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Acute and Prolonged Critical Illness as Different Neuroendocrine Paradigms*

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THROUGHOUT evolution, the human species has been selected to survive disease and trauma. Accordingly, the body has developed natural defense mechanisms to face a great diversity of insults, most of which are accompanied by temporary starvation, without having to rely upon external support. Consequently, the initial response to acute insults, such as illness or trauma, results in an increased availability of glucose, amino acids and free fatty acids. Utilization of these substrates is reduced and preferentially directed toward vital organs, such as the brain and the immune system (1–3). This acute metabolic response, which occurs even if food intake is maintained, is thought to be at least partly evoked by endocrine changes, including an activated hypothalamic-pituitary-adrenocortical axis, hypersecretion of PRL and GH in the presence of low circulating insulin-like growth factor I (IGF-I), and a low activity state of the thyroid and gonadal axis (4–9). These changes have consistently been viewed as adaptive or beneficial, as they may reduce and redirect energy consumption, postpone anabolism and, at the same time, activate the immune response while protecting the host against deleterious biological effects of the latter (4, 8, 10, 11). It is still unclear to which extent some of these defense mechanisms may hyperrespond and, as a consequence, be harmful. However, as they have been continuously selected by the challenges of nature and time, there is at present little argument for medical interference with these adaptive changes during the first hours or days of illness or after trauma.

Metabolic response to protracted critical illness in the intensive care setting

The development of intensive care medicine over the past 3 decades has enabled humans to survive conditions such as septic or cardiogenic shock, fecal peritonitis, multiple trauma, or extensive burns. The latter insults are examples of a magnitude and duration requiring nutritional and vital organ function support that are beyond the capacity of the natural defense systems. Patients previously died from these challenges, and it is therefore unlikely that nature has been able to select coping mechanisms for the chronic phase of these disorders or for the intensive care conditions in which survival is nowadays possible. Indeed, it has now become clear that survival mediated by intensive care also has a reverse side. The highly technological intervention in the natural course of the dying process has unmasked previously unknown conditions, including a nonspecific wasting syndrome: despite feeding, protein continues to be lost from vital organs and tissues due to both activated degradation and suppressed synthesis, whereas reesterification (instead of oxidation) of free fatty acids allows fat stores to build up (12, 13). Moreover, the wasting is accompanied by hyperglycemia and insulin resistance, hypoproteinemia, hypercalcemia, intracellular water and potassium depletion, and hypertriglyceridemia, which often prompt symptomatic treatment.

Protein hypercatabolism becomes functionally important when the critical condition is protracted for several weeks. An impaired capacity to synthesize protein underlies the inability to restore normal protein content and hereby hampers recovery of the dysfunctioning systems (13). Muscle atrophy and weakness are some of the most overt functional consequences of protein wasting and provoke, among other problems, failure of the muscular ventilatory system, thus perpetuating the need for mechanical support. Atrophy of the intestinal mucosa and disturbed motility of the gastrointestinal tract prolong the need for parenteral feeding. In addition, delayed tissue repair and immune dysfunction jeopardize the healing process. Hence, dependency on intensive care support is further prolonged (14, 15).

The development of the wasting syndrome and ensuing intensive care dependency does not appear to be related to the initial disease or trauma, but, rather, to the duration of the critical condition (13). In clinical practice, a limited number of patients, who survived an acute life-threatening insult, continue to occupy high dependency beds for a long time (weeks, often months) because of their catabolic state and require a considerable fraction of the resources for intensive

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care (14, 15). Many of these "long stay" patients ultimately die from (infectious) complications, for which they are increasingly vulnerable (14, 15).

Neuroendocrinology of protracted critical illness

It has long been known that the anterior pituitary gland plays a crucial role in normal metabolic and immunological homeostasis. However, until recently, data on the neuroendocrinology of prolonged critical illness within an intensive care setting were scarce, and data from models of acute catabolic state (such as healthy starved volunteers, the perioperative phase of elective surgery, the admission phase of trauma, or acute infection) were extrapolated, without validation, to this type of protracted catabolic state. Other confounding factors have been concomitant malnutrition, the heterogeneity of the studied populations, and the use of intensive care drugs with neuroendocrine side-effects, such as dopamine (6, 7, 16).

Human data on the neuroendocrine characteristics of prolonged critical illness (defined as dependent on intensive care support for at least 10 days) are now becoming available, and they appear to be quite different from those observed in the first few hours or days after the onset of a life-threatening disease or trauma (17–20). Whether they also represent a beneficial adaptation or, instead, a neuroendocrine dysfunction or exhaustion has not been established. The latter hypothesis, which implies major therapeutic consequences, is being actively explored and appears to gain plausibility.

This review provides a synopsis of the endocrine changes observed in the initial phase and in the prolonged intensive care-dependent phase of critical illness, focusing on the hypothalamic-pituitary-dependent axes. It will appear that the acute phase is mainly characterized 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 (Fig. 1). Thus, acute and prolonged critical illness may be different neuroendocrine paradigms, and this concept clarifies many of the currently apparent paradoxes.

Adrenocortical function

The activity of the hypothalamic-pituitary-adrenocortical axis displays a biphasic pattern during the course of critical illness (20). By 1856, Brown-Séquard had noted that immediate postoperative survival depends on adrenal function (21). It is now known that the high serum cortisol concentrations present during the initial phase after surgery, trauma, or sepsis are associated with augmented ACTH release, which, in turn, is presumably driven by CRH, cytokines, and the noradrenergic system (4, 22–24). Concomitantly, circulating aldosterone rises markedly, most likely under the control of an activated renin-angiotensin system (25).

Hypercortisolism acutely shifts carbohydrate, fat, and protein metabolism, so that energy is instantly and selectively available to vital organs such as the brain, that overall utilization of substrates is reduced, and anabolism is postponed. Intravascular fluid retention and the enhanced inotropic and vasopressor response to respectively catecholamines and angiotensin II offer hemodynamic advantages in the fight and flight reflex. In addition, as virtually all components of the immune response are inhibited by cortisol, the hypercortisolism elicited by acute disease or trauma can be interpreted as an attempt of the organism to mute its own inflammatory cascade, thus protecting itself against overresponses (26). Thus, available evidence is still compatible with the time-honored view that the hyperactive state of the adrenocorticotropic axis in the initial phase of severe illness or posttrauma is part of the "wisdom of the body" (27, 28).

In prolonged critical illness, serum ACTH levels are low whereas cortisol concentrations usually remain elevated, indicating that cortisol release may in this phase be driven through an alternative pathway, possibly involving endothelin (20). Why ACTH levels are low in prolonged critical illness is unclear; a role for atrial natriuretic peptide (20) or substance P (23) has been suggested. In contrast to serum cortisol, circulating levels of adrenal androgens such as dehydroepiandrosterone sulfate (DHEAS), which has immunostimulatory properties on Th1 helper cells, are low during

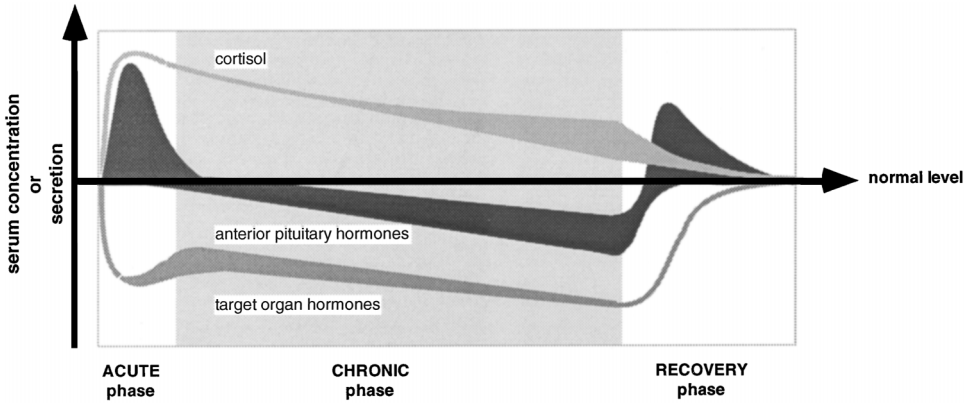

FIG. 1. Simplified concept of the pituitary-dependent changes during the course of critical illness. In the acute phase of illness (first hours to a few days after onset), the secretory activity of the anterior pituitary is essentially maintained or amplified, whereas anabolic target organ hormones are inactivated. Cortisol levels are elevated in concert with ACTH. In the chronic phase of protracted critical illness (intensive care dependent for weeks), the secretory activity of the anterior pituitary appears uniformly suppressed in relation to reduced circulating levels of target organ hormones. Impaired anterior pituitary hormone secretion allows the respective target organ hormones to decrease proportionately over time, with cortisol being a notable exception, the circulating levels of which remain elevated through a peripheral drive, a mechanism that ultimately may also fail. The onset of recovery is characterized by restored sensitivity of the anterior pituitary to reduced feedback control.

prolonged critical illness (29–31). Moreover, despite increased PRA, paradoxically decreased concentrations of aldosterone are found in protracted critical illness (32). This constellation suggests a shift of pregnenolone metabolism away from both mineralocorticoid and adrenal androgen pathways toward the glucocorticoid pathway, orchestrated by a peripheral drive. Ultimately, the latter mechanism may also fail, as indicated by a substantially higher incidence of adrenal insufficiency in prolonged critical illness (33).

Hypercortisolism in the chronic phase of critical illness probably continues to exert its beneficial hemodynamic effects. However, the benefit for the host defense of a sustained hypercortisolism in the presence of low levels of DHEAS is questionable, as prolonged imbalance between immunosuppressive and immunostimulatory hormones of adrenocortical origin may participate in the increased susceptibility for infectious complications. Other conceivable, although yet unproven, drawbacks of prolonged hypercortisolism include impaired wound healing and myopathy, complications that are often observed during protracted critical illness.

Somatotropic axis

The acute phase response of the somatotropic axis, as evoked by trauma, surgery, or acute infectious disease, has a characteristic presentation. Firstly, circulating levels of GH are elevated (5) (Fig. 2). Normally, the serum profile of GH consists of peaks alternating with virtually undetectable troughs. In acute illness, the total amount of GH released from the somatotropes appears to be increased, and interpulse concentrations of GH are relatively high (6, 7).

Secondly, serum concentrations of IGF-I are low (6, 34, 35). The concurrence of elevated GH and low IGF-I levels has been interpreted as resistance to GH, which may be related to decreased GH receptor expression (35).

Thirdly, there are changes in the circulating IGF-binding proteins (IGFBPs), which regulate IGF-I plasma half-life and bioavailability (36). The low serum concentrations of IGF-I are associated with low levels of IGFBP-3 and acid-labile subunit (11, 34, 37); the synthesis of these three polypeptides is normally up-regulated by GH, and together, they form a 150-kDa ternary complex in the circulation (34). In acute illness, there is increased presence of IGFBP-3 protease activity in plasma, resulting in increased dissociation of IGF-I from the ternary complex and a shortening of IGF-I plasma half-life (11, 34). IGFBP-1, which normally binds only a small amount of IGF-I compared to IGFBP-3, remains in the circulation in normal or slightly elevated concentrations (37, 38).

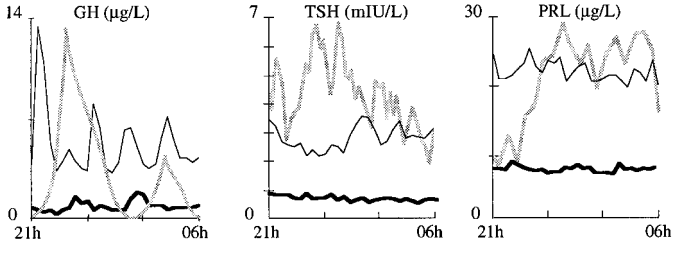

FIG. 2. Nocturnal serum concentration profiles of GH, TSH, and PRL illustrating the differences between the initial phase (*thin black line*) and the chronic phase (*thick black line*) of critical illness within an intensive care setting. The *gray lines* illustrate normal patterns.

As serum concentrations of free fatty acids and glucose are elevated by the acute stress response, and as nonfasting insulin levels are also increased, it is possible that the abundantly released GH still exerts direct lipolytic and insulin-antagonizing actions, whereas its indirect somatotropic effects are attenuated.

Inflammatory cytokines may be among the mediators of the aforementioned changes. Alternatively, nutritional factors may be involved, as most conditions of acute stress are accompanied by starvation or at least a degree of protein malnutrition (35, 39–41).

The constellation of changes observed within the somatotropic axis during acute stress, in balance with the response of the adrenocortical axis, has been interpreted as an attempt to provide essential substrates for survival while anabolism is postponed. In the human, this defense mechanism appears to be fundamental, as it can be activated before birth (42).

Therefore, in the acute phase of life-threatening disease or trauma, there is at present still no solid pathophysiological basis for endocrine intervention. Accordingly, it is anticipated that ongoing trials with exogenous GH may be unable to demonstrate major benefit in the acute phase of illness.

Prolonged critical illness, supported with intensive care for weeks, is characterized by a different set of changes in the somatotropic axis. Firstly, the pattern of GH secretion has been characterized as having a reduced pulsatile fraction (Figs. 2 and 3), whereas the nonpulsatile or tonic fraction is (still) somewhat elevated, and the number of pulses is high (17). This pattern results in mean serum GH concentrations that are low normal (17) (Fig. 2). Moreover, GH appears to be released in an erratic fashion, as indicated by a high calculated approximate entropy (17, 43).

Secondly, the reduced amount of GH that is released in pulses appears to correlate positively to the low circulating levels of IGF-I, IGFBP-3, and acid-labile subunit (17, 19). Indeed, it has been shown that when pulsatile GH secretion falls below a critical threshold during the chronic phase of illness, circulating IGF-I and acid-labile subunit progressively decrease over time (19). As low serum IGF-I levels and, even more so, low levels of acid-labile subunit are markers of protein wasting in this condition (11, 44), these findings suggest that the neuroendocrine component of the somatotropic axis participates in the pathogenesis of the wasting syndrome in prolonged critical illness. This hypothesis has been corroborated by studying the effects of GH secretagogue administration (17, 19); the whole somatotropic axis was found to be readily responsive to GH secretagogues in the chronic phase of critical illness, as evidenced by pulsatile GH secretion followed by substantial increases in the circulating levels of IGF-I, IGFBP-3, and the acid-labile subunit (Fig. 3). The presence of considerable responsiveness to restored endogenous GH secretion further delineates the distinct pathophysiological paradigm of the chronic phase of critical illness, as opposed to the acute phase, which is thought to be primarily a condition of GH resistance.

The pathogenesis of the secretory pattern of GH in prolonged critical illness is probably complex. One of the possibilities is a deficiency of the endogenous GH-releasing

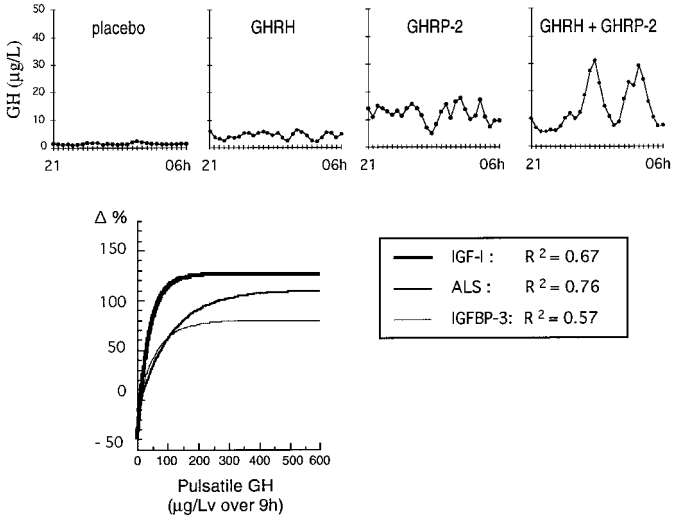

FIG. 3. *Upper part*, Nocturnal serum GH profiles in the prolonged phase of illness illustrating the effects of continuous infusion of placebo, GHRH (1 μg/kg·h), GHRP-2 (1 μg/kg·h), or GHRH plus GHRP-2 (1 + 1 μg/kg·h). The age range of the patients was 62–85 yr; the duration of illness was between 13–48 days; infusions were started 12 h before the onset of the respective profiles. Adapted from Refs. 17 and 19. *Lower part*, Exponential regression lines have been reported between pulsatile GH secretion and the changes in circulating IGF-I, acid-labile subunit, and IGFBP-3 obtained with 45-h infusion of either placebo, GHRP-2 or GHRH plus GHRP-2. They indicate that the parameters of GH responsiveness increase in proportion to GH secretion up to a certain point, beyond which a further increase in GH secretion has apparently little or no additional effect. It is noteworthy that the latter point corresponds to a pulsatile GH secretion of approximately 200 μg/Lv over 9 h or less, a value that can be evoked by the infusion of GHRP-2 alone. In the chronic, nonthriving phase of critical illness, GH sensitivity is clearly present, in contrast to the acute phase of illness, which is thought to be primarily a condition of GH resistance. Adapted from Ref. 19.

peptide (GHRP)-like ligand together with a reduced somatostatin tone and maintenance of some GHRH effect; this hypothetical combination would explain both reduced spontaneous GH secretion and pronounced responsiveness to GH secretagogues (17, 19, 45).

From a therapeutic perspective, the aforementioned data provide a sound pathophysiological basis to explore the safety and efficacy of GH secretagogue administration as a strategy to counter the wasting syndrome and, consequently, to actually accelerate the process of recovery from prolonged critical illness. As the administration of a hypothalamic releasing factor implies respect for pituitary feedback inhibition loops and allows for peripheral adjustment of metabolic pathways according to the needs determined by the disease, it is expected that the infusion of GH secretagogues will be a safer strategy than the administration of (high doses) GH and/or IGF-I in the chronic, GH-responsive, phase of critical illness, particularly in vulnerable elderly subjects (46).

In summary, the acute stress-regulated changes within the somatotropic axis appear to consist primarily of activated GH secretion and a peripheral shift toward its direct effects, whereas the chronic phase is mainly characterized by relative hyposomatotropism of essentially hypothalamic origin and preserved peripheral GH responsiveness. When a renewed acute phase, such as an intercurrent infection or surgical intervention, complicates the chronic phase, protease activity reappears in serum, and circulating levels of IGFBP-3 and IGF-I drop (34). In other words, repetitive episodes of GH resistance may appear on a background of relative hyposomatotropism, thus forming mixed conditions that may be difficult to interpret and may explain some of the apparent paradoxes in the literature.

Thyroid axis

Critical illness is characterized by multiple and complex alterations in the thyroid axis with, again, a dual presentation (9, 47). During the initial phase of severe illness and/or starvation, there appear to be mainly changes in peripheral metabolism, binding, and receptor occupancy of thyroid hormones, whereas a low activity state of primarily neuroendocrine origin predominates in prolonged critical illness within intensive care conditions (Figs. 1 and 2). Mixed forms are again possible and may further complicate the difficult interpretation of thyroid function tests in this setting.

Acute illness or trauma induces alterations in thyroid hormone equilibrium within hours. Although serum TSH usually remains normal, circulating T_3 rapidly drops partly due to decreased conversion of T_4 to T_3 (48) and/or increased turnover of thyroid hormones (49). The magnitude of the T_3 drop within 24 h reflects the severity of illness (50, 51). Serum rT_3 levels increase partly due to reduced rT_3 degradation (48). In animal models, hepatic nuclear T_3 receptors appear to decrease in number and in occupancy (52, 53). The absence of a TSH elevation in the face of low circulating T_3 levels suggests that there is also an altered feedback setting at the hypothalamic-pituitary level (54, 55). Experimental data indicate that reduced TRH gene expression as well as enhanced nuclear T_3 receptor occupancy within the thyrotropes may be involved (55, 56).

The cytokines TNF-α, interleukin-1 (IL-1), and IL-6 have been investigated as putative mediators of the acute low T_3 syndrome (55, 57–59). Although these cytokines are capable of mimicking the acute stress-induced alterations in thyroid status, cytokine antagonism in sick mice failed to restore normal thyroid function (60). Endogenous thyroid hormone analogs resulting from alternative deamination and decarboxylation, such as tri- and tetraiodothyroacetic acid, may also participate in the pathogenesis of the low T_3 syndrome by blunting the TSH response to low thyroid hormone feedback and by competing with active thyroid hormone for binding to transport proteins (61, 62). Finally, low concentrations of binding proteins and inhibition of hormone binding, transport, and metabolism by elevated levels of free fatty acids and bilirubin have been proposed as factors contributing to the low T_3 syndrome at tissue level (63).

Teleologically, the acute changes in the thyroid axis occurring during starvation have been interpreted as an attempt to reduce energy expenditure (64) and, thus, as an appropriate response that does not warrant intervention. Whether this is also applicable to other acute stress conditions, such as the initial phase of critical illness, is still a matter of controversy.

Alterations in the thyroid axis during the prolonged phase of critical illness appear to be different. Essentially, pulsatile

TSH secretion is diminished and positively related to the low serum levels of T_3 (18, 19). These findings indicate that the reduced production of thyroid hormones in the prolonged phase of critical illness may have a neuroendocrine origin. In line with this concept are the findings that hypothalamic TRH gene expression is positively related to serum T_3 in this condition (65) and that an increase in serum TSH is a marker of the onset of recovery from severe illness (54).

The neuroendocrine pathogenesis of the low T_3 syndrome of prolonged critical illness is unknown. As circulating cytokine levels are usually low (66), other mechanisms operational within the central nervous system are presumably involved. Endogenous dopamine and prolonged hypercortisolism may each play a role (16, 67); exogenous dopamine is known to provoke or aggravate central hypothyroidism in critical illness (68, 69).

As normal levels of T_3 are required for protein synthesis, lipolysis, fuel utilization by muscle, and GH secretion and responsiveness, central hypothyroidism has been hypothesized to contribute to the feeding-resistant catabolic state of prolonged critical illness. It remains speculative whether the low serum and tissue (70) concentrations of T_3 are also involved in several problems distinctively associated with prolonged critical illness, such as diminished cognitive status with lethargy (71), somnolence, or depression; ileus and gallbladder dysfunction; pleural and pericardial effusions; glucose intolerance and insulin resistance; hyponatremia; normocytic normochromic anemia; and deficient clearance of triglycerides.

The concept of a low T_3 syndrome of neuroendocrine origin has been corroborated by investigating the effect of TRH administration (19): the thyroid axis of patients with prolonged critical illness can be reactivated by TRH infusion, from TSH secretion to increases in circulating T_4 and T_3 (Fig. 4). Interestingly, coinfusion of TRH and GH secretagogues appears necessary to increase the pulsatile fraction of TSH release and to avoid a rise in circulating reverse T_3 (Fig. 4). During TRH infusion in prolonged critical illness, the negative feedback exerted by thyroid hormones on the thyrotropes was maintained, thus precluding overstimulation of the thyroid axis (19). Moreover, TRH infusion allows for peripheral shifts in thyroid hormone metabolism during intercurrent events and, accordingly, permits the body to elaborate appropriate concentrations of thyroid hormones in circulation and at the tissue level, thus setting the scene for a safer treatment than the administration of T_3.

The pioneering studies with T_4 or T_3 administration have failed to demonstrate clinical benefit in the intensive care setting (72, 73). The clinical significance of combined TRH- and GH secretagogue-induced stimulation of the thyroid axis in prolonged critical illness remains to be delineated.

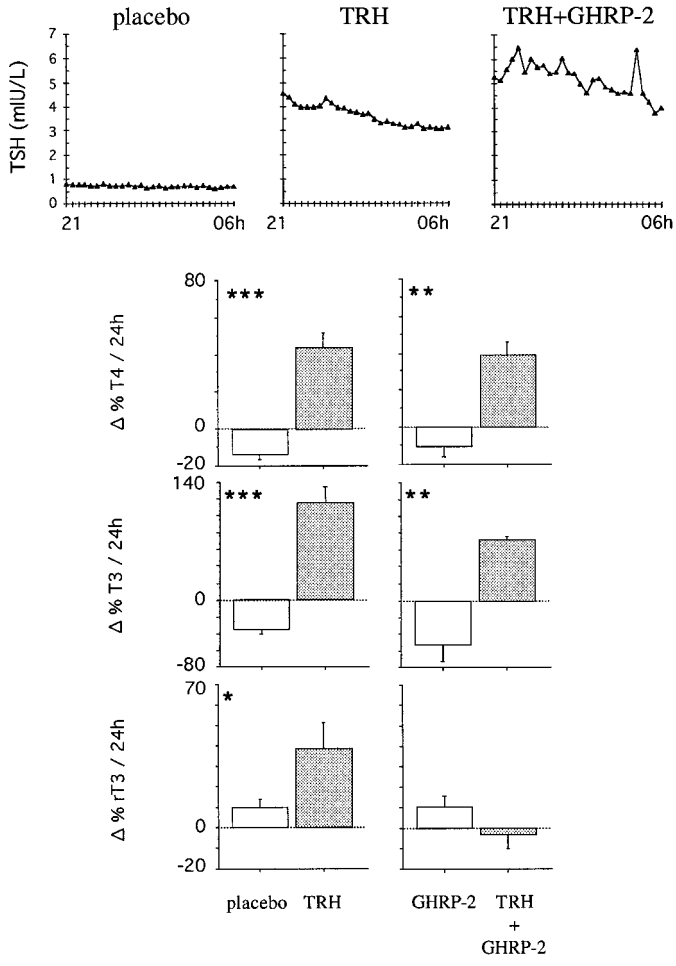

FIG. 4. *Upper part*, Nocturnal serum TSH profiles in the prolonged phase of illness (duration of illness, 15–18 days; patient's age, 69–80 yr), illustrating the effects of continuous infusion of placebo, TRH (1 μg/kg·h), and TRH plus GHRP-2 (1 μg/kg·h). Although TRH elevated TSH secretion, addition of GHRP-2 to the TRH infusion appeared necessary to increase its pulsatile fraction. Adapted from Ref. 19. *Lower part*, 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 T_4 and T_3 within 24 h. rT_3 is increased after the infusion of TRH alone, but not if TRH is coinfused with GHRP-2. The patients studied were ill for 12–59 days; the age range was 32–87 yr. *, $P < 0.05$; **, $P < 0.001$; ***, $P < 0.0001$. Adapted from Ref. 19.

Gonadal axis

A variety of catabolic states are associated with low serum testosterone levels in men. These conditions include starvation (74, 75), the postoperative phase (8), myocardial infarction (76), burn injury (77, 78), psychological and physical stress (79, 80), and prolonged critical illness (81).

It appears that acute injury primarily leads to an immediate and direct Leydig cell suppression. Indeed, low serum testosterone concentrations despite elevated LH levels have been documented during the acute stress of surgery or myocardial infarction, whereas FSH and inhibin levels remain normal (8, 76, 82). The mechanisms underlying the immediately decreased secretory Leydig cell responsiveness in humans remain largely unknown. A role for inflammatory cytokines (IL-1 and IL-2) is possible, as suggested by experimental studies (83, 84).

It may again be considered appropriate that the secretion of anabolic androgens be switched off in circumstances of acute stress to reduce the consumption of energy and substrates. When a severe stress condition becomes prolonged, hypogonadotropism ensues (77, 85). A progressive decrease in serum gonadotropin levels has been documented within 1 or 2 days, albeit lagging behind the rapid decline in serum

testosterone (76, 82, 86). In prolonged critically ill men within intensive care conditions, mainly the pulsatile fraction of LH release was attenuated (81). In critically ill women, a reversible reduction of LH and FSH secretion, and of serum estradiol concentrations, has been observed and correlated with outcome (85–87). Endogenous dopamine or opiates may be involved in the pathogenesis of hypogonadotropic hypogonadism, as iatrogenic factors such as exogenous dopamine and opioids may further diminish blunted LH secretion (81, 88). Animal data suggest that prolonged exposure of the brain to IL-1 may also play a role through the suppression of LHRH synthesis (83).

The pioneering studies evaluating androgen treatment in prolonged critical illness failed to demonstrate conclusive clinical benefit (89). In view of the secretory characteristics of the other anterior pituitary hormones, the therapeutic potential of androgens should perhaps be reappraised in a combined treatment. The effect of pulsatile GnRH administration remains to be explored.

PRL

PRL was among the first hormones known to have increased serum concentrations in response to acute physical or psychological stress (5), a rise that may be mediated by vasoactive intestinal peptide, oxytocin, dopaminergic pathways, and/or other still uncharacterized factors (90, 91). Cytokines may again play a signaling role. Although PRL appears to have immunostimulatory properties in animal models as well as in humans (91–93), it remains unclear whether the relative hyperprolactinemia during the initial phase of critical illness or posttrauma contributes to the initial activation of the inflammatory cascade.

In prolonged critical illness, serum PRL appears to be no longer elevated, and the secretory pattern is characterized by a reduction in the pulsatile fraction (18, 19) (Fig. 2). It is unknown whether the blunted PRL secretion plays a role in the anergic immune dysfunction or in the increased susceptibility for infections characterizing the chronically ill (15, 94). However, dopamine, which is often infused as an inotropic and vasoactive supportive agent in intensive care-dependent patients, has been shown to further suppress PRL (and DHEAS) secretion without altering elevated serum cortisol levels, and was found to aggravate concomitantly both T lymphocyte dysfunction and impaired neutrophil chemotaxis (31, 68, 93).

Conclusion

Acute and prolonged critical illness seem to result in different neuroendocrine paradigms and should perhaps be approached with different therapeutic strategies.

The initial endocrine response evoked by severe illness or trauma and by starvation consists primarily of a peripheral inactivation of anabolic pathways (low IGF-I, T_3, and testosterone levels), whereas pituitary activity is essentially maintained or amplified: substrates for survival are provided, anabolism is postponed, and the immune response is activated while the host is protected against deleterious systemic effects of the latter. At present, there still is no solid pathophysiological basis for hormonal intervention in this acute phase.

The development of intensive care has led to survival in previously lethal conditions, thus unmasking newly recognized disorders such as the wasting syndrome of protracted intensive care dependency. In the chronic phase of critical illness, reduced pulsatile secretion of anterior pituitary hormones correlates positively with reduced activity of target tissues; cortisol secretion is a notable exception, being maintained through a peripheral drive.

An acute event complicating the chronic phase of illness, such as an intercurrent infection or surgical intervention in a "long stay" intensive care unit patient, may be accompanied by mixed acute/prolonged endocrine patterns, which are difficult to interpret and may account for some of the apparently conflicting data in the literature.

It is unlikely that the reduced neuroendocrine drive, distinctively present in the chronic phase of illness within an intensive care setting, has been selected by evolution and should accordingly be considered as time-honored and appropriate. The hypothesis of inappropriate neuroendocrine function can be validated by studying the effects of either combined peripheral hormonal substitution or hypophysiotropic releasing peptide administration. The latter demonstrated that selected pituitary-dependent axes can readily be reactivated in the chronic phase of critical illness, with preserved peripheral responsiveness. Intervening at the hypothalamic-pituitary level appears a safer strategy than the administration of peripherally active hormones, as the presence of feedback inhibition protects from dose-related side-effects. It remains to be determined whether endocrine interventions in prolonged critical illness will result in beneficial metabolic effects and will, ultimately, accelerate the recovery of those patients who need it most.

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