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Glucocorticoid receptors in critically ill patients

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Abstract

In critically ill patients, the hypothalamic-pituitary-adrenal axis is activated and as a consequence these patients exhibit increased serum cortisol concentrations. However, a number of patients have relatively low cortisol levels for the degree of illness severity. Glucocorticoid actions are facilitated by the glucocorticoid receptor whose dysfunction leads to glucocorticoid tissue resistance. Most clinical studies in critically ill adult patients have studied cortisol availability, and only a few have investigated glucocorticoid receptor levels and function.

In this review we will explore the conflicting results that have arisen from the clinical studies that aimed to elucidate the role of glucocorticoid receptor in glucocorticoid resistance. The study of receptor function and expression might aid in identifying the patients who will benefit from corticosteroid administration.

Glucocorticoids, the end-products of the hypothalamic-pituitary-adrenal (HPA) axis, have been used for over half a century in sepsis, however not all patients benefit from their use [1-4]. In critically ill patients, the HPA axis is activated causing increased serum cortisol concentrations [5-8], though a high number of septic [9] or non-septic [10] patients exist with low serum cortisol levels for the severity of their illness. This cellular corticosteroid availability and/or activity for the degree of illness severity resulting from dysfunction of the HPA axis is termed critical illness-related corticosteroid insufficiency (CIRCI) [11].

Cortisol signalling is mediated by a ubiquitous intracellular receptor protein, the glucocorticoid receptor (GCR). Two highly homologous isoforms of GCR result from alternative splicing of the primary transcript [12]. GCR-α is the classic functionally active receptor; after hormone binding it translocates from the cytosol to the nucleus where it exerts transcriptional activation or repression by directly binding to genes containing glucocorticoid responsive elements (GREs) [13]. The final outcome is the inhibition of the inflammatory response [14,15]. The function of GCR-β is mostly unknown; it suppresses GCR-α activity and is unable to bind natural and synthetic ligands [16-18].

Current guidelines suggest the use of hydrocortisone in patients with septic shock resistant to vasoactive agents, however, not all patients respond appropriately pointing possibly towards glucocorticoid (GC) resistance [19]. GC resistance is the inability of glucocorticoids to exert their effects on target tissues [20]. It indicates a decrease in the sensitivity of immune cells to glucocorticoids, which under normal conditions terminate the inflammatory response [21]. So how tissues respond to cortisol is as important as the levels of the hormone itself. The extent of cortisol effect might be proportional to GCR expression, subtype, and affinity in a specific target cell [22]. For example, expression of GCR-β is increased in tissues in inflammatory diseases and seems to be associated with decreased sensitivity to glucocorticoids [23].

It is uncertain whether GC resistance is a result of reduced GCR expression, decreased affinity of GCR for the ligand, reduced nuclear translocation, decreased DNA binding, or altered transcription factor interaction. Most clinical studies have investigated cortisol availability in critically ill patients, however the importance of GCR function has only been explored in a few clinical studies in adults yielding conflicting results. One group has described glucocorticoid resistance in a cohort of septic patients; their results showed lower *GCR-α* and increased *GCR-β* expression levels in septic patients compared to healthy subjects, suggesting that steroid treatment might aggravate GC resistance in patients with high GCR-β levels [24]. A transient increased expression of *GCR-β* has been found in septic patients and furthermore, serum from these patients was able to induce GC resistance *in vitro* [25]. Another group reported reduced levels of *GCR-α* in sepsis [26], while reduced GCR protein levels has been reported in various organs during sepsis [27]. Also, in sepsis, decreased number of GCR-α and increased GCR-β in heart and liver biopsies has been shown [28]. Evidence that *GCR* expression increased during septic shock, while GCR binding capacity decreased, proposed that it is the decreased GCR binding capacity that blocks the response to exogenous or endogenous glucocorticoids, rather than the number of receptors [29]. On the contrary, it has been shown that the GCR count and affinity in septic patients did not differ from normal controls, suggesting that glucocorticoids could still be effective in the hemodynamic compensatory phase of sepsis [30]. A recent study also showed increased *GCR-α* expression in the acute phase of sepsis, possibly implying no need for exogenous steroids at this phase [31]. In critical illness, only one study has demonstrated down-regulation of cortisol binding in ventilated patients [32]. Finally, a very recent study

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from our group demonstrated that critically ill, steroid-free patients have highly variable expression of both *GCR* isoforms in peripheral polymorphonuclear cells, and moreover, the levels of both receptors decrease during ICU stay [33].

Conclusion

The results of the aforementioned studies suggest that during critical illness *GCR* expression is independently regulated. This might explain the differential response of patients to exogenously administered steroids or endogenously secreted cortisol. Apart from *GCR* expression, future clinical studies should focus on the role of post-translational modifications, the components of the GCR complex, and the efficiency of nuclear translocation of the GCR complex on tissue glucocorticoid sensitivity.

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