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Changes Within the Thyroid Axis During the Course of Critical Illness

Liese Mebis, MSc[a], Yves Debaveye, MD[a],
Theo J. Visser, PhD[b],
Greet Van den Berghe, MD, PhD[a,*]

[a]*Department of Intensive Care, Catholic University of Leuven, Leuven, Belgium*
[b]*Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands*

Thyroid hormone acts on virtually all cells of the body and has profound effects on many important physiologic processes, such as differentiation, growth, and metabolism [1,2].

The thyroid axis comprises thyrotropin-releasing hormone (TRH) at the hypothalamic level; thyrotropin at the pituitary level; and thyroxine (T_4), triiodothyronine (T_3), and reverse T_3 (rT_3) at the peripheral level. At the pituitary level, secretion of thyrotropin is stimulated by TRH from the hypothalamus. Thyrotropin is released in secretory bursts superimposed on nonpulsatile secretion and thereby stimulates the thyroid gland to release the prohormone T_4 into the circulation. Peripheral conversion of T_4 produces the metabolic active hormone, T_3, and rT_3, which is believed to be metabolically inactive. T_4 and T_3 in turn exert a negative feedback control on the level of the hypothalamus and the pituitary.

During critical illness, multiple and complex alternations occur in the hypothalamic-pituitary-thyroid (HPT) axis, resulting in what commonly is referred to as the euthyroid sick syndrome. More neutral terms, avoiding the assumption that patients really are euthyroid, are low T_3 syndrome or nonthyroidal illness.

Within 2 hours of the onset of acute stress, such as sepsis, surgery, myocardial infarction, or trauma, circulating T_3 levels drop and rT_3 levels increase. The magnitude of these changes reflects the severity of illness [3–6].

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* Corresponding author. Department of Intensive Care Medicine, Catholic University of Leuven, Herestraat 49, B-3000, Leuven, Belgium.
E-mail address: Greta.vandenberghe@med.kuleuven.be (G. Van den Berghe).

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At the same time, circulating levels of T_4 and thyrotropin rise briefly [7] but subsequently normalize. These observed changes in circulating thyroid hormone levels during the acute phase of critical illness are caused largely by disturbances in peripheral thyroid hormone metabolism and binding.

Patients requiring prolonged intensive care therapy enter a chronic phase of illness. In these prolonged critically ill patients, T_4 levels also start to decline and circulating T_3 levels may become very low or even undetectable [8]. Despite the major decreases in serum T_3 and, in severe cases, of T_4, the concentration of thyrotropin, measured in a single sample, typically remains within the normal range [8]. This may indicate that a neuroendocrine dysfunction adds to the pathogenesis of the low T_3 syndrome in the chronic phase of critical illness (Fig. 1).

This article reviews the mechanisms behind the observed changes in thyroid hormone parameters in the acute phase and the chronic phase of critical illness, focusing on the central and the peripheral parts of thyroid hormone metabolism.

Peripheral changes during critical illness

Disturbances in peripheral thyroid hormone metabolism play a major role in the pathogenesis of the low T_3 syndrome during critical illness, particularly during the acute phase of critical illness. These alterations continue to persist in prolonged critical illness, but here a neuroendocrine dysfunction leading to a decline of thyroidal release of T_4 is superimposed on the peripheral adaptations.

Deiodinases

The peripheral metabolism of thyroid hormone involves three deiodinases (D1, D2, and D3) [3]. D1 and D2 have enzymatic outer-ring deiodination activity, which is considered an activating pathway, whereas inner-ring deiodination is an inactivating pathway catalyzed by D3 [9]. D1 is expressed in the thyroid gland, liver, and kidney and generally is considered the main source of circulating T_3 [3,9]. D2 is expressed in the brain, anterior pituitary, thyroid, and skeletal muscle. This enzyme is important for local T_3 production, especially in the brain and pituitary, but skeletal D2 also is believed to contribute to circulating T_3 [10,11]. D3 is present in the brain, skin, placenta, and pregnant uterus and in various fetal tissues. It is the major inactivating enzyme, as it catalyzes the conversion of T_4 into rT_3 and of T_3 into 3,3′-diiodothyronine (3,3′-T2) and thereby is able to protect tissues from excess thyroid hormone [3,9].

During critical illness, multiple alterations occur in the peripheral thyroid hormone metabolism whereby the conversion of T_4 into active T_3 is reduced and, instead, T_4 is metabolized into inactive rT_3. The resulting reciprocal changes in T_3 and rT_3 were observed decades ago and decreased

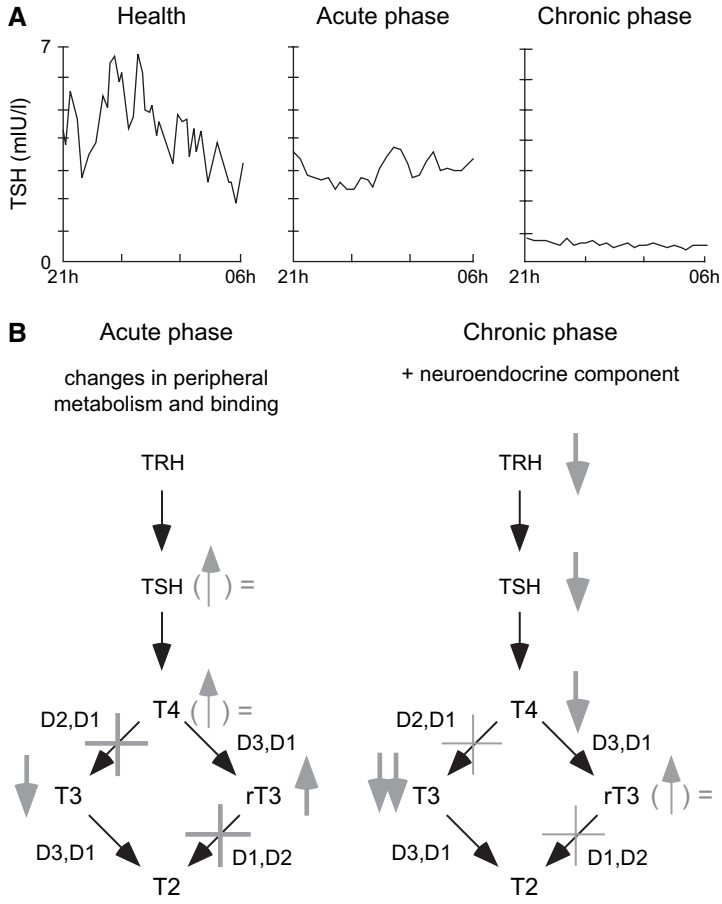

Fig. 1. Response of the thyroid axis to critical illness. (*A*) The nocturnal serum concentration profiles of thyrotropin in critical illness are abnormal and differ markedly between the acute and chronic phase of the disease. (*Modified from* Van den Berghe G, de Zegher F, Bouillon R. Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 1998;83:1827–34; with permission. © [1998] The Endocrine Society.) (*B*) Simplified overview of the major changes occurring within the thyroid axis during the acute and chronic phase of critical illness. The normal regulation of the thyroid axis is shown in black, whereas the alterations induced by critical illness are indicated in gray. As discussed in the text, for the acute phase of critical illness, thyrotropin and T4 levels are elevated briefly and subsequently return to normal, represented by (↑). T2, diiodothyronine. (*Reproduced from* Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol 2000;143:1–13; with permission. © [2000] Society of the European Journal of Endocrinology.)

monodeiodination of T_4 was suggested then as a possible mechanism [12,13]. Recently, this premise has been confirmed by Peeters and colleagues, showing that there is a decreased activation and an increased inactivation of thyroid hormone in patients who are critically ill [14]. The role of deiodinases during critical illness has been explored further in a rabbit model

of prolonged critical illness [15,16] and in mouse models of acute illness [17,18].

D1 in liver and kidney in general is considered the major source of circulating T_3 and the primary mechanism for rT_3 clearance. D1 activity is stimulated in hyperthyroidism and decreased in hypothyroidism, representing the regulation of D1 activity by T_3 at the transcriptional level [19]. Analysis of postmortem skeletal muscle and liver samples obtained from critically ill patients at the time of death in an ICU indeed showed a marked reduction in liver D1 activity compared with values observed previously in individuals who were healthy [16]. Serum T_3/rT_3 ratio, a marker for the severity of illness, correlated positively with liver D1 activity, being highest in patients who died from severe brain damage and lowest in patients who died from cardiovascular collapse. Furthermore, this has been confirmed in a rabbit model of prolonged critical illness, showing also that the decrease in D1 activity is reversible [15]. Infusion of TRH could restore D1 activity and serum T_4 and T_3 levels back to normal range [15].

D2 is the most recently cloned of the three deiodinases, and new data regarding its properties and function still are accumulating. D2 was known to be important particularly for local T_3 production in the brain [20] but recently it was shown that expression of D2 in the human muscle also may have a significant contribution to circulating T_3 [11,21]. Thyroid status controls D2 activity at the pre- and post-translational levels. T_3 decreases D2 mRNA expression, whereas T_4 and rT_3 facilitates the fast and irreversible degradation of D2 protein [3]. This means that D2 is up-regulated in a hypothyroid state, whereas hyperthyroidism leads to a decrease in D2. Despite low T_3 levels, D2 activity in skeletal muscle of patients who were critically ill was reported to be undetectable [14]. If this is the case, it could be explained by increased levels of rT_3 leading to an increased breakdown of D2 protein [22]. Loss of D2 activity during critical illness thus might contribute to low T_3 levels. From this perspective, decreasing D2 activity may be a cause of the low T_3 syndrome, because it would lead to a decrease in T_3 levels, in turn down-regulating D1 activity. Such a sequence of events during critical illness, however, remains speculative at this time.

D3 is the major thyroid hormone inactivating enzyme. It is expressed mainly in fetal tissues, the pregnant uterus, and the placenta, protecting the fetus against excess T_3 concentrations, which are detrimental to normal development [23]. In adult animals, D3 is expressed in the brain but high levels are restricted to the uteroplacental unit. Because D3 also is found in some tumors and malignant cell lines, D3 has been named an oncofetal protein [24]. These D3-expressing tumors give rise to a condition called consumptive hypothyroidism, wherein circulating thyroid hormone is inactivated massively [25]. The observed alterations in circulating thyroid hormone levels are similar to those during critical illness and induction of D3 activity in liver and skeletal muscle of patients who are critically ill has been documented recently [14]. This finding was confirmed in a rabbit model

of prolonged critical illness [15]. Both studies also could show a negative correlation between D3 activity and changes in circulating T_3 and the T_3/rT_3 ratio. By infusing TRH continuously to prolonged ill rabbits, D3 activity and T3 levels were normalized [15]. Addition of a growth hormone (GH) secretagogue to TRH, however, was necessary to prevent the rise in rT_3 observed with TRH alone.

From these data, it can be concluded that in addition to the down-regulation of D1, an induction of D3 activity in liver and muscle is likely to contribute to the low serum T_3 and high serum rT_3 levels seen in acute critically ill patients.

Thyroid hormone transport

To be metabolized by the deiodinases, thyroid hormone first must enter the cell. Until recently, the mechanism of thyroid hormone entry into cells was not clear. The assumption was that the lipophilic nature of thyroid hormones facilitated passive diffusion through the lipid bilayer. In contrast to previous beliefs, it now is known that thyroid hormones need specific transmembrane transporters to cross the plasma membrane. Thyroid hormone uptake in the human liver, for example, is temperature, Na, and energy dependent and rate limiting for subsequent iodothyronine metabolism [26]. In critical illness, T_4 uptake in the liver clearly is decreased and this may contribute to lowered T_3 production [27,28]. Inhibition of liver T_4 uptake during critical illness can be explained by liver adenosine triophosphate (ATP) depletion and increased concentrations of circulating inhibitors, such as indoxyl sulfate, nonesterified fatty acids, and bilirubin [29,30]. Serum of patients who are critically ill is shown to inhibit uptake of T_4 into hepatocytes [29,31,32].

Monocarboxylate transporter 8 (MCT8) is an example of an active and specific thyroid hormone transporter [33]. Expression analysis in liver and muscle tissue of patients who are critically ill, however, suggests that MCT8 is not crucial for transport of iodothyronines, at least not in these tissues [34]. The precise role of MCT8 and of other putative thyroid hormone transporters during acute and chronic critical illness remains to be addressed in future studies.

Tissue levels of thyroid hormone

As discussed previously, circulating thyroid levels are low and tissue uptake of T_4 also is impaired. It would be logical to assume that this results in low thyroid hormone concentrations in the tissue and, thus, a low bioactivity of thyroid hormone. Few data exist, however, on the actual tissue content of T_3 in patients who are critically ill. Arem and colleagues compared tissues from patients who were critically ill with tissues from patients who died acutely [35]. The general finding was a decreased concentration of T_3 in the tissues of patients who were critically ill. Also, in a larger study,

circulating T_3 levels are shown to correlate well with skeletal muscle and liver T_3 content in patients who died from critical illness [34]. Consequently, patients who had received thyroid hormone treatment showed higher serum T3 concentrations accompanied by higher levels of muscle T_3.

Thyroid hormone receptors

Once thyroid hormone has entered the cell, it interacts with specific nuclear thyroid hormone receptors (TRs) to exert its functions. TRs are expressed from two separate genes, resulting in two major isoforms, TRα and TRβ. Each gene can be spliced alternately, producing distinct isoforms: TRα-1, TRα-2, TRβ-1, and TRβ-2. The TRα-1 isoform is a bona fide T_3 receptor, whereas TRα-2 acts as a dominant negative isoform. The ratio of these splice variants, therefore, could have a marked influence on T_3-regulated gene expression. An inverse correlation was observed between the T_3/rT_3 ratio and the TRα-1/TRα-2 ratio in liver biopsies of prolonged critically ill patients [36]. Furthermore, higher TRα-1/TRα-2 ratios were present in sicker and older patients as compared with less sick and younger ones. Hence, patients who are critically ill may adapt to decreasing thyroid hormone levels by increasing the expression of the active form of the TR gene. A decline in number and in occupancy of hepatic nuclear T_3 receptors is, however, observed in animal models [37,38].

Sulfation

Recently, the role of sulfation of thyroid hormone in critical illness was investigated. Sulfated iodothyronines do not bind to the TRs, and sulfation mediates a rapid degradation of iodothyronines by D1 [39]. Therefore, the concentrations of sulfated iodothyronines in serum normally are low [40,41]. In prolonged critically ill patients, however, there was a marked elevation of sulfated T_4 (T_4S), which correlated with the severity of illness [42]. The strong negative correlation of hepatic D1 activity with serum T_4S suggests that a decreased liver D1 activity plays an important role in the increase of T_4S levels during critical illness.

Inhibition of thyroid hormone binding

Other factors involved during the acute phase of illness include low concentrations of thyroid binding proteins [43–45] and inhibition of hormone binding [46,47]. It is suggested that a binding inhibitor may be present in the serum or even throughout body tissues. This binding inhibitor can inhibit uptake of hormone by cells or prevent binding to nuclear TRs and, thus, inhibit action of thyroid hormone. This does not, however, explain the reduced generation of T_3 and the low thyrotropin levels. Moreover, the observation of Brent and Hershman that the T_4 pool of prolonged critically ill patients can be replenished easily by exogenous T_4 administration

strongly indicates that an inhibitor of binding is not a predominant cause of low serum T_4 [48].

Neuroendocrine changes during critical illness

Central changes play an important role in the pathophysiology of the low T_3 syndrome, especially in the prolonged phase of critical illness where they are superimposed on the peripheral changes (described previously) (see Fig. 1). Subtle changes in the central part of the HPT axis, however, already can be observed in the acute phase of critical illness. In normal physiology, a decrease in circulating thyroid hormone levels results in a fast and robust release of thyrotropin from the pituitary. During acute critical illness, however, levels of thyrotropin rise only briefly ($\pm$2 hours) [7] after which they return to normal despite ongoing decline in T_3 concentrations, thus indicating the presence of an altered set-point for feedback inhibition. In addition, the nocturnal thyrotropin surge seen in healthy individuals is absent in acute critically ill patients [7,49].

Prolonged critically ill patients present with a more severe central dysfunction. First, a dramatic reduction in the pulsatile fraction of thyrotropin release is observed. In addition, serum concentrations of T_4 and T_3 are low and correlate positively with the reduced pulsatile thyrotropin release [8,50]. Similar to what is described within the somatotropic axis, this constellation is in line with a predominantly central origin of the suppressed thyroid axis, suggesting reduced TRH availability in the chronic phase of critical illness [51]. Indeed, continuous infusion of TRH in prolonged critically ill patients increases thyrotropin secretion and, concomitantly, increases the low circulating levels of T_4 and T_3 back to normal levels [50]. Further evidence for this concept comes from the work of Fliers and coworkers, who confirmed reduced TRH gene expression in the hypothalamus of patients dying after chronic critical illness as compared with those who died after a road accident or an acute illness [52]. Additionally, a positive correlation of TRH mRNA with serum thyrotropin and T_3 was found. The onset of recovery from severe illness is shown to be preceded by an increase in circulating levels of thyrotropin [53–55].

The neuroendocrine pathophysiology behind these changes is understood incompletely. Injection of cytokines, such as tumor necrosis factor α (TNF-α), interleukin (IL) 1, and IL-6, is able to mimic the acute stress-induced alterations in thyroid status [56,57]. Therefore, it is suggested that these cytokines may play a role in evoking the low-T3 syndrome. Cytokine antagonism studies failed, however, to restore normal thyroid function in humans [58] and in animals [59]. Moreover, in contrast to the acute phase, circulating cytokines usually are low in the chronic phase of severe illness [60] and cytokines were not withheld as independent determinants of the variability in circulating T_3 in a large group of hospitalized patients [61,62], so other mechanisms must be involved. Endogenous dopamine

and prolonged hypercortisolism each may play such a role, as exogenous dopamine and corticoids are known to provoke or severely aggravate hypothyroidism in critical illness [63,64].

An up-regulation of D2 in the mediobasal hypothalamus, which is seen in rats and mice after lipopolysacharide (LPS) injection, also may contribute to the suppressed HPT axis by way of an increased local T3 production [17,65,66]. Theoretically, a down-regulation of D3 in the paraventricular nucleus (PVN) also would lead to relatively high hypothalamic T_3 concentrations, thereby suppressing TRH expression [67]. Less then half the concentration of tissue T_3, however, was measured in the hypothalamus of patients who died after chronic severe illness compared with patients who died from an acute trauma [35]. Because LPS injection induces an acute illness rather than a chronic illness, this might explain the contradicting results.

The melanocortin signaling system is another way of controlling TRH neuron function. This system consists of two groups of neurons with opposing functions that synthesize either α–melanocyte-stimulating hormone (α-MSH) or agouti-related protein (AGRP) (for review see Ref. [68]). α-MSH has an activating effect on TRH neurons whereas AGRP suppresses TRH mRNA in the PVN. In addition, neuropeptide Y (NPY) may be involved, as it potentiates the inhibitory effect of AGRP on TRH. The exact role of these neuropeptides in the central pathogenesis of the low T3 syndrome remains puzzling, however, as contradictory results are obtained under different conditions. Although fasting and administration of LPS resulted in an overall suppression of TRH in the PVN, this was accompanied with different patterns of expression of α-MSH and AGRP. During fasting, α-MSH expression decreases and AGRP increases [69], but intriguingly α-MSH expression increases when LPS was administered despite suppression of TRH in the PVN [70]. In addition, NPY expression showed a positive correlation with TRH levels in patients who died from severe illness [71], whereas an inverse correlation is seen during starvation [69]. The precise role of the melanocortin system in critical illness remains to be unraveled.

The human MCT8, a specific thyroid hormone transporter, and the organic anion transporter, OATP1C1, a high-affinity T_4 transporter, are expressed in the hypothalamus, suggesting their regulation also may be important in the altered hypothalamic set-point in critical illness [67,72]. Also, expression TR isoforms are shown to be regulated differentially by thyroid hormone status in different brain regions, including the PVN [73]. All these possibilities need to be addressed in future studies of critical illness.

Should the low triiodothyronine syndrome be treated?

It hitherto has not been clear whether or not the low T_3 syndrome is an adaptive, protective mechanism against hypercatabolism or, alternatively, its cause. It is important to realize the differences between the acute and

the chronic phases of critical illness [74–76]. In the acute phase, peripheral changes predominate, and these changes are similar to the ones observed in fasting. Teleologically, the decrease in T3 observed during fasting has been interpreted as an attempt of the body to reduce energy expenditure, to survive, and to prevent severe protein wasting [77,78]. Similarly, the acute changes within the thyroid axis, uniformly present in all types of acute illnesses, could be looked on as a beneficial and adaptive response that does not warrant intervention.

The prolonged phase of critical illness, however, is in a way an unnatural condition. These patients would have died at one time, but with the development of intensive care medicine, they now have a much greater chance of survival. Therefore, the alterations observed during prolonged critical illness cannot be interpreted as selected by evolution; thus, it is unlikely that they represent an adaptive response. In this phase, thyroid hormone levels are correlated inversely with biochemical markers of accelerated catabolism (urea production and bone degradation). These markers of hypercatabolism, however, can be reduced when thyroid hormone is restored to physiologic levels by continuous infusion of TRH in combination with a GH secretagogue (Fig. 2) [79]. This observation may be in favor of low thyroid hormone levels contributing to, rather than protecting from, the hypercatabolism of prolonged critical illness. The negative feedback inhibition, exerted by thyroid hormones on the thyrotrophs to prevent overstimulation of the thyroid axis, was maintained during TRH infusion in prolonged critical illness [50,80]. This self-limitation may be important during critical illness to protect against hyperthyroidism, which inadvertently would aggravate catabolism.

It remains controversial whether or not direct administration of T_3 or T_4 to raise circulating T_3 levels has clinical benefits [35,81]. To date, administration of T_4 has failed to demonstrate a clinical benefit, although the impaired conversion of T_4 to T_3 may be a factor in the lack of success [48,82]. Substitution doses of T_3, however, after correction of congenital cardiac anomaly in dopamine-treated pediatric patients are associated with improvements in postoperative cardiac function [83]. A benefit of T_3 treatment in iatrogenic, dopamine-induced hypothyroidism, however, still does not provide evidence of clinical benefit of treating the noniatrogenic low T_3 levels characteristic of prolonged critical illness [84,85]. The advantage of treatment with hypothalamic-releasing factors is that the body remains capable of using its normal feedback systems to generate the appropriate amount of thyroid hormones in the circulation and at the tissue level. This provides a safer treatment strategy than the direct administration of T_3 [50]. In addition, the response of the peripheral tissue to the normalization of serum levels of insulin-like growth factor I (IGF-I) and binding proteins via GH-releasing peptide (GHRP) infusion seems to depend on the co-infusion of TRH and the resultant normalization of the thyroid axis. Although infusion of GHRP-2 alone is accompanied by increases in GH secretion and in serum

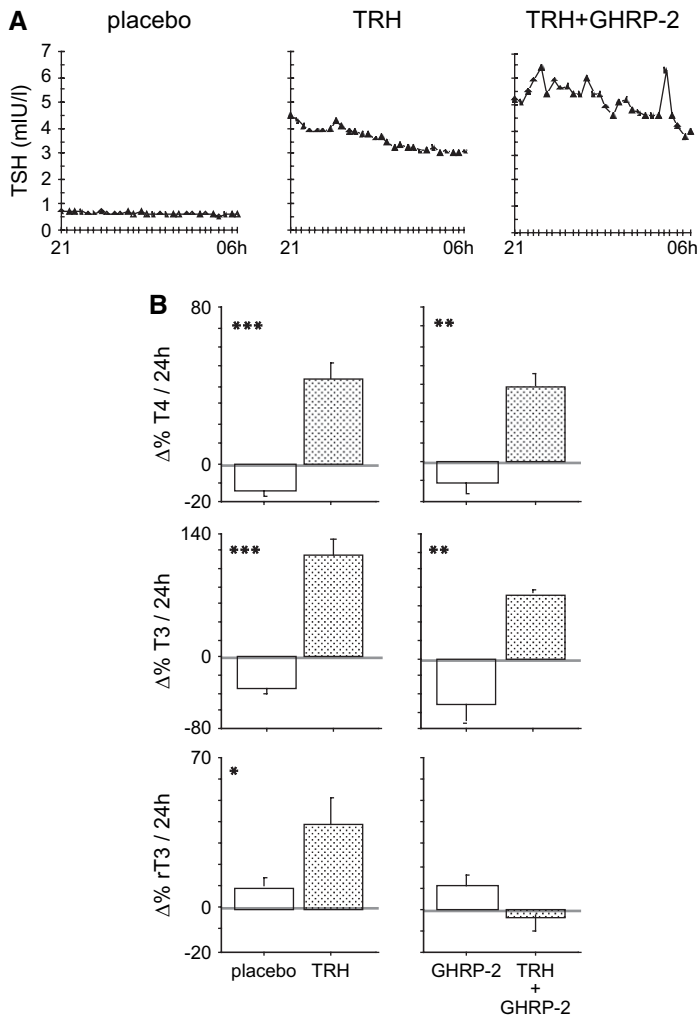

Fig. 2. Effects of TRH and a GH secretagogue on the thyroid axis in prolonged critical illness. (*A*) Nocturnal serum thyrotropin profiles, with continuous infusion of placebo, of TRH (1μg/kg/h) or of TRH plus GHRP-2 (1 + 1 μg/kg/h). The age range of the patients was 68 to 80 years and duration of illness was between 15 and 18 days. Although TRH elevated the thyrotropin secretion, addition of GHRP-2 to the TRH infusion seemed necessary to increase its pulsatile fraction. (*B*) Continuous administration of TRH (1 μg/kg/h), infused alone or together with GHRP-2 (1 + 1 μg/kg/h), induces a significant rise in serum T4 and T3 within 24 hours. Here, rT3 is increased after the infusion of TRH alone, but not if TRH is co-infused with GHRP-2. The patients studied were ill for 12 to 59 days; the age range was 32 to 87 years. (*Reproduced from* Van den Berghe G, de Zegher F, Bouillon R. Acute and prolonged critical illness as different neuroendocrine paradigms. J Clin Endocrinol Metab 1998;83:1827–34; with permission. © [1998] The Endocrine Society.)

concentrations of IGF-I, IGF-binding protein 3, and its acid-labile subunit, none of the anabolic tissue responses, which are evoked by the combined infusion of GHRP and TRH, are present [80]. Further studies need to be undertaken to assess the clinical benefits on morbidity and mortality of TRH infusion alone or in combination with GH secretagogues in prolonged critical illness.

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