Anterior pituitary function in critical illness

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Abstract

Critical illness is hallmarked by major changes in all hypothalamic–pituitary–peripheral hormonal axes. Extensive animal and human studies have identified a biphasic pattern in circulating pituitary and peripheral hormone levels throughout critical illness by analogy with the fasting state. In the acute phase of critical illness, following a deleterious event, rapid neuroendocrine changes try to direct the human body toward a catabolic state to ensure provision of elementary energy sources, whereas costly anabolic processes are postponed. Thanks to new technologies and improvements in critical care, the majority of patients survive the acute insult and recover within a week. However, an important part of patients admitted to the ICU fail to recover sufficiently, and a prolonged phase of critical illness sets in. This prolonged phase of critical illness is characterized by a uniform suppression of the hypothalamic–pituitary–peripheral hormonal axes. Whereas the alterations in hormonal levels during the first hours and days after the onset of critical illness are evolutionary selected and are likely beneficial for survival, endocrine changes in prolonged critically ill patients could be harmful and may hamper recovery. Most studies investigating the substitution of peripheral hormones or strategies to overcome resistance to anabolic stimuli failed to show benefit for morbidity and mortality. Research on treatment with selected and combined hypothalamic hormones has shown promising results. Well-controlled RCTs to corroborate these findings are needed.

Key Words
- critical illness
- pituitary function
- neuroendocrine axis
- CIRCI
- NTI

Introduction

Critical illness is defined as the presence of acute, life-threatening organ dysfunction requiring vital organ support and can be evoked by major trauma, extensive surgery, large-scale burn injuries and severe medical diseases. A hallmark of critical illness, is the immediate initiation of multiple physiologic processes in an attempt to rebalance the complex dynamic equilibrium, commonly known as homeostasis. This so-called ‘stress response’ comprises many tightly controlled neural and endocrine adaptations to provide sufficient energy and hemodynamic stability to survive and overcome the immediate phase after onset of critical illness. Supported by advancements in modern health care such as mechanical ventilation, renal replacement therapy or broad-spectrum antibiotics, the majority of critically ill patients will survive the acute phase of their illness. However, a significant number of patients admitted to the ICU fail to recover sufficiently within a few days and enter a more prolonged phase of critical illness, also known as ‘chronic critical illness’ (1). Although timing of this transition is unclear, after approximately 10 days of critical illness, the severity of illness upon admission is no longer predictive for mortality (2). Depending on the used criteria, 5–30% of the patients admitted to an ICU will eventually suffer from chronic critical illness.

Independent of the underlying cause for admission to the ICU, the hormonal stress response to critical illness follows a biphasic pattern related to the time course of critical illness (3, 4). A first phase, further referred to as the acute phase of critical illness, starts within minutes or hours after the occurrence of the deleterious event. An evolutionary hormonal ‘fight or flight’ state is activated...
by the abundancy of released proinflammatory cytokines, the overwhelming activation of sensory neurons, the release of catecholamines and/or the presence of pathogens in the bloodstream (5, 6). Further augmented by an illness-induced reduction in nutritional intake, hormonal changes during the acute phase of critical illness are directing the organism toward a catabolic state in an attempt to provide sufficient energy to overcome and survive the insult. A reduction in cellular oxygen and/or energy delivery, and insufficiently activated defense mechanisms induce mitochondrial dysfunction and consequently, a downregulation of cellular metabolism (7, 8). Although survival from previously lethal conditions is enhanced by the provided critical care, recovery does not always follow fluently. When patients outlive the acute phase of critical illness but remain dependent on vital organ support, sometimes for multiple weeks, the central activation of most neuroendocrine axes is attenuated, together with complex alterations in peripheral hormone levels.

Two tandem key players in regulating the stress response in critically ill patients are the hypothalamus and pituitary. The hypothalamus, the major control center of the different neuroendocrine axes, gains a complex set of sensory input from a variety of internal and external stimuli. This collection of information together with the input of endocrine feedback loops triggers the hypothalamus to produce and secrete tropic hormones in the hypophyseal portal system mainly targeting the anterior pituitary. Highly regulated by these stimulating or inhibiting hypophysiotropic hormones and various feedback loops, the anterior pituitary produces a set of hormones targeting peripheral glands, such as the thyroid, the adrenal or the gonads or end organs directly such as the liver, muscle and bone.

In this paper, we will review the anterior pituitary function and the five main neuroendocrine axes during health and critical illness, both in the acute and the chronic phase.

The five main neuroendocrine axes

The somatotropic axis during health

Growth hormone (GH), the most abundant pituitary hormone, is synthesized by the somatotropes in the anterior pituitary. Hypothalamic GHRH stimulates production and release of stored GH into the bloodstream. Counteracting, somatostatin inhibits production of both GHRH and GH. Upon stimulation, GH is secreted in a pulsatile manner, noticeable by the highly fluctuating serum concentrations, with peaks every 3–4 h followed by a decline down to undetectable levels (Fig. 1). Whereas GHRH levels positively correlate with the amplitude of the GH peak, high somatostatin levels determine the end of the GH release and thus the initiation of the interpulse-trough (9). On top of this straightforward interplay between two regulating hormones, a third key player in GH production is the in the stomach synthesized hormone ghrelin. Through binding with the GH secretagogue receptor (GHS-R) at the level of the pituitary and hypothalamus, ghrelin stimulates, directly and indirectly, pituitary secretion of GH. Ghrelin has similar but less potent effects on pituitary ACTH and PRL secretion (10). Furthermore, ghrelin has a profound orexigenic effect, which appears to be mediated by the GHS-R but in a GH-independent fashion, as suggested by GH-deficient animal studies (11).

GH, acting in a direct and indirect manner, the latter by stimulating the hepatic production of the para-/autocrine hormone insulin-like growth factor-I (IGF-I), is named for one of its main functions: mediating linear bone and organ growth. Whereas adequate nutritional intake and adequate sex hormone levels are the main growth promoters during respectively infancy and puberty,
GH takes up this role during childhood. In adults, GH remains important as a regulator of metabolism. The set of complex actions of GH and IGF-I on carbohydrate, fat, and protein metabolism is highly variable depending on the nutritional status of the individual. In well-nourished, healthy individuals IGF-I stimulates protein synthesis and peripheral free fatty acid uptake, whereas in prolonged fasting, GH will enhance the release and oxidation of free fatty acids and antagonize insulin actions.

The somatotropic axis during critical illness

GH serum concentrations start to rise in the hours after the onset of critical illness. An increment in both amplitude and frequency of GH peaks and the loss of the typical troughs during the interpulse periods contribute to the elevated serum concentrations (Fig. 1) (4, 12, 13). Furthermore, the hepatic GH receptor function is oppressed, often referred to as ‘peripheral GH resistance’, leading to low circulating levels of IGF-I, IGF-binding protein 3 (IGFBP-3), its acid label subunit (ALS) and GH-binding protein (GHBP) (14). Combined, these alterations in the GH axis lead to a shift from the anabolic effects of IGF-I to more catabolic actions of GH, such as lipolysis, insulin antagonism and to immune stimulation (15). When recovery does not ensue within a week and patients enter the chronic phase of critical illness, the pulsatile pattern of GH secretion fades and GH peaks become blunted with IGF-I, IGFBP-3 and ALS levels remaining low (Fig. 1). Interpulse GH concentrations also decrease but still appear to be higher than in healthy subjects (16). Whereas in the acute phase of critical illness hepatic GH resistance has a key role in altering the GH axis, the main driver of hyposomatotropism during the prolonged phase of critical illness is thought to be an impaired hypothalamic drive. Hepatic GH resistance does not seem to persist during chronic critical illness (17). This hypothesis is supported by a high GH responsiveness to administration of GH secretagogues (GHRPs) in chronic critically ill patients. Indeed, restoration of pulsatile GH secretion pattern can be evoked by the administration of GHRP, alone or with the co-administration of GHRH, leading to a six-fold and ten-fold increase in amplitudes of GH serum peaks, respectively. Strikingly, administration of GHRH alone is not capable of restoring the typical pulsatile pattern of GH secretion (18). Besides an altered hypothalamic drive, another possible contributor to the attenuated GH levels during chronic critical illness may be the scarcity of the active form of ghrelin, the endogenous ligand of the GHS receptor and a powerful GH secretagogue (19). The low circulating IGF-I and its binding proteins levels are associated with biochemical markers of impaired anabolism, such as low serum osteocalcin and leptin (20). The chronic GH deficiency, with reduced anabolism and ongoing catabolism, thus likely contributes to the wasting syndrome, a hallmark of chronic critical illness.

A large RCT, investigating the effect of high-dose GH injection to prolonged critically ill patients, unexpectedly marked a doubling in mortality in the intervention cohort (21). Since GH resistance at least partially resolves in the chronic phase, it is likely that such high doses of GH, and consequently high levels of IGF-I, evoked toxic side effects such as excessive fluid retention, hypercalcemia and pronounced insulin resistance with hyperglycemia. Although small studies showed the ability of GHRP-2 to restore a normal GH pulsatile pattern in severe ill patients, and of the combination of GHRP-2 and thyrotropin-releasing hormone (TRH) to induce an anabolism and suppress catabolism in prolonged critically ill patients (16, 22), the clinical outcome of infusion with GH secretagogues has not yet been studied. Also substitution with ghrelin has recently been investigated in smaller animal and in vitro studies and appeared to enhance autophagy, reduce catabolism and improve hemodynamics (23). As ghrelin induces appetite, infusion of ghrelin during the chronic phase of critical illness when patients restart oral intake may enhance food intake and could lead to improvement in clinical outcome (24). Large-scale RCTs in humans, to corroborate these findings, have not yet been performed.

The thyroid axis during health

Stimulated by the hypothalamic TRH, thyrotropes in the pituitary gland produce and secrete thyroid-stimulating hormone (TSH) in a dual fashion: a basal secretion with a circadian pattern (nocturnal levels up to a twofold of daytime levels) and pulses approximately every 90 min (25). TSH binds the G-protein-coupled TSH receptor (TSH-R), predominantly but not exclusively found on thyroidal cells, adipocytes and orbital fibroblasts. Activation of the thyroidal TSH-R induces thyroid gland growth, transformation of cell morphology, iodine metabolism and synthesis of thyroid hormones thyroxin (T4) and to a lesser extent triiodothyronine (T3). In peripheral tissues, T4 crosses the cell membrane through specific transporters and subsequently undergoes outer- or inner-ring deiodination, resulting in the formation of respectively the metabolic active T3 or the metabolic inactive reverse T3 (rT3). The nuclear thyroid hormone

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receptor (THR) exists in three active isoforms (TRa1 and TRβ1 and 2) and one inactive isoform TRa2. As the TRHs are found in virtually every human organ, physiologic effects of thyroid hormones are heterogeneous, ranging from basal cellular metabolism to growth and facilitating local tissue functions. Thyroid hormones T4 and T3 exert inhibitory feedback control on both the hypothalamus and pituitary.

The thyroid axis during critical illness

Within hours after the onset of critical illness, circulating levels of T3 rapidly decline, whereas rT3 plasma concentrations increase. These characteristic changes are due to an altered peripheral conversion of T4 with a typical decrease in the peripheral activity of the activating type 1 deiodinase (D1) and increase in the inactivating type 3 deiodinase (D3) (26, 27). Apart from the absence of the nocturnal surge in TSH and a swift and transient rise in TSH and T4, both hormone levels remain relatively normal (Fig. 2) (28). These changes are often referred to as ‘non-thyroidal illness’ (NTI). Alterations in the affinity of thyroid hormone-binding proteins, thyroid hormone transporters and the nuclear THR further contribute to the NTI.

Low circulating levels of T3 reduce energy expenditure, but also to optimize bacterial killing capacity through increased D3 activity in cells of the innate immune system, which could play a role in the observed reduction in nosocomial infections and therefore could be beneficial, at least in the acute phase of critical illness (29, 30, 31, 32). When patients remain dependent on vital organ support for multiple days or even weeks and are under full nutritional support, by enteral and/or parenteral feeding, TSH and T4 levels start to decline with T3 levels remaining low. Similar to the observed alterations of the GH axis during prolonged critical illness, the pulsatile pattern of TSH fades and secretory peaks become blunted (Fig. 2) (33). Interestingly, in chronic critical illness, peripheral tissues seem to adapt to the sustained low T3 levels by enhancing local hormone availability and effectiveness. Indeed, a peripherally increased expression of the thyroid membrane transporter MCT-8, upregulated D2 expression and increased TRα1/TRα2 ratio expression have been observed (34, 35). Nevertheless, ongoing low levels of T3 have been associated with more pronounced catabolism and worse outcome (18, 36). Furthermore, ICU patients who received an infusion of TRH combined with GHRP-2 showed normalized thyroid hormone levels and lowered markers of hypercatabolism (18). During the acute phase of critically ill patients, especially with the concomitantly reduced nutritional intake, treatment of the low T3 levels, in the absence of preadmission thyroid pathology, is probably not indicated (37). Whether or not the central hypothyroidism during the chronic phase of critical illness would benefit from treatment is not yet clear from available small human studies (38). In animal models, normal substitution doses had no impact on thyroid hormone levels, due to the highly increased metabolism. High doses of T4, T3 or the combination could restore normal hormone serum concentrations but led to overtreatment with further suppression of TSH and rise in rT3 (39, 40, 41). Interestingly, TRH infusion alone led to a twofold increase in basal TSH secretion, and co-infusion of TRH and GHRP-2 increased pulsatile TRH secretion by five-fold in prolonged critically ill patients (18). In addition, also anabolic markers (osteocalcin and leptin) appeared to be higher compared to placebo-infused controls (20). In contrast to T3 and T4 infusions, treatment with a hypothalamic releasing factor allows normal feedback inhibition, but until today RCT’s testing this treatment on short- and long-term clinical outcome of prolonged critically ill patients are lacking.
The adrenal axis during health

Pro-opiomelanocortin (POMC), synthesized in the corticotropic cells of the pituitary, is spliced to adrenocorticotropic hormone (ACTH) by proteolytic cleavage enzymes. ACTH is stored into dense core secretory granules and released into systemic circulation either spontaneously, in pulses every 30–40 min with a diurnal rhythm or acutely, upon stimulation with hypothalamic CRH (42). CRH activity is potentiated by the presence of vasopressin (VP). At the adrenal gland, ACTH binds to the G-protein-coupled melanocortin-2-receptor (MC2R). MC2R activation leads to increased expression of cholesterol uptake receptors (such as low-density lipoprotein-receptor) and the cholesterol synthesis enzyme 3-hydroxyl-3-methylglutaryl-coenzym A reductase (HMG CoA reductase). Unesterified intracellular cholesterol is then converted to prenenolone by P450 side chain cleavage enzyme. The expression of this enzyme, that is, the rate-limiting step in adrenal steroidogenesis, is also upregulated by ACTH-induced MC2R activation (43). Likewise, the final enzyme for cortisol synthesis, 11-β-hydroxylase, which converts 11-deoxycortisol into cortisol is upregulated upon ACTH stimulation. In contrast to pituitary hormones, steroid hormones are not stored in the adrenal gland but directly secreted after synthesis. This at least partially explains the tight correlation between serum ACTH and serum cortisol concentrations during health. Cortisol mitigates its own production via negative feedback inhibition on the hypothalamus and the pituitary.

Due to its lipophilic nature, 90% of the total circulating cortisol is bound to a protein carrier (80% to cortisol-binding globulin (CBG) and 10% to albumin), the other 10% is unbound in the blood and therefore biologically active. Cortisol plays an important role in the stress response and contributes to the provision of energy by increasing catabolism and delaying anabolism. Other important systems requiring adequate levels of cortisol for normal functioning include the immune system, cardiovascular system, fluid and electrolyte homeostasis. Cortisol exerts its effects by binding to the intracellular glucocorticoid receptor (GR). Unbound, inactive GR resides in the cytoplasm as part of a multimeric complex with one or more heat shock proteins (hsp90). Upon cortisol binding, the multimeric complex dissolves and GR is transported to the nucleus where it regulates gene expression. Several receptor isoforms and subtypes with unique functional profiles are derived from a single gene (NR3C1) by alternative splicing and posttranslational modifications.

The adrenal axis during critical illness

A hallmark of critical illness, irrespective of the causal event, is the increase in plasma concentrations of the stress hormone cortisol. It was long assumed that the sustained several-fold rise in cortisol levels following a deleterious insult was caused by ongoing central, ACTH-driven adrenal cortisol synthesis and secretion (44). However, this concept now no longer stands as several studies have reported low rather than high ACTH plasma concentrations already from admission to the ICU onward (Fig. 3) (45). Moreover the diurnal rhythm of ACTH and cortisol seemed to be lost (45). In a recent prospective observational study, it was demonstrated that this ACTH–cortisol dissociation was present in all ICU patients, with or without sepsis/septic shock and survivors and non-survivors alike, and that it protracted throughout ICU stay. However, after a prolonged ICU stay of more than 4 weeks, cortisol levels decreased to normal levels, without a concomitant rise in ACTH (46).

As ACTH levels are low, the increase in systemic cortisol availability has to be brought about by non-ACTH-driven mechanisms. By using stable isotopes, elevated cortisol levels could indeed be attributed to suppressed cortisol metabolism, and, only in patients suffering from hyperinflammation, to a moderately increased cortisol production (47). The attenuated cortisol metabolism seems to be brought by reduced hepatic expression and activity of cortisol-metabolizing enzymes 5α- and 5β-reductase and renal 11β-hydroxysteroid dehydrogenase-2 (11βHSD2) (47). Cortisol-binding proteins CBG and albumin, also suppressed throughout ICU stay, further increase circulating levels of free cortisol and thus systemic cortisol availability (46, 47). A recent experimental mouse study documented a key role of reduced signaling of the hepatic GR in both suppression of cortisol metabolism and lowering levels of cortisol-binding proteins and thus attributing to hypercortisolemia (48).

The local tissue effects of highly elevated free cortisol levels during critical illness, such as modulation of the immune response, enhancement of hemodynamics and provision of energy, could also be affected by altered GR expression in various target organs. In analogy with the observed reduction of hepatic GR expression, the activity and expression of the active GR isoform (GRα) in target cells found in immune tissue seems to be reduced, whereas the negative GR isoform (GRβ) was transiently increased (49). This so-called ‘glucocorticoid resistance’, if present in other tissues such as the vasculature, and seemingly associated with disease severity, would pose a problem
during critical illness as it would counteract any potential beneficial effects of cortisol (50). However, further research on tissue-specific changes of GR expression during critical illness is required.

Altogether, depressed ACTH-dependent secretion altered cortisol metabolism, and tissue-specific glucocorticoid resistance could lead to a state during critical illness in which the systemic cortisol availability could be insufficient for survival and recovery. Initially referred to as ‘relative adrenal insufficienty’, this state is nowadays labelled ‘critical illness-related corticosteroid insufficiency’ (CIRCI). In contrast to the occurrence of absolute adrenal failure in critically ill patients, neither a clear definition nor reliable diagnostic criteria nor an irrefutable treatment of CIRCI exist, as illustrated by the lack of consensus in recent guidelines (51, 52, 53).

However, recent research revealed that cosyntropin stimulation tests are confounded by the increased cortisol distribution volume during critical illness. Indeed, low total cortisol responses to cosyntropin during critical illness rather reflect the increased cortisol distribution volume, given the low plasma binding, and can thus not provide reliable information on the functional status of the adrenal cortex (52). Controversy regarding the treatment of CIRCI and also regarding the overall use of glucocorticoids in septic shock, was further evoked by the recent publication of two large RCTs: the APROCCHSS trial and the ADRENAL trial (54, 55). In the APROCCHSS trial, irrespective of CIRCI as defined by the response to cosyntropin, 90-day all-cause mortality was lower among patients receiving hydrocortisone-plus-fludrocortisone compared to placebo, whereas this outcome did not significantly differ in the ADRENAL trial (54, 55).

Although differences in inclusion and exclusion criteria, studying different stages of sepsis, as well as in the therapeutic agent, dosage and posology used, could partly explain the discordant findings, the studies contribute to the long-lasting controversy of adjunctive glucocorticoid therapy in critical illness (56).

The recent findings that low cortisol plasma-binding proteins and suppressed cortisol breakdown determine the systemic free cortisol availability during the first 4 weeks of critical illness, but that cortisol plasma concentrations return to normal levels beyond that timeframe, despite high severity of illness, suggests that especially these prolonged stayers might require treatment (46). Indeed, the persistently low levels of ACTH during a prolonged ICU stay could eventually lead to adrenal atrophy. This hypothesis is supported by the ten-fold higher prevalence of absolute adrenal insufficiency in ICU long-stayers (>14 days) compared to shorter-stayers (57). Also, only for patients with a prolonged ICU stay, adrenal atrophy and suppressed ACTH-regulated gene expression was documented postmortem (58). Whether these long stay patients would benefit from treatment with ACTH (or CRH) infusion, over exogenous glucocorticoids, in analogy with what has been described for the thyroidal axis should be investigated in future studies.

The lactotropic axis during health

In non-pregnant humans, lactotropes secrete a burst of prolactin (PRL) every 2–3 h, varying in amplitude throughout the day (59). Unlike for other hypophyseal hormones, lactotropes show a high grade of spontaneous intrinsic activity.
Indeed, when hypothalamic control is withheld, an unrestrained secretion of PRL is observed (60). In the normal physiological state, however, this intrinsic high-secretory tone is suppressed by dopamine (DA). Far less potent than DA, several other hormones such as TRH, oxytocin and vasoactive intestinal peptide (VIP) are known stimulators of PRL synthesis and secretion. Besides its important reproductive role by stimulating lactation and maternal behavior, PRL also affects several other functions such as maintenance of immune competence of lymphocytes and liver growth and is crucial for survival (61).

The lactotropic axis during critical illness

In patients with sepsis or septic shock a clear rise in PRL levels is seen in the first days after the occurrence of a stressful life-threatening event (62). Interestingly, in one study of critically ill patients without sepsis or shock, prolactin levels on admission did not differ with those of matched healthy controls (63). When critical illness is prolonged, PRL levels start to decrease and eventually becomes suppressed. The mechanism behind this observation is not clear; however, a role of endogenous and exogenous DA has been suggested (33).

The gonadal axis during critical illness

Gonadal steroid levels decrease after the onset of severe illness. In men, testosterone levels drop in face of apparently normal or even high LH levels (66). Cytokines that can reduce Leydig cell function and increase peripheral aromatization of androgens seem to mediate this effect (67). When recovery is not initiated and critical illness is prolonged, testosterone levels further decrease and may become unmeasurably low (68). The pulsatile pattern and amplitudes of LH fall and eventually lead to severe hypogonadotropism (69).

Levels of female gonadal hormones, estrogen and progesterone, are decreased in women who experience abnormal levels of stress, such as women with anxiety disorders, female athletes and women with various chronic diseases. This estrogen and progesterone deficiency is presumed to be the result of a combination of a central inhibition of the gonadal axis, through increased portal levels of CRH, because of an activated HPA axis and inhibition at the level of the hypothalamus, pituitary and ovaries exerted by the increase in systemic cortisol availability (70). However, most studies supporting this hypothesis arise from research studying minor physical and psychological stress. Furthermore, as described earlier, the central component of the HPA axis is rather suppressed instead of activated during prolonged critical illness. Importantly, most female ICU patients are postmenopausal and have an altered hypothalamic–pituitary–gonadal axis homeostasis. In these patients a paradoxically rise in estrogen levels is seen, presumably caused by an increase in peripheral aromatase activity (71).

In the early 2000s, a growing body of evidence suggested that the administration of the anabolic synthetic androgenic steroid oxandrolone in patients suffering from severe burns was associated with shorter hospital stay (72). Furthermore, in pediatric burn patients the use of oxandrolone was associated with fewer long-term catabolic complications such as burn-induced growth arrest (73). Despite the promising results of supplementation of estrogens in several animal models of critical illness, including traumatic brain injury and hemorrhagic shock, well-designed human studies are lacking (74, 75).

Studies on the use of androgens in prolonged critical illness failed to demonstrate any conclusive clinical benefit. Exogenous pulsatile GnRH administration, given together with GHRP2 and TRH infusion, induced an anabolic response, but research focusing on the potential clinical outcome benefit is still lacking (76).
Are the neuroendocrine changes illness- or fasting-induced in the acute phase?

**Cytokines**

At the onset of critical illness, cells from the innate immune system are activated by binding of pathogen-associated and damage-associated molecular patterns on the pattern recognition receptors. Following such activation, most leukocytes will release a number of small protein mediators, such as cytokines, which play an important role not only in the proinflammatory, but also in the anti-inflammatory response to critical illness. Circulating cytokines are able to induce or repress the production of other cytokines, creating a complex interplay, also called ‘cytokine networks’, with an important role in the pathogenesis of critical illness (77, 78).

Cytokines have been proposed to play an important role in the increase in circulating levels of pituitary hormones GH and PRL, the swift, transient rise in TSH and the decrease in plasma concentrations of ACTH, possibly through mediating an inflammatory response in the pituitary gland (79, 80). Moreover, at the level of the hypothalamus, cytokines as stimulators of local nitric oxygen (NO) secretion were shown to be able to induce apoptosis of hypothalamic neurons and glial cells (81). In a small post mortem study, reduced pituitary ACTH levels without a concomitant rise in hypothalamic CRH or vasopressin expression with increased iNOS expression have been reported in patients who died after septic shock (82). In contrast, the observation that in patients who recovered from critical illness ACTH and cortisol levels rose to supra-normal levels 1 week after ICU discharge (46) and suppressed ACTH responses to CRH infusion in the prolonged but not acute phase of critical illness (83), argues against a severely damaged hypothalamus and pituitary in critically ill patients. Moreover, in an experimental study, neutralization of TNF did not influence circulating levels of thyroid hormone or TSH (84). These mechanisms are distinct from the anatomical damage to the hypothalamus and/or the pituitary present in some patients suffering from traumatic brain injury (85).

**Central feedback inhibition**

Besides cytokines, the increase in circulating GH can also be explained by a decrease in feedback due to low effector hormone IGF-I (52). Also, the observed increase in peripheral PRL levels could be mediated by altered stimulating and inhibiting effects of dopamine, oxytocin and VIP (80). High circulating levels of total and free cortisol on the other hand could exert a strong inhibitory effect on the hypothalamus and pituitary through negative feedback (83). This hypothesis is supported by the observation that ACTH levels fully recover or even become elevated after ICU discharge (46). Among other potential contributors to a centrally suppressed HPA axis are bile acids, as these are elevated during critical illness and have been observed to suppress the HPA axis in patients with and animal models of cholestasis (86). Altogether, pituitary hormone synthesis and release is highly influenced by feedback of the effector hormones, which may take place between the different pituitary cell types (87).

**Drugs**

Patients admitted to the ICU often receive multiple drugs to support vital organ function. Several drugs frequently used at the modern ICU are well-known inhibitors of the adrenal axis in a dose-dependent manner and may possibly contribute to decreased ACTH production and secretion at the level of the pituitary (88). However, nowadays obsolete in most ICUs, nearly half a century ago intravenous infusion of dopamine was the first choice as inotrop, agent, as historic studies showed a mortality benefit in critically ill patients with septic and cardiogenic shock with renal- and splanic-sparing effects (89). However, two decades ago, it became clear that infusion with dopamine, in analogy with increased endogenous dopamine levels, aggravates suppression of circulating pituitary-dependent hormones, TSH, PRL and LH in the acute phase of critical illness and GH in the chronic phase (90).

**Nutritional signals**

A third mechanism that may drive the alterations in pituitary and peripheral hormones is the lack of full (enteral) nutrition in the acute phase of critical illness. As critically ill patients are often unable to eat by mouth, nutritional support has to be initiated by the caregiving physician. However, nutrition guidelines recommend the early initiation of enteral feeding (EN) if enteral feeding fails to meet the prespecified nutritional target (30, 31, 93, 94). Interestingly, most neuroendocrine changes in the acute phase of critical illness resemble those during fasting in healthy individuals: an increase in GH in face of low levels of IGF-I, a decrease in T3 with concomitant rise in rT3
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During critical illness, the neuroendocrine axes are altered in a biphasic manner (Fig. 4). Neuroendocrine changes during the acute phase of critical illness resemble, at least partially, a fasted state and seem to be evolutionary selected and likely beneficial for survival. Therefore, treatment of altered hormone levels in this phase of critical illness might not be indicated. When patients fail to recover sufficiently, central and peripheral hormone levels further alter. These profound alterations no longer represent a natural fasting state and could be interpreted as maladaptive and may hamper recovery. Although treatment with exogenous peripherally active hormones in this more chronic phase of critical illness seems a reasonable option, experimental studies in the past have highlighted difficulties with optimal dosing and posology, sometimes even causing harm. A more physiological solution would be the use of central releasing factors instead of peripheral hormones.

A uniform central suppression in the chronic phase of critical illness

The chronic phase of critical illness is hallmark by a uniform suppression of all neuroendocrine axes (Fig. 4). Some of the proposed drivers of the neuroendocrine changes in the acute phase of critical illness are unlikely to play a prominent role in the chronic phase. Cytokines could be involved, although their levels substantially decline during the time course of severe illness (97). Also nutritional signals are different compared to patients in the acute phase of critical illness as most patients are now fully fed, either by enteral feeding, parenteral feeding or a combination of both (98).

The most plausible mechanism behind this uniform pituitary suppression is probably the decrease in hypothalamic, mostly activating, hypophysiotropic hormones. Indeed, a post mortem analysis of hypothalamic tissue demonstrated markedly reduced TRH gene expression in patients who died after severe illness compared to healthy patients who succumbed from a sudden lethal insult (99). Furthermore, ongoing hypercortisolism and high levels of endogenous dopamine may enhance negative feedback and therefore contribute to decreased pituitary hormone production and secretion (100).

Interestingly, hypothalamic type 2 deiodinase (D2) and local expression of thyroid hormone transporters are increased during critical illness and could theoretically increase local T3 availability and therefore alter the set point for feedback inhibition (101). Whether such alteration in set point for feedback is present in other pituitary cell types is unknown.

Conclusion

During critical illness, the neuroendocrine axes are altered in a biphasic manner (Fig. 4). Neuroendocrine changes during the acute phase of critical illness were found to aggravate NTI in the late PN cohort, which statistically explained at least part of the outcome benefit of not feeding early (37, 96).
allowing a normal feedback regulation which would avoid toxic levels of peripherally active hormones. Further intervention studies are needed to investigate the future role of treatment with releasing factors in chronic critical illness.

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

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