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Neuroendocrine-Immune Interactions in Rheumatoid Arthritis: Mechanisms of Glucocorticoid Resistance

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Introduction

In the 1940s, Philip Hench discovered that patients with autoimmune disorders, such as rheumatoid arthritis (RA), produced an endogenous substance under 'stressful' conditions that had anti-inflammatory/immunosuppressive properties and hence, ameliorated the symptoms of the autoimmune disease. Isolation and characterization of this endogenous compound by Edward Kendall led to the discovery of the adrenal steroid, cortisone, which along with other glucocorticoids, has become a mainstay in the treatment of autoimmune and inflammatory diseases. Of note, Hench and Kendall shared the Nobel Prize in Medicine for their discovery in 1950.

Although the immunomodulatory effects of glucocorticoids initially were believed to be mediated by pharmacological rather than physiological concentrations, seminal work by Hugo Besedovsky and colleagues in the 1970s and 1980s substantiated a physiological role for glucocorticoids in regulating immune responses. Besedovsky and del Rey [1] were also one of the first to demonstrate that immune system activity could influence the release of glucocorticoids. Since then, many others have provided evidence for the bidirectional communication between the neuroendocrine and immune systems [2, 3]. Today, in contrast to the traditional view of glucocorticoids as immunosuppressive hormones, they are more accurately...
Conceptualized as immunomodulatory hormones that can stimulate as well as suppress immune function, depending on glucocorticoid concentration, the type of immune response, the immune compartment and the cell type involved [4]. Once glucocorticoids are released into the general circulation, maintenance of appropriate glucocorticoid activity is accomplished by local tissue regulation of glucocorticoid availability and action by factors such as corticosteroid binding globulin (CBG), the multidrug resistance transporter (MDR), 11β-hydroxysteroid dehydrogenase (11β-HSD), and ultimately, the glucocorticoid receptor (GR). Altered expression and/or function of these factors have been found in RA and have become the subject of interest for the development of new therapeutic interventions.

### Impaired HPA Axis Activity and Other Stress Systems in RA

Conditions of chronic inflammation are often associated with impaired anti-inflammatory stress response systems. In addition to absolute plasma levels of stress hormones (as exemplified below), it is important to study hormone levels in relation to inflammation or steroid hormone shifts, which can indicate preferential production of one hormone over another and influence the progression of chronic inflammatory diseases [5]. In RA, alterations in neuroendocrine function include inadequate ACTH and cortisol secretion (impaired HPA axis function), an increased sympathetic tone at rest but an inadequate response during stress, functional loss of synovial sympathetic nerve fibers concomitant with the presence of proinflammatory sensory fibers, a local beta-to-alpha adrenergic receptor shift and local uncoupling of cortisol and norepinephrine. In addition, a decrease in adrenal androgen production, such as DHEAS, DHEA and androstenedione, has been reported with a preference for cortisol production (although insufficient in relation to inflammation). Early morning peaks in plasma proinflammatory cytokine levels (e.g., TNF-α, IL-6) are shifted a couple of hours later (to around 5–7 a.m.) and are of greater amplitude and longer duration in RA patients versus controls. These circadian changes, despite the similarity of the circadian curves for serum cortisol (in amplitude and shape), also indicate inadequate cortisol secretion in relation to inflammation in RA. Elevated proinflammatory cytokines probably account for the increased morning stiffness (due to edema) and pain that are usually experienced by RA patients.

A defective HPA axis has also been associated with susceptibility to autoimmune/inflammatory diseases in several animal models. In regard to RA, the neuroendocrine differences observed between Lewis (LEW/N) and Fischer (F244/N) rat strains are a prime example. Lewis rats are highly susceptible, whereas Fischer rats are relatively resistant, to the development of a wide range of autoimmune diseases in response to a variety of proinflammatory/antigenic stimuli. Injection of group A streptococcal cell wall peptidoglycan polysaccharide (which mimics human RA) into inflammatory-susceptible Lewis rats produces a blunted HPA axis response (ACTH and corticosterone) compared to the exaggerated HPA axis response observed in inflammatory-resistant Fischer rats. Moreover, the replacement or removal of glucocorticoids in Lewis and Fischer rats, respectively, reverses their susceptibility to streptococcal cell wall-induced arthritis [9]. Dysfunctional HPA axis activity in Lewis rats has been shown to be due to the altered expression of multiple factors that regulate the HPA axis, including hypothalamic corticotrophin-releasing hormone, pituitary proopiomelanocortin, CBG and GR [10]. Local factors regulating glucocorticoid bioavailability and actions are discussed below.

### Local Factors Regulating Glucocorticoid Bioavailability and Action

#### Factors Regulating Glucocorticoid Bioavailability

While circulating levels of glucocorticoid hormones are relevant to steroid action, at the cellular level, activity of glucocorticoids is determined by local factors that regulate the access of free hormone to its receptor. Such factors include CBG, the MDR and 11β-HSD (fig. 1). All of the above have been shown to be altered under conditions of immune activation. Proinflammatory cytokines tend
to lower CBG levels, decrease MDR expression and/or function, and increase 11β-HSD-1 expression and reductase activity (and decrease 11β-HSD-2 expression/activity), thereby favoring an increase in glucocorticoid bioavailability. However, the opposite trend in each of these factors, which would favor a decrease in glucocorticoid bioavailability, may lead to an increased susceptibility to the development of autoimmune/inflammatory diseases.

Corticosteroid Binding Globulin
Only free or unbound glucocorticoids are capable of diffusing across the plasma membrane and activating the GR. Over 90% of circulating glucocorticoids are bound to CBG [11]. Therefore, the relative concentration of CBG is an important determinant of ‘free’ and available glucocorticoids. For example, decreases in the circulating level of CBG have been associated with evidence of occupation/activation of GR in the spleen of stressed rats [12]. Likewise, several studies have shown that in response to endotoxin administration in rats [13] and in a murine model of systemic lupus erythematosus [14], reduced CBG levels are observed. In addition, a decrease in plasma CBG-binding capacity has been reported in human septic shock and trauma [15–17]. In numerous studies, IL-6 has been shown to be a negative regulator of CBG production, and hence a determinant of cortisol bioavailability [16, 18]. In contrast, two studies examining plasma CBG during viral infection detected no change in CBG levels in infected subjects compared to controls [19, 20]. It is important to note that even if a change in plasma CBG levels is not detected, local changes in the concentration and/or affinity of CBG during inflammation (for instance, within the microenvironment of the various lymphoid compartments or inflamed tissue) remain a consideration. In some cases, discrepancies exist between the concentration of free glucocorticoid levels in the plasma versus locally inflamed tissue, such as in RA patients who exhibit a greater percentage of bound corticosteroids in the synovial fluid relative to that found in plasma [21]. This observation demonstrates that the synovial membrane plays an important role in the local bioavailability of glucocorticoids in patients with RA.

Multidrug Resistance P-Glycoprotein
Multidrug resistance P-glycoprotein is an ATP-dependent multidrug efflux pump that decreases intracellular concentrations of potentially toxic chemicals (drugs and hormones). It is expressed in both human and rodent tissues, including the adrenal gland, kidney, liver, colon, small intestine, and brain and testis capillary endothelial cells [22]. The MDR pump at the blood-brain barrier, in both mice and humans, transports cortisol and the synthetic glucocorticoid dexamethasone, but not corticosterone, out of endothelial cells lining the brain [23]. In vitro studies have indicated that cytokines, such as IL-1, IL-6 and TNF-α, decrease MDR expression and/or function.
in rodent hepatocytes [24, 25], human colon carcinoma cells [26] and human brain endothelial cells [27]. Moreover, rodents treated with LPS or turpentine exhibit reduced hepatic [24, 28–30], intestinal [31] and brain [28] MDR expression/activity. In contrast, humans with autoimmune diseases, such as RA [32, 33], colitis/Crohn’s disease [34, 35] and lupus [36, 37], tend to exhibit high lymphocytic MDR expression and/or activity, which positively correlate with disease activity in some cases. However, this increased MDR expression may be secondary to treatment with high-dose glucocorticoids [35, 38]. Increased MDR expression has been found to be more prominent in a subpopulation of colitis [39] and RA [33, 40] patients who are resistant to steroid (or disease-modifying antirheumatic drugs) therapy and may be an underlying cause of their refractory response. Therefore, evaluation of MDR expression/activity may allow prediction of the efficacy of specific drug treatments. In addition, the use of MDR inhibitors (e.g., verapamil, cyclosporin A) may help to overcome treatment resistance or to improve incomplete responses in some RA patients, as has been shown in the case of chemotherapeutic agents [41]. Combined therapy with glucocorticoids and verapamil in a small group of lupus patients was shown to reduce MDR expression [36]; however, the clinical usefulness of this approach remains to be established.

Greater MDR function in immune cells may reduce glucocorticoid availability, thereby enhancing the synthesis/release of proinflammatory cytokines and exacerbating inflammatory responses. One possible reason for the discrepancy between the in vitro cytokine/animal studies and studies in humans with autoimmune disorders may be the differential effects of acute versus chronic inflammation on MDR expression. During acute inflammation, cytokines may downregulate MDR expression and increase local glucocorticoid concentrations, thereby limiting local inflammation and further cytokine release. In contrast, an upregulation of MDR expression may develop as a compensatory mechanism during chronic inflammatory conditions, and hence predispose humans toward autoimmune disease. In support of this contention, higher levels of peripheral blood mononuclear cell (PBMC) TNF-α mRNA were reported in RA patients exhibiting greater lymphocytic MDR activity, where reduced amounts of cortisol would be able to act intracellularly to inhibit proinflammatory responses [33]. Both high MDR activity and TNF-α levels were associated with poor outcome in RA. Another possible consideration regarding discrepant results is that changes in MDR expression/function may be cell type specific (e.g., PBMCs vs. synovial cells). Indeed, synovial cells express MDR; however, it may be an atypical MDR phenotype [42].

11β-Hydroxysteroid Dehydrogenase

Another factor regulating the access of glucocorticoids to their receptors in target cells and tissues is 11β-HSD. There are two isoforms of this enzyme, type 1 and type 2. Whereas 11β-HSD-1 is a reversible oxidoreductase, 11β-HSD-2 only exhibits oxidative or dehydrogenase activity [43]. 11β-HSD-2 breaks down naturally occurring glucocorticoids (but not synthetic glucocorticoids) as they enter the cell, leaving the hormones in the form of inactive metabolites (i.e., cortisol to cortisone in humans; corticosterone to 11-dehydrocorticosterone in rodents). Significant differences in 11β-HSD-2 activity have been found among immune compartments, and there is a direct correlation between 11β-HSD-2 activity and the preferential production of Th1 versus Th2 cytokines by T cells residing in particular lymphoid organs [44]. Inhibition of 11β-HSD-2 activity (which would enhance the available amount of hormone to bind to GR) leads to reduced Th1 responses and enhanced Th2 cytokine production by activated T cells [44].

Recent studies suggest that the bidirectional 11β-HSD-1 prefers the reductase direction unless cells are disrupted [43]. Therefore, in intact tissues, 11β-HSD-1 reactivates the inactive 11-keto glucocorticoids (cortico-sterone/11-dehydro-corticosterone) into their active 11-hydroxy glucocorticoid form (cortisol/corticosterone). Proinflammatory cytokines, such as TNF-α and IL-1β, have been shown to upregulate 11β-HSD-1 and/or downregulate 11β-HSD-2 expression/activity in numerous cell types, including rat glomerular cells [45], human adipose stromal cells [46], and more related to RA, human bone cells, such as osteoblasts [47], human fibroblasts [48] and human and mouse vascular smooth muscle cells [49]. Inflamed colon specimens (in rats and humans) also exhibit elevated 11β-HSD-1 and reduced 11β-HSD-2 expression [50], thereby favoring the formation of active glucocorticoids and counterbalancing the proinflammatory effect of cytokines.

In immune cells, 11β-HSD-1 is induced during the maturation of antigen-presenting cells, such as human macrophages [51] and murine dendritic cells [52]. It also has been shown to play a role in promoting macrophage phagocytosis of apoptotic leukocytes [53]. Moreover, 11β-HSD-1 mRNA, protein, and (reductase) activity are expressed in murine lymphocytes, where activation of CD4+ T cells into Th1 or Th2 cells increases 11β-HSD-1...
activity [52]. In this case, the presence of greater levels of active glucocorticoids would reduce proinflammatory cytokine synthesis in Th1 cells and increase anti-inflammatory cytokine synthesis in Th2 cells. Therefore, changes in the relative activity of 11β-HSD in immune tissues during inflammation may influence the relative impact of glucocorticoids on immune responses. Thus, the microenvironment of the various immune compartments is a potentially important site for intracrine regulation of neuroendocrine-immune interactions.

Reduced capacity for local reactivation of cortisone to cortisol has been observed in RA synovial cells, as evidenced by a greater ratio of 11β-HSD-2:11β-HSD-1-positive macrophages in the synovial tissue (compared to osteoarthritis synovium) [54]. This may be due to the local loss of catecholaminergic activity (loss of sympathetic nerve fibers and β-adrenergic receptor density on RA leukocytes) that would usually inhibit the inactivation of glucocorticoids. In addition, 11β-HSD-2 was shown to be the second most overexpressed gene in RA and 11β-HSD-2 protein levels correlated with inflammation scores [55]. Moreover, cortisone-induced inhibition of IL-6 in synovial fibroblasts has been shown to be dependent on 11β-HSD-1 activity [48] and synovial macrophages from RA patients exhibit a reduced ability of the anti-inflammatory cytokine, IL-10, to induce 11β-HSD-1 mRNA expression [56]. This defective reactivation of cortisone may be an important factor in the perpetuation of inflammation in patients with RA. The therapeutic value of 11β-HSD-2 inhibitors has not been evaluated in RA, but may serve as another target of interest.

The Glucocorticoid Receptor

The ultimate effect of glucocorticoids on immune system regulation occurs at the level of the GR. Upon glucocorticoid binding to cytosolic GRs, a conformational change in GR causes heat-shock protein 90 (hsp90) and other ancillary proteins to dissociate from the receptor, and the ligand-bound receptor then translocates into the nucleus. Here, the glucocorticoid/GR complex acts as a transcription factor that regulates gene transcription through binding to glucocorticoid response elements (GREs) in the promoter regions of genes (requires GR dimerization) or through protein-protein interactions with other transcription factors (e.g., NF-κB and AP-1; does not require GR dimerization). A tissue’s sensitivity to glucocorticoid activity can be influenced by a change in (1) GR number or affinity or (2) GR function, including its ability for nuclear translocation, its interaction with other signal transduction pathways and the expression of particular GR isoforms (fig. 1). Proinflammatory cytokines have been shown to impact a number of these factors.

GR Number and Affinity

There is a large body of data on the impact of cytokines on GR number [57]. However, the results are split into those studies that report an increase in GR number following cytokine administration and those that report a decrease. The discrepancy in results appears to depend on how the receptors were measured. Studies using whole-cell assay binding techniques tend to find an increase in cytokine-induced GR expression, while those using cytosolic receptor binding techniques tend to find a decrease. Few studies have documented changes in receptor affinity. Sher et al. [58] report that lymphocytes (T cells) simultaneously exposed to Th1 (IL-2) and Th2 (IL-4) cytokines (simulating the conditions of steroid-resistant asthma) exhibit a reduced affinity of GR for glucocorticoids. GRs on synovial fluid cells and PBMCs (but not synovial tissue cells) from RA patients have also been shown to exhibit reduced binding affinity [59]. However, no differences in GR binding affinity in PBMCs from RA patients compared to healthy controls have also been reported [60].

The GR number expressed in PBMCs of RA patients may be one factor in assessing glucocorticoid sensitivity and predicting which patients will respond to lower doses of steroid (e.g., prednisone) treatment and, therefore, avoid the unwanted side effects of higher doses. However, studies investigating GR expression in RA patients have given rise to contradictory results. Early diagnosed, untreated female (but not male) RA patients [61] and those with active disease of longer duration (off glucocorticoid therapy for at least 6 months) [60] exhibited reduced GR density in PBMCs compared to healthy controls, but GR density was not correlated with disease activity, suggesting that differential GR expression may not be involved in the pathogenesis of RA. Other studies have shown diminished GR numbers in PBMCs of glucocorticoid-treated patients, while those of untreated RA patients exhibited upregulated GR expression [62, 63], indicating that whether or not RA patients are undergoing drug therapy or are treatment naive can influence the level of GR expression. Interestingly, when measuring mRNA rather than protein, GRα mRNA expression in PBMCs was negatively correlated with disease activity [64]. Discrepant results may be due to the different sensitivities in change of expression levels between mRNA and protein.
Reduced PBMC GR density has not been associated with functional glucocorticoid resistance in the sense that proliferation and cytokine release of lymphocytes of RA patients and healthy controls were inhibited by glucocorticoids to the same extent [65]. On the other hand, when subpopulations of glucocorticoid-resistant versus glucocorticoid-sensitive RA patients are selected, differences in PBMC proliferation can be detected between the two groups. Inhibition of PBMC proliferation after steroid treatment was significantly lower in a glucocorticoid-resistant as compared to a glucocorticoid-sensitive group [66]. Moreover, a positive correlation has been shown between glucocorticoid-induced inhibition of PBMC proliferation and the clinical outcome of glucocorticoid treatment in RA [67]. Therefore, the measurement of steroid sensitivity of peripheral lymphocytes (not necessarily reflected by GR number) may be a useful tool in predicting the therapeutic efficacy of glucocorticoids in RA patients.

Although all nucleated cells in humans have GRs, in RA, it is important to consider possible abnormalities in GR expression/function in the synovium, and hence glucocorticoid sensitivity at the site of inflammation. Indeed, GRs are expressed by multiple cell types in synovial tissue, including lymphocytes, fibroblasts, endothelial cells and smooth muscle cells in the sublining layer [68], suggesting that glucocorticoids directly target the synovium. GR expression on subsynovial fibroblastic cells of RA patients pretreated with glucocorticoids was significantly lower compared to patients who had not received GC treatment; however, less suppression of GR expression was observed in patients on low-dose GC treatment [68], supporting the majority of findings regarding GR expression in PBMCs of RA patients. Further investigation is needed to determine how synovial GR expression may relate to disease activity.

GR Function

Several autoimmune/inflammatory disorders have been associated with impaired GR function, possibly contributing to the excessive inflammation characteristic of these illnesses [69]. Proinflammatory cytokines (i.e., TNF-α, IL-1, and IL-6) and cytokines that mediate lymphocyte growth and differentiation (i.e., IL-2, IL-4) have been found to inhibit GR function [57].

Although the mechanism by which cytokines inhibit GR is unknown, several possibilities have been considered. First, cytokines may influence GR function through their effects on GR translocation from the cytoplasm into the nucleus. For example, TNF-α and IL-1 have been shown to block dexamethasone-induced GR nuclear translocation [70, 71]. Another possible mechanism by which cytokines may influence GR is through cross talk among signal transduction pathways. For example, downstream in the IL-1 and TNF-α signal transduction pathways are the transcription factors NF-kB and AP-1 (which consists of jun and fos proteins). GR and NF-kB/AP-1 have been shown to mutually antagonize each other’s transcriptional activity through multiple mechanisms [72–74]. In addition, IL-1 and TNF-α activate mitogen-activated protein kinase (MAPK) signaling pathways [i.e., p38 MAPK and jun N-terminal kinase (JNK)], which have been shown to be inhibitory to GR function [75–78]. It has recently been shown that a major mechanism by which glucocorticoids exert their inhibitory action on MAPK pathways, and therefore inflammation, is by the upregulation of the MAPK phosphatase, MKP-1 [79]. Other cytokines, such as IL-6, IFN-α/β, IFN-γ, IL-12, IL-2, and IL-4, induce janus kinase (JAK)/signal transduction and activator of transcription (STAT) signaling pathways, and STAT proteins have been found to reciprocally influence GR activity by direct protein-protein interactions [72, 74, 80]. Indeed, immune-related transcription factors, such as NF-κB, AP-1, MAPKs and STATs, are elevated in PBMCs and/or synovial tissue of RA patients [81–85], and may serve as another mechanism by which cytokines can confer a glucocorticoid-resistant state. On the other hand, a deficit in inhibitory signaling molecules, such as MKP-1, may also contribute to reduced glucocorticoid sensitivity in inflammatory/autoimmune diseases [79]. Interestingly, elevated levels of macrophage inhibitory factor, a proinflammatory cytokine that directly counteracts the immunosuppressive actions of glucocorticoids, have been demonstrated in RA and other chronic inflammatory diseases, and has been shown to exert its antiglucocorticoid effects through MKP-1 inhibition [86, 87]. Therefore, therapeutic interventions aimed at antagonizing inflammatory signaling pathways may be another way to increase glucocorticoid sensitivity.

Finally, cytokines may affect GR function by altering the ratio of GRα:GRβ isofrom expression. Alternative splicing of the human GR primary transcript produces multiple isoforms [88]. The two that have received the most attention are GRα, the classical transcriptionally active isoform, and GRβ, which may negatively regulate GRα activity. The GRα isoform binds hormone and activates glucocorticoid-responsive genes, while the GRβ isoform fails to bind hormone and activate glucocorticoid-responsive genes and attenuates the trans-activation...
of the hormone-bound GRα isoform [89]. These findings suggest that when GRβ is present in excess in various tissues (reduced GRα:GRβ ratio), it can act as a dominant negative inhibitor of GRα activity. In fact, Webster et al. [90] have shown that IL-1 and TNF-α lead to the selective accumulation of GRβ protein in cells of lymphoid origin and the development of a glucocorticoid-resistant state. Interestingly, glucocorticoid sensitivity in different immune cell types has been associated with varied degrees of GRβ expression [91, 92]. Moreover, increases in GRβ levels have been found in immune cells of patients with glucocorticoid-resistant asthma [93, 94], colitis/Crohn’s disease [95, 96] and RA [97].

Derijk et al. [98] were the first to demonstrate that a polymorphism in the human GRβ gene, which increases its mRNA stability, is associated with RA. Other polymorphisms of the GR have also been associated with RA, whereby those that confer an increased glucocorticoid sensitivity (i.e., N363S and BclI) are associated with a decreased susceptibility to develop RA and those related to reduced glucocorticoid sensitivity (i.e., ER22/23EK and GRβ-A3669G) are associated with an enhanced predisposition to develop RA [van Oosten et al., unpubl. data]. However, other studies have failed to find an association with GR polymorphisms and RA susceptibility [99, 100]. Screening for GR polymorphisms in RA patients may also aid in the identification of those who will benefit the most from glucocorticoid treatment [for a review of common GR polymorphisms and their associations with disease, see 101, 102]. Alternative translation initiation of GRα mRNA can also lead to the expression of GR isoforms with different transcriptional activity [103]. The unique transcriptional activities and distinct tissue-specific distribution patterns of GRα isoforms could provide a novel mechanism for tissue-specific glucocorticoid responses.

<table>
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<th>Table 1. Molecular mechanisms of glucocorticoid resistance</th>
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<tr>
<td>↑ CBG</td>
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<td>↑ MDR Pgp expression</td>
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<td>↑ 11β-HSD-1/11β-HSD-2</td>
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<td>↑ GR affinity for GCs</td>
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<td>↑ GR translocation into nucleus</td>
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<td>↑ Expression of AP-1 and NF-κB</td>
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<td>↑ Expression of MAPKs (p38, JNK)</td>
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<td>↑ Expression of GRβ isomor</td>
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MDR Pgp = Multidrug resistance P-glycoprotein.

**Conclusion**

A variety of factors have been shown to regulate GC availability or bioactivity. A change in any of them towards reduced glucocorticoid function can lead to the development of glucocorticoid resistance (table 1). Should this occur during chronic inflammation, patients would be expected to be more susceptible to the deleterious, tissue-damaging effects of an overproduction of proinflammatory cytokines, which may increase vulnerability to the development of autoimmune disease. Further investigation is required to assess the safety and efficacy of new therapeutic strategies, including inhibitors of the multidrug resistance P-glycoprotein, 11β-HSD-2 and downstream inflammatory signaling molecules (e.g., AP-1, NF-κB, STAT, MAPKs), which may help to reverse a state of glucocorticoid resistance.

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