SECTION "UNDERSTANDING THE DISEASE"

Understanding the HPA response to critical illness: novel insights with clinical implications

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The stress response, essential for life during health and disease, is governed by the hypothalamus-pituitary-adrenal (HPA) axis. It starts by hypothalamic CRH release which, via the hypophyseal portal system activates the corticotrophes in the anterior pituitary gland to secrete ACTH. ACTH stimulates steroidogenesis by binding to the melanocortin-2-receptor on adrenocortical cells. ACTH upregulates expression of this receptor, mediates cholesterol release from lipid droplets while activating expression of genes encoding proteins for cholesterol uptake and synthesis.[1-5] ACTH also increases expression of genes encoding key steroidogenic enzymes.[1-5] Besides this feed-forward activation of cortisol secretion, feed-back inhibition of CRH and ACTH by cortisol occurs at the pituitary and hypothalamic level.

Within this classical stress response concept, the hypercortisolemia of critical illness is thought to be brought about by elevated circulating ACTH which increases adrenocortical cortisol production several-fold. However, the few studies that reported plasma ACTH concentrations during critical illness showed that these are only elevated briefly and then are lower than normal.[6-8] This "ACTH-cortisol dissociation" is not what one would expect with a sustained HPA axis activation. In fact, Polito *et al.* reported suppressed *ACTH mRNA* levels in pituitary glands harvested postmortem from 9 patients with septic shock, without a rise in CRH or vasopressin expression in the hypothalamus.[9] Also in experimental sepsis models, it was recently shown that pituitary ACTH expression levels quickly become suppressed,[11] possibly explained by nitric oxide or by suppressed orexin signaling.[9,10] If suppression of pituitary ACTH expression would be a primary manifestation of organ damage, this should quickly cause low plasma cortisol concentrations, which does not often happen in human ICU patients. Another possible explanation is increased adrenocortical sensitivity to ACTH.[11] However, the adrenocortical cortisol secretory response to a given endogenous plasma ACTH level is not increased during critical illness[12] and in response to exogenous ACTH often low. Furthermore, a recent study of human adrenal glands showed that ACTH signaling was severely suppressed specifically in the

prolonged phase of critical illness[13], similar to what occurs in POMC deficiency. Hence, a more plausible explanation for the high plasma cortisol concentrations with low plasma ACTH levels and, with time, reduced ACTH-regulated gene expression in the adrenal cortex, is negative feedback inhibition exerted by elevated plasma cortisol that is brought about during critical illness by alternative, non-ACTH driven, pathways.

Although it is generally accepted that cortisol production rate should be >6-fold increased to bring about the degree of hypercortisolemia observed during critical illness, it was never quantified in ICU-patients until recently. Boonen *et al.* documented by stable isotopes that daytime cortisol production rate was only moderately increased, less than doubled, in critically ill patients suffering from the systemic inflammation response syndrome (SIRS) and indistinguishable from healthy control subjects in patients without SIRS, while plasma total and free cortisol levels were several-fold higher in all patients.[8] The stable isotope technique also allowed to accurately quantify cortisol plasma clearance, which was found suppressed to less than half in all patients, irrespective of inflammation status.[8] Cortisol half-life and plasma clearance of a 100 mg bolus of hydrocortisone administered during critical illness gave similar results: plasma clearance reduced to 40% of normal and a median 5-fold longer cortisol half-life.[8] Reduced cortisol breakdown during illness is due to reduced expression/activity of the cortisol metabolizing enzymes in liver and kidney.[8] With the knowledge that cortisol half-life and plasma clearance is uniformly reduced during critical illness, further study of nocturnal ACTH and cortisol secretion rates and the interaction between ACTH concentrations and cortisol secretion was recently performed by constructing time series of plasma concentrations measured every 10 minutes over 9 hours in critically ill patients and in matched control subjects.[12] The plasma concentration time series were transformed into hormonal secretion profiles with deconvolution analysis, that takes into account elimination half-life of the hormone. Both nocturnal ACTH and cortisol pulsatile and total secretion rates were shown to be reduced

in critically ill patients.[12] Interestingly, the 'dose-response' between a given ACTH concentration and cortisol secretory response was preserved normal, suggesting that the term 'ACTH-cortisol dissociation' may not be justified. Indeed, cortisol secretion was still 'connected' to circulating ACTH, but *both* were suppressed, not increased, in the presence of high total and free plasma cortisol concentrations.[12] Together, these new data revealed that overall 24h cortisol production rates during critical illness may not be, or at best only moderately, higher than during health (Figure).

These new insights have clinical implications. 'Absolute' and 'relative' adrenal failure may occur during critical illness. Absolute adrenal failure can be due to pre-existing adrenal disease, adrenocortical hemorrhage, drugs that interfere with cortisol synthesis or adrenal atrophy. The latter is due to prolonged ACTH suppression, not only by chronic corticosteroid treatment but possibly also, as shown recently, by sustained negative feedback inhibition through endogenous cortisol in prolonged critical illness[13]. Absolute adrenal failure requires immediate treatment to prevent a life-threatening Addisonian crisis. 'Relative' adrenal failure is a term that was proposed to describe the condition occurring during critical illness in which plasma cortisol concentrations, although higher than during health, are insufficiently high to cope with the stress level.[14] The exact underlying mechanisms remain[15] unclear but pituitary ischemia/inflammation, more subtle forms of adrenal hemorrhage or target tissue resistance to cortisol are thought to play a role. Whether such 'relative' adrenal insufficiency needs treatment also remains unclear. However, since it is now known that cortisol production is at most only moderately increased in critically ill patients with a well-functioning HPA axis, and as cortisol breakdown is substantially and robustly reduced, the therapeutic doses of 200 mg or more hitherto proposed for absolute and relative adrenal insufficiency, the equivalent of >6-fold the normal daily cortisol production, may be too high. Such high hydrocortisone doses in the

presence of severely reduced clearance may accumulate and induce side effects that could offset any potential benefit.

In summary, recent studies showed that increased cortisol exposure for an optimal stress response during critical illness is much less determined by cortisol production than by reduced cortisol breakdown. These insights have clinical implications that should be further investigated.

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Conflict of interest : nothing to declare

Two sentences summary with key points:

The vital increase in cortisol availability during critical illness appears to be brought about primarily by reduced cortisol breakdown rather than by an activated HPA axis or by an alternatively activated cortisol production. These new findings explain suppressed plasma ACTH through feedback inhibition which, with time, may evoke loss of adrenal gland integrity

and function due to lack of adrenocortical ACTH signaling. Also, these new findings have implications for correct dosing of hydrocortisone treatment.

Figure: The differences between the healthy HPA axis and that during critical illness are illustrated. Modified and adapted from ref. 16.