

COMMENTARY

# Steroid responses in sepsis: some novel thinking that may provide new insight

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See related research by Guerrero *et al.*, <http://ccforum.com/content/17/3/R107/abstract>

## Abstract

Glucocorticoid use in sepsis is controversial. In contrast to other extracellular signaling molecules, glucocorticoid receptors (GRs) are intra-cytoplasmic. Several GR isoforms have been identified. A study in *Critical Care Forum* suggests that sepsis alters the abundance of the dominant negative GR $\beta$ . Here we discuss GR isoforms and how they may affect cellular responses to glucocorticoids in sepsis.

The use of glucocorticoids in the management of patients with sepsis remains controversial. In this issue of *Critical Care Forum*, Guerrero and colleagues [1] present findings that may bring some clarity to the topic.

The dispute regarding steroid use in sepsis touches on the most basic aspects of glucocorticoid action. Trials performed in the 1970s and 1980s indicated that pharmacologic doses were harmful [2], and glucocorticoid use was abandoned, only to resurface with the seminal article by Annane and colleagues [3] in 2002. These data suggested that glucocorticoids would be of value in septic patients incapable of mounting a sufficient endogenous response (that is, in patients with relative adrenal insufficiency). The work by Annane and colleagues was followed by the CORTICUS (Corticosteroid Therapy of Septic Shock) trial [4], the data of which did not confirm the findings of Annane and colleagues. However, significant methodological differences between the two studies leave the issue unresolved. To this day, the debate continues.

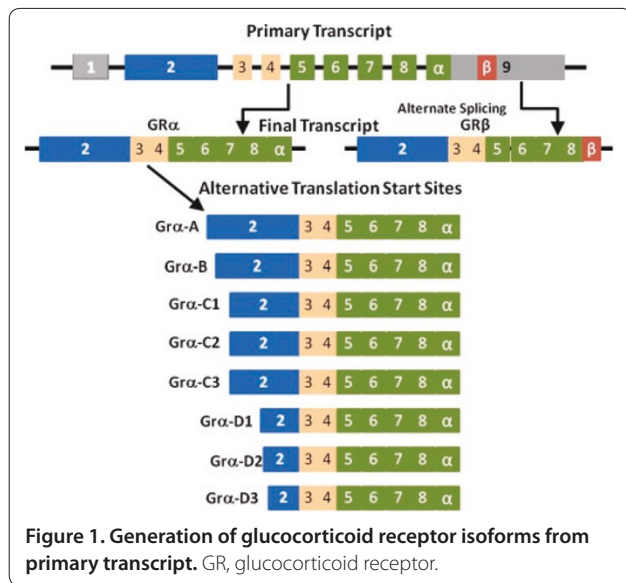
In the discrepant results of these trials, two specific findings in patients with sepsis are of particular importance. First, glucocorticoids induce polar opposite

responses in different tissues. Steroids limit activity in white blood cells and thus function as anti-inflammatory agents. But in the liver and heart, glucocorticoids stimulate reactions that are pro-inflammatory: expression of genes encoding acute-phase reactants and potentiation of the cardio-stimulatory actions of catecholamines. The second key finding relates to serum levels, which are often quite elevated, a finding that may reflect changes in cortisol metabolism induced by critical illness [5]. Given these issues, it is not surprising that the role of glucocorticoids in sepsis is confounding.

One possible answer becomes apparent when the mechanisms underlying steroid activity are examined. Unlike protein hormone pathways, steroid pathways are wholly intracellular and do not involve cell-surface receptors. Rather, steroid receptors are intra-cytoplasmic. Several years ago, Revollo and Cidlowski [6] began a series of experiments examining the structure of the glucocorticoid receptor (GR). These studies demonstrated that GRs arise from a single gene that is located on chromosome 5Rq31-32 and that contains nine exons and gives rise to three mRNAs (Figure 1), two of which are germane to this discussion. The first, GR $\alpha$ , contains the entirety of all nine exons. The second, GR $\beta$ , is generated by an alternative splicing site that removes a long segment at the beginning of exon 9 and splices the shorter remaining portion of exon 9 onto exon 8. GR $\alpha$  contains several potential translational start sites, resulting in the formation of at least eight additional isoforms that differ in the length of their N-termini (Figure 1). Although the affinity for glucocorticoids is the same in each isoform, their ability to bind co-factors and DNA polymerase II, and thus to act as transcription factors, differs markedly. Gross and Cidlowski [7] suggest that this differential ability to induce gene expression is responsible for the tissue-specific actions of glucocorticoids.

In contrast to the isoforms of GR $\alpha$ , GR $\beta$  does not bind glucocorticoids. By means of mechanisms that are unclear, GR $\beta$  acts as a dominant negative inhibitor of glucocorticoid-responsive gene expression. Guerrero and colleagues found that the expression of GR $\beta$  in white

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blood cells of nine patients with septic shock was significantly higher on admission than on discharge. Serum from these patients enhanced the *in vitro* expression of both GR $\alpha$  and GR $\beta$  in cultured T and B cells but had a more profound effect on GR $\beta$ . The serum also induced glucocorticoid resistance in mononuclear cells *in vitro*. These findings suggest that septic shock inhibits the activity of glucocorticoids by enhancing expression of the dominant negative GR $\beta$ .

Variability in the abundance of GR $\beta$  might explain why exogenous glucocorticoids exert such capricious effects in patients with sepsis. Enhanced GR $\beta$  expression might also explain why glucocorticoid levels are so dramatically elevated in patients with sepsis: the presence of a receptor that inhibits glucocorticoid activity will induce increased release of the hormone to compensate for and stimulate the desired response. We have invoked a similar explanation for the markedly increased interleukin-6 (IL-6) levels observed in sepsis. Our work on IL-6 has demonstrated impairment of the GP130/JAKS1/STAT-3 signal transduction pathway that mediates many of that cytokine's effects [8]. To overcome this block, increasingly massive amounts of IL-6 are produced and released. The

implication of these findings may be that the increased abundance of glucocorticoids, IL-6, and perhaps a number of additional mediators and hormones is an adaptive response that should be augmented. However, most trials of cytokine-based therapy attempt exactly the opposite: blocking activity. Perhaps it is time to reconsider the hypothesis underlying these interventions. Certainly, the findings of Guerrero and colleagues reinforce the notion that sepsis is a complex disorder and mono-therapy is unlikely to work.

#### Abbreviations

GR, glucocorticoid receptor; IL, interleukin.

#### Competing interests

The author declares that he has no competing interests.

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# Primary Transcript

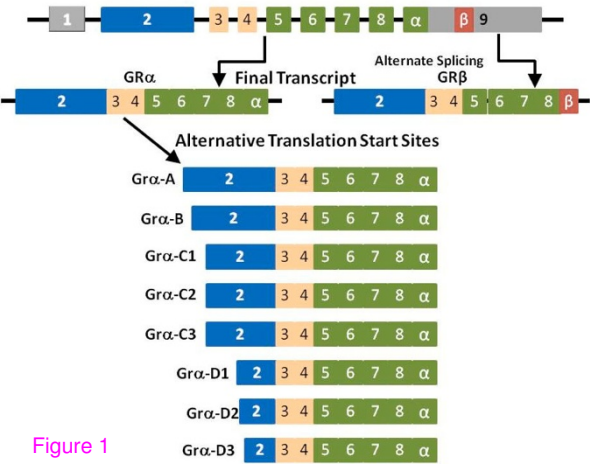


Figure 1