EDITORIAL

Adrenal Dysfunction in Critically Ill Patients

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Critical illness elicits a major stress response that activates the hypothalamic–pituitary–adrenal (HPA) axis. Furthermore, the administration of corticotropin stimulates cortisol secretion and causes structural changes in the adrenal gland that include adrenal-cell hypertrophy and hyperplasia.[1] Adrenal glands that are obtained on autopsy from patients who have died after a prolonged critical illness[2] are relatively heavy, and progressively compact lipid-depleted cells replace lipid-laden fasciculata cells.[2]

The symptoms of patients with critical illness vary: many have hypotension and are receiving inotropes or vasopressors, whereas others have sepsis, and many have the systemic inflammatory response syndrome (SIRS).[3] Subsequent adrenal failure in critically ill patients may be due to structural damage from hemorrhage and necrosis, although for most survivors adrenal failure is reversible and based on dysfunction of the HPA axis.[3] The criteria for determining which patients have an adequate adrenal response to severe stress and which have an inadequate response are arbitrary and controversial.[3] However, many studies suggest that in some patients with adrenal failure glucocorticoid therapy confers a survival benefit.[3]

Although severe stress activates the HPA axis, a dissociation between plasma corticotropin levels and cortisol levels may occur, marked by suppressed corticotropin levels and elevated plasma cortisol levels.[3-5] The cause of such dissociation is unclear, but there is evidence that a systemic inflammatory response heralded by marked elevations of various cytokines, including interleukin-6 and tumor necrosis factor α (TNF-α), might be involved.[5]

What are the mechanisms underlying adrenal dysfunction in critical illness? Boonen et al.[5] now report in the *Journal* a study in which they infused deuterated cortisol and cortisone in patients in the intensive care unit and in matched controls and then measured labeled and unlabeled cortisol, cortisone, and metabolites to show that a decrease in cortisol metabolism substantially contributed to elevated cortisol levels in critically ill patients. The authors used deuterated D4-cortisol labeled in the 9, 11, 12α, and 12β positions to determine production rates and metabolism of cortisol. Loss of deuterium in the 11-position when the hydroxyl group is converted to a keto group tracks the conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase 2 enzyme (Fig. 1). The remaining D3-cortisol levels indicate the portion of the initial D4-cortisol that is converted to cortisone and then converted back to cortisol by 11β-hydroxysteroid dehydrogenase 1.

The authors observed that critically ill patients have a significant decrease in the formation of D3-cortisol, reflecting a decrease in the initial conversion to D3-cortisone, although the conversion of cortisone to cortisol is unimpaired. Reduction in levels of A-ring reductases (5β-reductase and 5α-reductase) that inactivate cortisol, as reflected by a decrease in their metabolites, also appeared to contribute to the decreased clearance of cortisol (Fig. 1).

The study by Boonen et al. provides a convincing explanation for some of the elevation in plasma cortisol levels observed in critically ill patients. However, the authors do not address the mechanism of cortisol hypersecretion in the presence of suppressed corticotropin. Study pa-

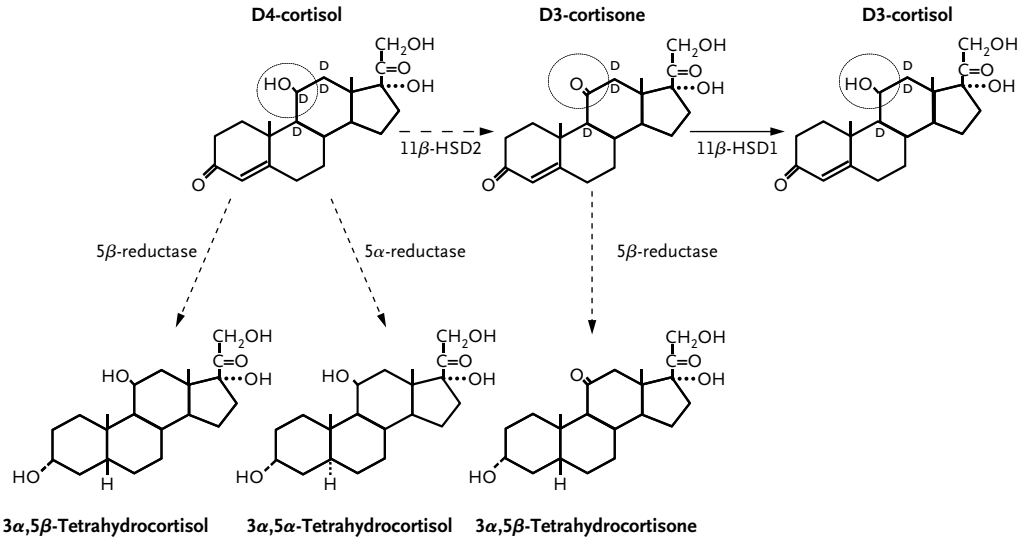

Figure 1. Metabolism of Deuterated D4-Cortisol and Conversion of Cortisol and Cortisone into Their Tetrahydro-Metabolites.

The dashed lines with arrows indicate a decrease in metabolic conversion by 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), 5β-reductase, and 5α-reductase enzymes, which may contribute to the decreased clearance of cortisol in critically ill patients. In the upper row, the letter D indicates the presence of a deuterium label. The abbreviation 11β-HSD1 denotes 11β-hydroxysteroid dehydrogenase 1.

tients with SIRS had increased adrenal cortisol production; those without SIRS had normal production.[5] Critically ill patients have a marked reduction in levels of cortisol-binding protein with proportional increases in free cortisol, which can diffuse into tissues. Levels of interstitial cortisol obtained by microdialysis in patients with sepsis correlated only moderately with total plasma cortisol levels, suggesting that plasma cortisol may not reflect tissue availability.[6]

Inflammatory cytokines induce the dominant negative β isoform of the glucocorticoid receptor, which decreases the action of glucocorticoid receptors.[7] However, low-to-moderate doses of cortisol that were recommended by a consensus group are 2 to 10 times as high as the levels of cortisol produced in patients who are critically ill or in those with Cushing's syndrome.[3,5,8]

Systemic inflammatory responses to severe illness may be relevant here and include marked elevations of various cytokines, including interleukin-6 and TNF-α, associated with corticotropin suppression and stimulation of cortisol secretion in experimental models.[5] The development of adrenal insufficiency in some critically ill patients is unexplained. However, there is evidence that endothelial dysfunction in the highly vascularized adrenal gland may be involved in the inflammation-related reversible adrenal insufficiency of SIRS. For example, Del-1 (an endothelial homeostatic factor encoded by the developmental endothelial locus-1 gene) is expressed in adrenal glands in both mice and humans.[9] Endotoxin decreases Del-1 expression in mice, along with a significant decrease in levels of corticosterone and corticotropin, an effect that is exaggerated in Del-1 knockout animals.[9]

In summary, multiple changes in cortisol homeostasis occur in critically ill patients, including adrenal stimulation by cytokines, the suppression of corticotropin, a substantial decrease in cortisol breakdown, and probably adrenal endothelial dysfunction. These alterations contribute to functional adrenal failure, and the study by Boonen et al. clarifies several aspects of these changes.

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