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Glucocorticoid and mineralocorticoid receptor expression in critical illness: A narrative review

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Abstract

The glucocorticoid receptor (GCR) and the mineralocorticoid receptor (MR) are members of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. They are localized in the cytosol and translocate into the nucleus after ligand binding. GCRs and MRs can be co-expressed within the same cell, and it is believed that the balance in GCR and MR expression is crucial for homeostasis and plays a key role in normal adaptation. In critical illness, the hypothalamic-pituitary-adrenal axis is activated, and as a consequence, serum cortisol concentrations are high. However, a number of patients exhibit relatively low cortisol levels for the degree of illness severity. Glucocorticoid (GC) actions are facilitated by GCR, whose dysfunction leads to GC tissue resistance. The MR is unique in this family in that it binds to both aldosterone and cortisol. Endogenous GCs play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations can differ greatly from blood levels due to the action of the two 11 β -hydroxysteroid dehydrogenase isozymes, type 1 and type 2. 11 β -hydroxysteroid dehydrogenases interconvert endogenous active cortisol and intrinsically inert cortisone. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability within cells and tissues. In this review, we will explore the clinical studies that aimed to elucidate the role of MR and GCR expression in the inflammatory response seen in critical illness.

Key Words: Mineralocorticoid receptor; Glucocorticoid receptor, Critical illness; 11beta-hydroxysteroid dehydrogenase; Aldosterone; Cortisol

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Core Tip: Endogenous glucocorticoids (GCs) play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations can differ greatly due to the action of the two 11 β -hydroxysteroid dehydrogenase isozymes. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability. The GC receptor and the mineralocorticoid receptor are members of the steroid receptor superfamily of hormone-dependent transcription factors. The study of the mineralocorticoid receptor and GC receptor expression and function in the inflammatory response seen in critical illness might aid in identifying the patients who will benefit from exogenous corticosteroid administration.

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INTRODUCTION

The glucocorticoid receptor (GCR) and the mineralocorticoid receptor (MR) are members of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. They are localized in the cytosol and translocate into the nucleus after ligand binding. GCRs and MRs can be co-expressed within the same cell, and it is believed that the balance in GCR and MR expression is crucial for homeostasis and plays a key role in normal adaptation.

In critical illness, the hypothalamic-pituitary-adrenal (HPA) axis is activated, and as a consequence, serum cortisol concentrations are high. However, in a number of patients cortisol levels are relatively low for their illness severity. Glucocorticoid (GC) actions are mediated by GCR, whose dysfunction leads to GC tissue resistance. The MR is unique in this family in that it binds to both aldosterone and cortisol.

Endogenous GCs play a critical role in controlling inflammatory responses in critical illness. Intracellular GC concentrations may be greatly different compared to blood levels due to the action of the 11 β -hydroxysteroid dehydrogenase (11 β -HSD) isozymes, type 1 and type 2. 11 β -HSDs interconvert endogenous active cortisol and intrinsically inert cortisone. The degree of expression of the two isozymes has the potential to dramatically influence local GC availability within cells and tissues.

GCR

During critical illness the HPA axis is activated, resulting in increased serum adrenocorticotrophic hormone and cortisol concentrations[1-4]. However, a subset of patients present with low serum cortisol levels despite their illness severity[5,6]. Critical illness-related corticosteroid insufficiency (CIRCI) is characterized by the organism's inability to produce adequate cortisol or tissue resistance to its actions, or both[7].

Sepsis and septic shock are the most common causes of mortality in critically-ill patients. GCs, the end-products of the HPA axis, have been used for over 40 years in the treatment of sepsis. The Surviving Sepsis Campaign Guidelines 2016 recommended hydrocortisone administration when despite adequate fluid resuscitation and vasopressor therapy, the hemodynamic stability in septic shock cannot be restored[8]. However, not all patients benefit from their administration, and as yet the patients who would benefit from their use cannot be accurately identified[9-12].

Cortisol signaling is mediated by GCR, a ubiquitous intracellular receptor protein. Alternative splicing of the primary transcript gives rise to two highly homologous GCR isoforms[13]. GCR- α is the functionally active receptor; once it binds to cortisol, the receptor-cortisol complex translocates from the cytosol to the nucleus. In the nucleus, the complex exerts transcriptional activation or repression by directly binding to genes that contain GC responsive elements[14], resulting in the inhibition of the

inflammatory response[15,16]. On the contrary, the function of GCR- β has not been well-explored. It is known to suppress GCR- α activity and is unable to bind both natural and synthetic ligands[17-19]. Figure 1 diagrammatically represents cortisol signaling *via* GCR.

The Sepsis-3 guidelines suggest the use of hydrocortisone in septic shock patients who are resistant to fluid administration and vasoactive agents[20]. Not all patients respond to this therapy, suggesting the existence of GC resistance. GC resistance is defined as the inability of GCs to exert their effects on target tissues[21]. It is characterized by decreased sensitivity of immune cells to GCs, which under normal conditions terminate the inflammatory response[22]. Therefore, it becomes apparent that apart from cortisol levels, how tissues respond to cortisol is as important. It has been suggested that the extent of cortisol's effect might be analogous to GCR expression, subtype and affinity in a specific target cell[23]. Such an example is the increased expression of GCR- β in certain tissues in inflammatory diseases, which has been associated with decreased sensitivity to GCs[24].

GC resistance may be a consequence of decreased GCR expression, GCR affinity for the ligand, nuclear translocation and DNA binding or may be due to altered transcription factor interaction. Most data on GC resistance in critical illness originates from experimental models involving sepsis-induced injury[25-29]. Essentially these studies have shown downregulation of GCR- α and induction of GCR- β expression[30-33].

Human clinical studies in critically-ill patients have mostly investigated cortisol availability, while only a few have explored the role of GCR. GC resistance has been described in a cohort of septic patients, demonstrating reduced GCR- α and elevated GCR- β expression levels in septic patients compared to healthy subjects; these results suggest that treatment with steroids might aggravate GC resistance in patients with increased GCR- β levels[34]. A transient, increased GCR- β expression has been reported in sepsis; moreover, the septic patients' sera could induce GC resistance *in vitro*[35]. Another study reported reduced GCR- α expression levels in sepsis[36], and diminished GCR protein levels have also been described in various organs during sepsis[37]. A decreased number of GCR- α and increased GCR- β receptors has been shown in heart and liver biopsies in the context of sepsis[25]. It has been shown that in septic shock, GCR expression increased, while GCR binding capacity decreased, proposing that it is the decreased GCR binding capacity and not the number of receptors that interferes with the response to exogenous or endogenous GCs[38]. In contrast, GCR number and affinity in septic patients did not differ from control subjects, suggesting that GCs could be effective in the hemodynamic compensatory phase of sepsis[39]. Increased GCR- α expression has been shown in the acute phase of sepsis, questioning the need for exogenous steroids at this phase[40]. Only one study has demonstrated downregulation of cortisol binding in critically-ill, ventilated patients[41]. Finally, our group was able to demonstrate that critically-ill steroid-free patients have a highly variable expression of both GCR isoforms in peripheral polymorphonuclear cells. Moreover, GCR expression and HPA axis function undergo a biphasic response during acute or subacute critical illness; this dissociation of reduced GCR expression and elevated cortisol might imply an abnormal stress response[42,43].

In coronavirus disease 2019 (COVID-19), results from the RECOVERY trial suggested significant benefits of steroid administration in critically-ill COVID-19 patients[44]. Specifically, the trial demonstrated that dexamethasone reduced mortality risk by 17%. A study in noncritically-ill COVID-19 patients showed that the HPA axis was activated. Patients exhibited an increase in cortisol, which was significantly higher than in those without COVID-19 infection, and these cortisol levels were associated with higher mortality rates[43]. Another study found that cortisol levels were lower in critically-ill COVID-19 patients compared to critically-ill non-COVID-19 patients[45]. In fact, nearly 70% of the COVID-19 critically-ill patients had plasma cortisol concentrations < 10 μ g/dL, meeting CIRCI criteria. However, so far, data on COVID-19 and GCR- α expression are lacking.

Ascorbic acid (vitamin C) levels are depleted in critically-ill patients. This vitamin has been shown to play a crucial role in HPA axis function. The adrenal glands contain very high concentrations of ascorbic acid and use it to synthesize cortisol[46]. At the cellular level, vitamin C works synergistically with corticosteroids by restoring GCR function. Specifically, ascorbic acid reverses GCR oxidation, restoring GC-responsiveness in oxidant conditions. The end result is increased GC availability and GCR- α activation[47].

Overall, it seems that during critical illness GCR expression is independently regulated. This might explain the different responses seen in patients to exogenously administered steroids or endogenously secreted cortisol. Apart from GCR expression,

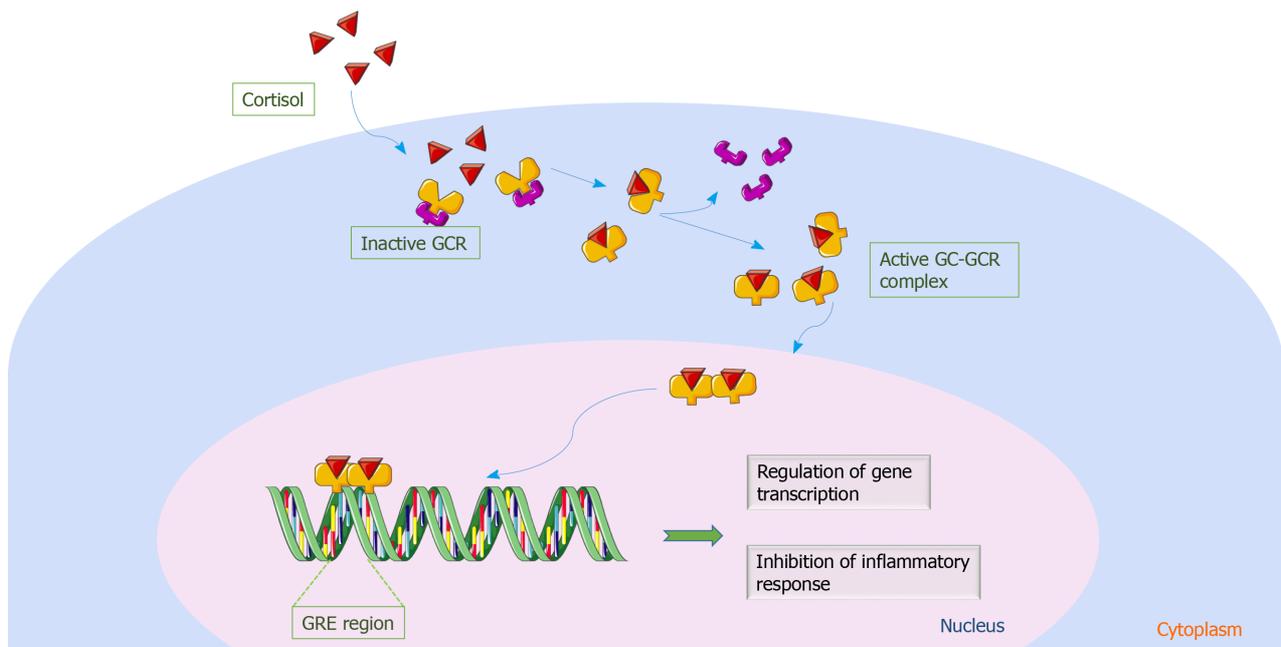


Figure 1 Cortisol signaling through the glucocorticoid receptor. Cortisol signaling is mediated by a ubiquitous intracellular receptor protein, the glucocorticoid receptor (GCR). Once it binds to cortisol, the receptor-cortisol complex translocates from the cytosol to the nucleus. In the nucleus, the complex exerts transcriptional activation or repression by directly binding to genes that contain glucocorticoid (GC) responsive elements (GREs), resulting in the inhibition of the inflammatory response. GC-GCR: Cortisol-glucocorticoid receptor complex.

the role of post-translational modifications, GCR complex components and the efficiency of nuclear translocation of the GCR complex should be the focus of future clinical studies.

MR

The MR is, along with the GCR, a member of the steroid receptor superfamily of hormone-dependent transcription factors. The receptors are structurally and functionally related. Similar to GCR, MR is also localized in the cytosol and translocates into the nucleus after ligand binding. In the nucleus, the ligand-receptor complex recognizes specific DNA regions and activates target gene expression[48]. While GCR is relatively ubiquitously expressed and exclusively binds GCs, the MR shows a more restricted expression pattern, and can bind both aldosterone and cortisol. MR is mostly expressed in epithelial cells of renal distal tubules, colon, sweat and salivary glands, and is implicated in sodium reabsorption, water homeostasis and potassium secretion[49]. The classical ligand for MR is aldosterone, the main mineralocorticoid steroid hormone, through activation of the renin-angiotensin system. Aldosterone is the principal regulator of salt and water balance but can also act on nonepithelial sites, contributing significantly to cardiovascular disease[50].

Hyperreninemic hypoaldosteronism may occur during critical illness and has been associated with a greater proinflammatory status, a higher degree of acute organ failure, and worse prognosis. It has been attributed to impaired adrenal response to increasing renin levels[51-53]. The recent demonstration of the reduced mortality in septic shock patients treated with adjunctive GCs combined with fludrocortisone[9], and the effectiveness of angiotensin II in treating vasodilatory shock[54] has renewed interest in the role of the MR in critical illness[55].

The MR, originally thought to be expressed only in kidneys, is now known to have a wider distribution. At the organ level, it is expressed in heart, vessels, brain, and adipose tissue[56]. MR signaling induces inflammation, oxidative stress, and fibrosis/remodeling, thereby causing tissue and organ damage, particularly in the heart and vessels[49]. Furthermore, clinical studies have reported a beneficial outcome of MR antagonism in patients with cardiovascular diseases, mainly due to the prevention of inflammatory damage[57]. At the cellular level, MR is expressed in vascular cells, adipocytes, and immune cells[58]. This inflammatory involvement of MR and aldosterone in cardiovascular diseases suggests an association with immune

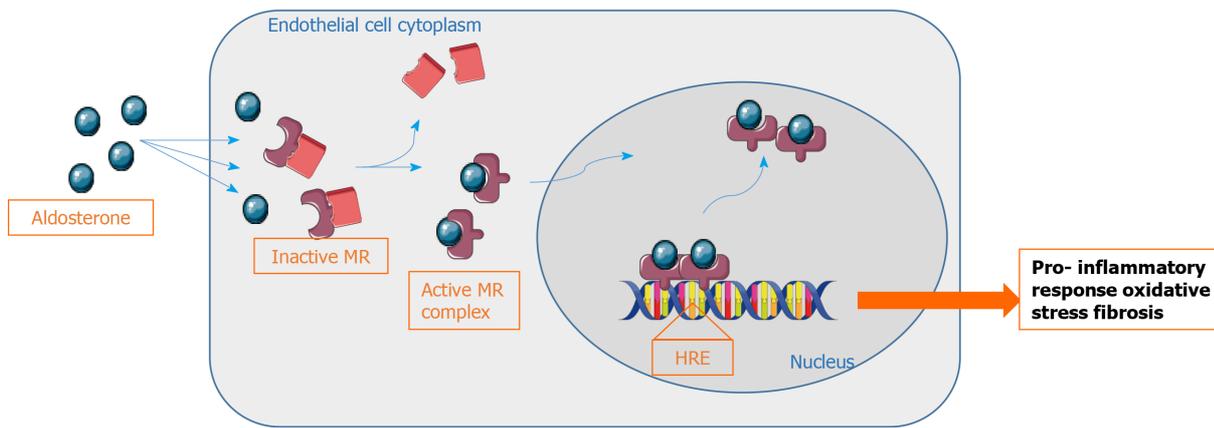


Figure 2 Mineralocorticoid signaling. The mineralocorticoid receptor is localized in the cytosol and translocates into the nucleus after ligand binding. In the nucleus, the aldosterone-mineralocorticoid receptor (MR) complex recognizes specific DNA regions, and activates target gene expression. MR signaling induces inflammation, oxidative stress, and fibrosis/remodeling, thereby causing tissue and organ damage. HRE: Hormone response element.

system changes. It has been consistently reported that aldosterone stimulation promotes proinflammatory responses[59,60]. In human leukocytes, MR expression has been shown in CD34+ hematopoietic progenitor cells, in peripheral blood T and B lymphocytes, macrophages, dendritic cells, and neutrophils[61]. In macrophages, lymphocytes and dendritic cells, MR signaling induces proinflammatory responses[62, 63]. The MR antagonist, spironolactone, was shown to have anti-inflammatory effects on cultured human peripheral blood mononuclear cells isolated from healthy subjects. Furthermore, angiotensin II induced aldosterone synthesis and enhanced cytokine production through an MR-dependent mechanism in human peripheral blood mononuclear cells[64,65]. In Figure 2, MR signaling is depicted.

11 β -HSD

Both the innate and adaptive immune responses depend on the adhesion and migration of leukocytes across endothelial cells towards the inflamed site, where they protect against invading pathogens and repair damaged tissue. At the inflamed site, neutrophils undergo constitutive apoptosis to be removed from the inflammatory environment. Normally, acute inflammation rapidly resolves. However, failure to rapidly remove apoptotic neutrophils prolongs the inflammatory response. As mentioned above, endogenous GCs play a critical role in controlling inflammatory responses. Although GCs have an immunosuppressive effect on immune cells, they exert contradictory effects on neutrophils. At the inflamed sites they exert an anti-inflammatory effect by blunting neutrophil priming, whereas they increase circulating neutrophil count by delaying their apoptosis[66]. In circumstances of uncontrolled inflammation, polymorphonuclear cells can become detrimental by causing tissue injury and organ damage in critical illness[67].

Intracellular GC concentrations may vary compared to blood levels due to the action of the two 11 β -HSD isozymes. 11 β -HSD interconverts endogenous active cortisol and inert cortisone, which does not bind to GCR[68]. 11 β -HSD2 (encoded by the *HSD11B2* gene) inactivates GCs, while 11 β -HSD1 (encoded by *HSD11B1*) regenerates active GCs from inert keto forms, and hence modulates GC-regulated functions. Moreover, 11 β -HSD1 is widely expressed in tissues that express high levels of GCR, suggesting that 11 β -HSD1 modulates ligand access to GCR- α [68]. The degree of expression of these two isozymes may drastically affect local GC availability within individual cells and tissues.

11 β -HSD1 is widely distributed, with its expression being highest in the liver, but is also expressed in adipose tissue, vessels, brain, and immune cells. In immune cells, 11 β -HSD1 is primarily expressed in macrophages and lymphocytes, especially during inflammation[56,62,69]. 11 β -HSD1 activates functionally inert GC precursors (cortisone) to active GCs (cortisol) within target tissues, and amplifies local GC actions. 11 β -HSD2, except being expressed in the classical aldosterone-target tissues, is also expressed in the pancreas and the reproductive system[68]. 11 β -HSD2 protects the MR from illicit occupancy by cortisol by inactivating cortisol within cells.

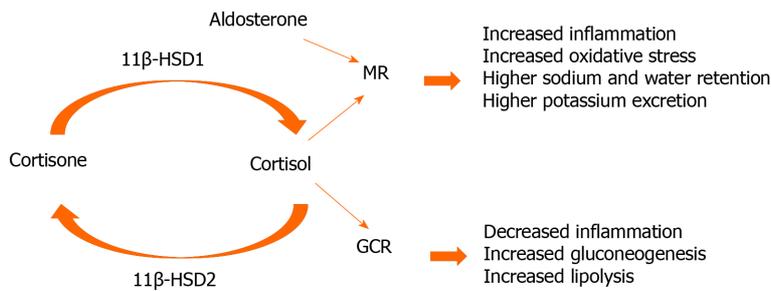


Figure 3 Glucocorticoid and mineralocorticoid receptor function, and the role of 11β-dehydrogenase isozymes. The ubiquitous glucocorticoid receptor (GCR) binds exclusively to cortisol, whereas the mineralocorticoid receptor (MR) is a receptor with equal affinity for mineralocorticoids and glucocorticoids. In epithelial tissues, MR activation leads to the expression of proteins regulating ionic and water transports, resulting in the reabsorption of sodium, and as a consequence an increase in extracellular volume, increase in blood pressure, and excretion of potassium to maintain a normal salt concentration in the body. The MR is activated by aldosterone and cortisol. Target cells for aldosterone express the enzyme 11β-dehydrogenase (11β-HSD) 2 that has no effect on aldosterone, but converts cortisol to cortisone, which has only a very weak affinity for the MR. In essence, this enzyme “protects” the cell from cortisol and allows aldosterone to act appropriately. 11β-HSD1 activates functionally inert cortisone to active cortisol within target tissues and amplifies local glucocorticoid actions.

Aldosterone and cortisol bind the MR and have a similar affinity for the MR. The binding of cortisol or aldosterone to the MR results in different cellular responses[55]. Under physiological conditions, plasma cortisol levels are 100 × higher than aldosterone levels, and most MRs are occupied by GCs. The 11β-HSD enzymes regulate whether cortisol or aldosterone will bind to the MR. 11β-HSD type 2 metabolizes cortisol to inactive cortisone. Cortisone is unable to bind or activate the MR, and aldosterone occupies the MR. When 11β-HSD2 is not present or not functional, the ligand binding site on the MR is occupied by cortisol.

11β-HSD2 is mainly expressed in the classical aldosterone (mineralocorticoid)-target tissues, including the distal nephron, sweat and salivary glands, and colonic epithelium. 11β-HSD1 catalyzes the regeneration of active GCs, particularly in GC-target tissues, where it amplifies GC actions. *In vitro*, colocalization of the two enzymes within a cell results in their reciprocal regulation to minimize simultaneous expression [68]. Figure 3 diagrammatically shows the interplay between the corticoid receptors, their ligands and the 11β-HSD isozymes.

Although the immunosuppressive and anti-inflammatory activities of GCs are well documented, the expression of 11β-HSD enzymes in immune cells, and in particular polymorphonuclear cells, is not well understood. Overall, an anti-inflammatory role for 11β-HSD1 has been proposed in leukocytes, while studies have suggested that 11β-HSD2 is not expressed in these cells[70]. In human T-lymphoblastic leukemia cells, both 11β-HSD2 expression and reciprocal regulation of 11β-HSD1 and 11β-HSD2 have been shown to be associated with GC resistance[71,72].

Data for tissue resistance to GC activity are limited in critical illness. Indirect evidence suggesting altered tissue 11β-HSD activity comes from studies that found increased plasma cortisol:cortisone ratio in critically-ill septic and trauma patients[73, 74]. A recent study showed that in septic shock patients, sensitivity to GCs does not appear to be mediated by changes in the expression of the 11β-HSD2 isozyme[75]. Whether the reciprocal change in 11β-HSD1/11β-HSD2 is part of an adaptive response to inflammation or contributes to GC resistance remains to be established.

CONCLUSION

Studies on the expression of GCR, MR, 11β-HSD1 and 11β-HSD2 in critically-ill patients may allow a better understanding of homeostatic regulations of GCR and MR.

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