hormonal reponse to critical illness [created by Paul Young 03/12/07]

general

- Critical illness is characterized by a uniform dysregulation of all hypothalamic- anterior pituitary axes, long known to contribute to the high risk for morbidity and mortality. It is now clear that the neuro-endocrine responses to acute and prolonged critical illness are substantially different.
- In the acute phase of critical illness, the pituitary is secreting actively, but target organs become resistant and concentrations of most peripheral effector hormones are low. These acute adaptations probably are beneficial in the struggle for short-term survival,for which no need for intervention seems necessary.
- In contrast, prolonged, intensive care-dependent critical illness is hallmarked by a uniform suppression of the neuroendocrine axes, predominantly of hypothalamic origin,which contributes to the low serum levels of the respective target-organ hormones. These chronic alterations no longer may be beneficial, as they participate in the general wasting syndrome of prolonged critical illness.

overview

Overview of the neuroendocrine changes in the acute and in the prolonged phase of critical illness

Hormone	Acute phase	Prolonged phase
1. Somatotropic axis		
Pulsatile GH release	↑	↓
IGF-I	↓	↓↓
ALS	↓	↓↓
IGFBP-3	↓	↓↓
2. Thyroid axis		
Pulsatile TRH release	↑≡	↓
T_4	↑≡	↓
T_3	↓	↓↓
rT_3	↑	↑≡
3. Gonadal and lactotropic axis		
Pulsatile LH release	↑≡	↓
Testosterone	↓	↓↓
Pulsatile PRL release	↑	↓
4. Adrenal axis		
Corticotropin	↑	↓
Cortisol	↑↑	↑≡↓
CBG	↑	≡

Abbreviations: ↑, increase in circulating levels; ↓, decrease in circulating levels; ≡, recurrence to normal circulating levels.

gonadal and lactotropic axis

general
- Gonadotropin-releasing hormone (GnRH), secreted in a pulsatile pattern by the hypothalamus, stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the gonadotropes in the pituitary.
- In women, LH mediates androgen production by the ovary, whereas FSH stimulates the aromatization of androgens to estrogens in the ovary.
- In men, LH stimulates androgen production by Leydig's cells in the testes, whereas the combined action of FSH and testosterone on Sertoli's cells supports spermatogenesis.
- Prolactin (PRL) is a well-known stress hormone produced by the lactotropes in the pituitary, which is physiologically secreted in a pulsatile and diurnal pattern, and is presumed to have immune-enhancing properties. Physiologic control of PRL secretion largely is under the control of dopamine, but several other PRL-inhibiting and -releasing factors can modulate PRL secretion

The acute phase of critical illness
- Acute physical stress, such as surgery or myocardial infarction, brings along an immediate fall in the serum levels of testosterone, even though LH levels are elevated. This suggests an immediate suppression of androgen production Leydig's cells, which may be viewed, at least in the short term, as an attempt to reduce energy consumption and conserve substratesfor more vital functions. Involvement of cytokines again is possible, as put forward by experimental studies.
- PRL levels rise in response to acute physical or psychologic stress. Factors possibly involved are vasoactive intestinal peptide, oxytocin, and dopaminergic pathways, but again cytokines or as yet uncharacterized factors also may play a role.
- The rise in PRL levels after acute stress is believed to contribute to the vital activation of the immune system early in the disease process, but this remains speculative.

The prolonged phase of critical illness
- More dramatic changes develop within the male gonadal axis with prolongation of the disease, and hypogonadotropism ensues. The circulating levels of testosterone become extremely low and often even are undetectable, in the presence of suppressed mean LH concentrations and pulsatile LH release.
- Total estradiol levels also are relatively low but the level of bioavailable estradiol probably is maintained in view of the simultaneous decrease in sex-hormone-binding globulin. Alternatively, a remarkable rise in estrogen levels is observed in other studies
- As testosterone is the most important endogenous anabolic steroid, the abnormalities in the gonadal axis could be important with regard to the catabolic state of critical illness.
- The pulsatile fraction of PRL release becomes suppressed in patients in the prolonged phase of critical illness. It is unclear whether or not the blunted PRL secretion contributes to the immune suppression or increased susceptibility to infection associated with prolonged critical illness

thyroid axis

General
- Thyrotropin-releasing hormone (TRH), secreted by the hypothalamus, stimulates the pituitary thyrotropes to produce thyrotropin, which in turn regulates the synthesis and secretion of thyroid hormones in the thyroid gland.
- Thyroid hormones are essential for the regulation of energy metabolism and have profound effects on differentiation and growth. Although the thyroid gland predominantly produces thyroxine (T4), the biologic activity of thyroid hormones is exerted largely by triiodothyronine (T3)

The acute phase of critical illness
- The early response of the thyroid axis after the onset of severe physical stress consists of a rapid decline in the circulating levels of T3 and a rise in rT3 levels, predominantly because of altered peripheral conversion of T4.
- Thyrotropin and T4 levels are elevated briefly but subsequently normalize, although in those who are more severely ill, T4 levels also may decrease.
- Although serum thyrotropin levels measured in a single daytime sample are normal in acute critical illness, the thyrotropin profile already is affected, as the normal nocturnal thyrotropin surge is absent.
- The low T3 levels persist beyond thyrotropin normalization, a condition referred to as "the low T3 syndrome." The decrease in circulating T3 during the first 24 hours after an insult reflects the severity of illness. Furthermore, T3 levels correlate inversely with mortality.

The prolonged phase of critical illness
- Patients who need prolonged intensive care show, in addition to the absent nocturnal thyrotropin surge, a dramatically reduced pulsatile thyrotropin secretion. Furthermore, serum levels of T4 and T3 are low, and in particular, the decline in T3 correlates positively with the diminished pulsatile release of thyrotropin. The prognostic value of the disturbed thyroid axis with regard to mortality is illustrated by lower thyrotropin, T4, and T3 and higher rT3 levels in patients who ultimately die compared with those who survive prolonged critical illness.
- In the chronic phase of critical illness, the peripheral metabolism of thyroid hormone also is disturbed and contributes to the low T3 syndrome. Regulation of thyroid hormone action at the level of the thyroid hormone receptor also seems to be altered by critical illness, possibly causing an upregulated thyroid hormone sensitivity in response to low T3 levels.

somatotrophic axis

General
- Growth hormone (GH) is secreted by the somatotropes in the pituitary and is essential for linear growth during childhood but serves many more important functions throughout life.
- The regulation of the physiologic pulsatile release of GH, consisting of peak serum GH levels alternating with virtually undetectable troughs, is important for its metabolic effects
- Hypothalamic GH-releasing hormone (GHRH) stimulates, and somatostatin inhibits, the secretion of GH.
- GH exerts direct and indirect effects, the latter mediated by insulin-like growth factor-I (IGF-I)

The acute phase of critical illness
- During the first hours to days after an acute insult, the GH profile changes dramatically. The pulse frequency is increased, peak GH levels are elevated, and interpulse concentrations are high.
- Concomitantly, a state of peripheral GH resistance develops, triggered in part by cytokines, such as tumor necrosis factor a and interleukin 6.
- Despite the clearly enhanced GH secretion, serum concentrations of IGF-I decrease
- Theoretically, this may enhance the direct lipolytic and insulin- antagonizing effects of GH, resulting in elevated fatty acid and glucose levels in the circulation, whereas indirect, IGF-I-mediated somatotropic effects of GH are attenuated. As a result, costly anabolism, largely mediated by IGF-I is decreased during the struggle for survival.

The prolonged phase of critical illness
- In prolonged critically ill patients, when recovery does not occur within a few days, a different GH secretion pattern arises.
- The pulsatile release of GH becomes suppressed, whereas the nonpulsatile fraction of GH release remains somewhat elevated. A strong positive correlation is found between the pulsatile fraction of GH release and circulating IGF-I levels, which suggests that the loss of pulsatile GH release contributes to the low levels of IGF-I in prolonged critical illness.
- This chronic GH deficiency, resulting from lack of pulsatile GH secretion, could contribute to the pathogenesis of the wasting syndrome that characterizes prolonged critical illness.

adrenal axis

General
- The hypothalamic corticotropin-releasing hormone (CRH) controls the pituitary corticotropes for release of corticotropin, which stimulates the adrenal cortex to produce cortisol.
- In stress-free healthy humans, cortisol is secreted according to a diurnal pattern and exerts a negative feedback control on both hormones. More than 90% of circulating cortisol is bound to binding proteins, predominantly corticosteroid-binding globulin (CBG) but also albumin; however, only the free hormone is biologically active.

The acute phase of critical illness
- In the early phase of critical illness, cortisol levels usually rise in response to an increased release of CRH and corticotropin, but the diurnal variation in cortisol secretion is lost.
- Cortisol production and glucocorticoid receptor number or affinity are modulated by cytokines in acute illness.
- Stress-induced hypercortisolism in critically ill patients fosters the acute provision of energy by shifting carbohydrate, fat, and protein metabolism; protects against excessive inflammation by suppression of the inflammatory response; and improves the hemodynamic status by induction of fluid retention and sensitization of the vasopressor response to catecholamines.

The prolonged phase of critical illness
- Cortisol levels usually remain elevated in the chronic phase of critical illness, which seems to be driven by non-corticotropin-mediated pathways, because corticotropin levels are decreased.
- Cortisol levels slowly decrease, only reaching normal levels in the recovery phase. CBG levels recover in the chronic phase of illness. Whether or not the persisting elevation in cortisol is beneficial exclusively in prolonged critical illness remains uncertain. Theoretically, it could contribute to the increased susceptibility to infectious complications. Alternatively, the risk for "relative adrenal failure" may increase in the chronic phase of critical illness and may predispose to adverse outcome

therapeutic implications

- Administration of pharmacologic doses of GH, inspired by the assumption of sustained GH resistance in the prolonged phase of critical illness, unexpectedly increases morbidity and mortality.
- Initial trials studying administration of high doses of glucocorticoids clearly show that this strategy is ineffective and perhaps even harmful. In contrast, studies using still supraphysiologic low-dose glucocorticoid replacement therapy for relative adrenal insufficiency report beneficial effects, at least in patients who have septic shock.
- It remains controversial whether or not administration of thyroid hormone to patients who are critically ill is beneficial or harmful
- There is no conclusive clinical benefit demonstrated for androgen treatment in prolonged critical illness