D1 activity in the liver suggesting that a decreased liver D1 activity could play an important role in the increase of T4S levels during critical illness. However, analysis of serum T4S levels in children with meningococcal sepsis has led to different results. In these children, average T4S levels were decreased as compared with healthy controls.[41]

D3 is normally absent in adult tissue but Peeters *et al.* showed a reactivation of D3 in liver and muscle of critically ill patients.[31] In a rabbit model of prolonged critical illness, D3 activity could be suppressed when T3 levels were increased either by the continuous infusion of TRH in combination with a growth hormone (GH) secretagogue or by the administration of growth hormone.[28] Together, the reduction in D1 and reactivation of D3 result in a decreased activation and an increased inactivation of thyroid hormone in critically ill patients.[31]

D2 activity is controlled by thyroid status both at the pre- and post-translational level: D2 is upregulated during hypothyroidism, whereas high T3 levels will lead to diminished D2 activity.[26] These characteristics make D2 an ideal player for regulating local T3 levels, which has been demonstrated clearly in the rat brain.[42,43] Surprisingly, a report by Larsen *et al.'s* group showed that skeletal muscle D2 may significantly contribute to circulating T3 as well, particularly in the hypothyroid state.[33] The investigators therefore suggested that diminished D2 activity during critical illness could play a key role in the reduced activation of T4 into T3 in that condition. In contrast to this hypothesis, however, our research group found increased levels of D2 gene expression and activity in skeletal muscle of prolonged but not acute critically ill patients.[29] These findings were not explained by changes in circulating cortisol, cytokines or by altered organ function. The data suggest that at least in the prolonged phase of critical illness, D2 adapts appropriately to the low T3 levels, and likely does not contribute to the 'low T3 syndrome' in this condition

**Thyroid hormone binding and transport**

The majority of T3 and T4 in serum is bound to thyroid hormone-binding proteins such as T4-binding globulin (TBG), transthyretin (TTR) and albumin.[44] During health, approximately 0.03% of the total serum T4, and 0.3% of the total serum T3 are present in free or unbound form and it is only this free fraction that is available for transport across the cell membrane.[45,46] In acute events such as sepsis or coronary bypass surgery it has been shown that circulating levels of T4-binding proteins are low, which contributes to the decreased serum T4 levels.[41,47,48] Also, studies suggest that in the serum of critically ill patients, disease-specific inhibitors of thyroid hormone binding may be present.[49,50] This could potentially result in diminished uptake of thyroid hormone by cells or in a distortion of the normal interaction between thyroid hormone and its nuclear receptors. This was shown by adding serum of critically ill patients to cultured hepatocytes which inhibited the uptake of T4 into these cells.[51-53] This has led to the identification of several inhibitors, such as indoxyl sulphate, nonesterified fatty acids, and bilirubin which circulate in increased concentrations during critical illness.[51,54] However, a study by Brent and Hershman showed that exogenous T4 administration to prolonged critically ill patients could restore circulating T4 back to normal levels. Therefore, an inhibitor of binding cannot be the predominate cause of low serum T4 during critical illness.[15]

During critical illness, T4 uptake in the liver is decreased which can also contribute to lowered T3 production.[55,56] Possibly, this can be explained by an existing negative energy balance leading to hepatic adenosine-5'-triphosphate (ATP) depletion.[57,58] This idea is supported by the observation that administration of fructose to healthy volunteers, transiently decreasing liver ATP levels, was followed by a temporary decrease in liver T4 uptake.[59]

Recently, it was shown that gene expression of the very specific thyroid hormone transporters MCT8 is upregulated in liver and skeletal muscle of prolonged critically ill patients. This coincided with a significant inverse correlation between circulating thyroid hormone parameters and MCT8 gene expression in skeletal muscle.[30] This means that patients with the lowest serum T3 and T4 levels show the highest upregulation of MCT8 mRNA. Furthermore, in a rabbit model of prolonged critical illness, treatment with a combination of T3 and T4, thereby increasing circulating levels of T3 and T4, reduced transporter expression levels in liver and skeletal muscle.[30] This shows that in this animal model, thyroid hormone transporter expression levels are regulated by the thyroid hormone status during critical illness resulting in increased MCT8 expression levels when circulating and tissue iodothyronine levels are low and a decrease in MCT8 expression when circulating and tissue iodothyronine levels are high. These data suggest that some tissues may try to adapt to the low circulating T3 levels by increasing expression of thyroid hormone transporters in order to facilitate cellular uptake of thyroid hormone.

**Thyroid hormone tissue levels**

There are many studies showing that circulating iodothyronine levels are reduced during critical illness,[60-63] but only a few attempted to measure iodothyronine concentrations in tissues. Peeters *et al.* showed that there is a good correlation between circulating T3 levels and skeletal muscle as well as liver T3 content in critically ill patients.[64] In this study, the investigators also showed that in patients who had received thyroid hormone treatment, serum T3 concentrations were higher with concomitantly and proportionally higher skeletal muscle T3 concentrations.[64] This confirmed the findings of Arem *et al.* who showed that, in general, T3 concentrations were decreased in the tissues of patients who died after prolonged critical illness, as compared with the levels observed in tissues obtained from patients who died suddenly from a car accident.[65] This suggests that low circulating iodothyronine levels actually result in hypothyroidism at tissue level during critical illness. However, the bioactivity of thyroid hormone is not only dependent on its concentration in the cell; it can also be modulated at the level of its nuclear receptors. There are three functional thyroid hormone receptors: TRα1, TRβ1 and TRβ2 and they all bind T3 with similar affinity.[66,67] The TRs bind to thyroid hormone response elements in specific target genes which are then transcriptionally activated or repressed. In the absence of thyroid hormone, TRs repress or silence basal transcription of positively regulated genes in proportion to the amount of receptor and the affinity of receptor binding sites.[68] Of special interest is TRα2, which is also encoded by the TRα gene. It lacks a functional ligand binding domain and acts as a dominant negative inhibitor of thyroid hormone action.[69] A study by Thijssen-Timmer *et al.* showed that the TRα1/TRα2 ratio in postmortem liver biopsies from critically ill patients was inversely related to the T3/rT3 ratio.[32] Also, sicker and older patients showed higher TRα1/TRα2 ratios as compared with the less sick and younger ones. Increasing the expression of the active form of the thyroid hormone receptor gene could be a mechanism to enhance sensitivity to T3 in the oldest and sickest patients and can be regarded as an adaptive response to decreasing levels of circulating thyroid hormone.

## NEUROENDOCRINE CHANGES DURING CRITICAL ILLNESS

In addition to the peripheral changes in thyroid hormone metabolism, critical illness is hallmarked by some very distinct neuroendocrine alterations that are quite different in the prolonged phase of critical illness as compared with the first few hours or days after the onset of a severe illness.[70] In the acute phase of critical illness, circulating T3 levels drop which is followed by a brief rise in serum TSH concentrations. TSH levels subsequently return to normal levels despite ongoing decline in T3 levels.[8,11] But the nocturnal TSH surge that is present in healthy individuals is shown to be absent in these patients.[11] The fact that TSH levels remain relatively normal in face of declining T3 concentrations can be indicative of an altered set-point for feedback inhibition within the hypothalamic-pituitary-thyroid axis.[8,11]

In the prolonged phase of critical illness, TSH secretion loses its pulsatility and this loss of pulsatility is positively correlated to the low serum levels of T3.[8,9] When patients start to recover from their illness, an increase in serum TSH can be observed.[71,72] In the hypothalamus, TRH gene expression is also shown to be dramatically reduced in patients dying after chronic critical illness as compared with those who died after a road accident or an acute illness.[73] Furthermore, a positive correlation is shown between TRH mRNA levels and serum T3.[73] These findings indicate that the reduced production of thyroid hormones in the prolonged phase of critical illness may have a neuroendocrine origin. This is further substantiated by the finding that a continuous infusion of TRH can increase TSH secretion and, concomitantly, increase the low circulating levels of T4 and T3 back into the normal ranges.[9] This suggests a predominantly central origin of the suppressed thyroid axis in prolonged critical illness.

### Role of cytokines

Cytokines have been investigated as putative mediators of the acute low T3 syndrome.[74-77] Mice were injected with tumour necrosis factor-α (TNFα), interleukin (IL)-1, IL-6 or IFNγ, but only IL1 was able to induce a systemic illness.[74] Despite this systemic illness, serum T3, T4 and TSH levels were unchanged. Only IFNγ decreased serum T4 and T3 in a dose-dependent manner without changes in serum TSH.[74] Studies in humans on the other hand showed a relation between IL-6 levels and serum T3 values[78] and when TNFα was injected in healthy male subjects, changes in circulating thyroid hormone levels were observed that were reminiscent of the low T3 syndrome.[77] On the other hand, there are several arguments against a causative role of cytokines in directly evoking the low T3 syndrome. Cytokine antagonism for example failed to restore normal thyroid function both in humans[79] and in animal studies.[80] And in a large group of hospitalised patients, cytokines were not withheld as independent determinants of the variability in circulating T3.[75]

### TRH feedback in the hypothalamus

One of the marked features in prolonged critical illness is the suppressed TRH gene expression in the hypothalamus in the face of low circulating thyroid hormone levels. Several mechanisms have been proposed for the suppression of the HPT axis during critical illness, among which a local thyrotoxicosis in the hypothalamus. Increased hypothalamic T3 availability, despite low circulating T3 levels, could indeed explain feedback inhibition of the TRH gene in the context of the low T3 syndrome. One way to increase the local concentration of T3 in the hypothalamus is by increased local conversion of T4 to T3. More than 80% of T3 in the brain originates from local T4 to T3 conversion by D2.[42] Therefore, an upregulation of D2 in the mediobasal hypothalamus could lead to a local hyperthyroid state which in turn would suppress TRH in hypophysiotropic neurons. This has recently been shown in a study of prolonged critically ill rabbits.[81] Injection of LPS in rats and mice has also shown to upregulate hypothalamic D2 expression and activity.[27,82,83] This effect did not seem to be induced by hypothyroidism[84] but could be a direct effect of induced cytokines on D2 expressing tanycytes.[85,86] Alternatively, decreased inactivation of T3 and T4 by D3 could also lead to higher hypothalamic thyroid hormone levels suppressing TRH. In line with this, a mouse model for chronic inflammation showed decreased D3 mRNA expression in the region of the hypothalamic paraventricular nucleus.[87] Another possible mechanism, by which local iodothyronine levels in the hypothalamus could be increased, is elevated transport of iodothyronines into the hypothalamus. Study of MCT8 null-mice suggests that its expression is necessary for normal feedback regulation of hypophysiotropic TRH neurons.[88,89] Recently, in a rabbit model of prolonged critical illness, upregulation of other thyroid hormone transporters, MCT10 and OATP1C1, was documented.[81]

Although increased local T3 availability in the hypothalamus could explain reduced TRH expression by feedback inhibition, there is one report of a study in critically ill patients wherein thyroid hormone content was measured in the hypothalamus. In this study, hypothalami from critically ill patients contained less than half the concentration of T3 as compared with patients who died from an acute trauma.[65] Also in the rabbit model of prolonged critical illness, T3 content in the hypothalamus was not increased.[81] Therefore, other possible mechanisms driving the suppression of TRH expression and release in the context of critical illness should be considered and investigated. In the presence of such suppressors, the alterations observed in D2 and in thyroid hormone transporters during prolonged critical illness could be interpreted as a compensatory response.

**Feedback by neuronal afferents**

TRH neurons in the PVN also receive input from the melanocortin signalling system which consists of at least two antagonising neuron populations located in the arcuate nucleus of the hypothalamus. One group of neurons synthesise alpha melanocyte stimulating hormone (α-MSH) and co-express cocaine and amphetamine-regulated transcript (CART), while the other group of neurons synthesise neuropeptide Y (NPY) and co-express agouti-related peptide (AGRP). The α-MSH neurons have an activating, while NPY neurons have an inhibiting effect on TRH expression.[90] Interestingly, the action of these two neuron populations is also modulated by leptin, a hormone produced by adipocytes, which declines in the fasting state and returns to normal levels by refeeding. The changes in serum thyroid hormones and TSH during fasting could be the result of declining leptin levels which results in an inhibition of α-MSH production and increased AGRP production.[91,92] In critical illness however, the mechanisms for reducing TRH seem to be different. Endotoxin administration in rodents, which simulates infection, increases rather than decreases α-MSH gene expression and does not alter the expression of NPY in arcuate nucleus neurons.[93] Furthermore, in patients who died from severe illness, NPY expression was reduced and showed a positive correlation with TRH levels[90] while an inverse correlation was seen during starvation.[88]

## THERAPEUTIC INTERVENTIONS

Although circulating thyroid hormone levels are inarguably low during critical illness, there is no consensus on the potential role for thyroid hormone treatment in this patient group. The clinical studies with T4 or T3 administration have failed to demonstrate important clinical benefit in critically ill patients.[15,94] These studies have several limitations, however. Firstly, they were not well powered to detect clinically significant changes. Secondly, it could be argued that, with a rise in D3 and reduced D1, T4 is not an appropriate therapy due to the preferential conversion of T4 to rT3 rather than to T3. Also, prolonged infusion of T3 alone is not ideal, as this will hold risk of suppression of endogenous T4 production, due to feedback inhibition. Theoretically, this could evoke hypothyroidism at the time of interruption of the T3 treatment. Brief administration of substitution doses of T3 after cardiac surgery in paediatric patients has been shown to improve postoperative cardiac function[14] and very brief, merely intraoperative, T3 treatment in adult cardiac surgery patients provided acute haemodynamic improvements, without detectable longer-term clinical benefits.[16] The paediatric patients in the study mentioned above, however, were treated with dopamine which induces iatrogenic hypothyroidism and therefore that study does not provide hard evidence of clinical benefit with treatment of the non-iatrogenic low T3 syndrome of prolonged critical illness.[95,96] Several other frequently used ICU drugs can also affect the HPT axis (*table 2*). Whether these drugs induce an iatrogenic suppression of the HPT axis, such as clearly shown with dopamine infusion, is not well documented. Furthermore, it remains unclear whether iatrogenic hypothyroidism

**Table 2.** *Frequently used ICU drugs interfering with thyroid hormone economy*

| |
|---|
| Glucocorticoides |
| Iodinated contrast agents, iodine wound dressings |
| Propranolol |
| Amiodarone |
| Barbiturates |
| Dopamine |
| Opiates |
| Benzodiazepines |
| Sulphonamides |
| Somatostatin |
| Furosemide |

adversely affects outcome. One population in which such a risk for adverse outcome can be inferred and thus dopamine treatment should be avoided is the neonates, as the importance of adequate thyroid function for neurocognitive development is beyond debate.

Alternatively, treatment with hypothalamic releasing peptides may be a better strategy. Studies by our group have shown that TRH infusion in critically ill patients could reactivate the thyroid axis.[9] Interestingly, when TRH is co-infused with GH secretagogues a rise in circulating rT3 is avoided.[9] Experiments in rabbits have further shown that infusion of TRH with GH secretagogues could reduce D3 activity and increase hepatic D1 activity.[28] In addition, the negative feedback exerted by thyroid hormones on the level of the pituitary is maintained, avoiding unnecessary overstimulation of the thyroid axis,[97] making it a potentially safer treatment than the administration of T3. The clinical outcome benefit of combined TRH and GH secretagogue-induced stimulation of the thyroid axis in prolonged critical illness remains to be investigated.

## NOTE

This work was supported by the Fund for Scientific Research Flanders, Belgium (FWO) and by long term structural funding, Methusalem – funding, by the Flemish Government.

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