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# One Hormone, Two Actions: Anti- and Pro-Inflammatory Effects of Glucocorticoids

**Angelica Merlot***

*Department of Pathology, University of Sydney, Australia*

## Abstract

Glucocorticoids are essential steroid hormones secreted from the adrenal gland in response to stress. Since their discovery in the 1940s, glucocorticoids have been widely prescribed to treat inflammatory disorders and hematological cancers. In the traditional view, glucocorticoids are regarded as anti-inflammatory molecules; however, emerging evidence suggests that glucocorticoid actions are more complex than previously anticipated.

## Introduction

The anti-inflammatory activity of glucocorticoids is attributed to the repression of pro-inflammatory genes through signal transduction by their steroid receptor, the glucocorticoid receptor (GR). The mechanisms modulating the pro-inflammatory effects of glucocorticoids are not well understood. In this review, we discuss recent findings that provide insights into the mechanism by which GR signaling can play a dual role in the regulation of the immune response [1]. We hypothesize that these apparently opposite processes are working together to prepare the immune system to respond to a stressor (pro-inflammatory effects) and subsequently restore homeostasis (anti-inflammatory effects) [2]. Finally, we propose that determining the mechanisms which underlie the tissue-specific effects of glucocorticoids will provide an excellent tool to develop more efficient and selective glucocorticoid therapies.

Glucocorticoids are steroid hormones synthesized and secreted by the adrenal gland in response to stress. Upon exposure to stress, the hypothalamus is stimulated to release corticotrophin-releasing hormone, which then acts on the anterior pituitary gland to stimulate the synthesis of adrenocorticotropic hormone (ACTH) [3]. ACTH then acts on the adrenal cortex to induce the secretion of glucocorticoids. Once in circulation, glucocorticoids exert a variety of tissue-specific effects. Therefore, glucocorticoid imbalances can result in pathological conditions such as the severe cardiovascular, metabolic and immunological complications observed in Cushing's syndrome (glucocorticoid excess) and Addison's disease (glucocorticoid deficiency) [4].

Regulation of glucocorticoid secretion in response to stress by the hypothalamic-pituitary-adrenal axis. Upon exposure to environmental or psychological stress the hypothalamus is stimulated to release corticotropin-releasing hormone (CRH). CRH then stimulates the anterior pituitary gland to secrete ACTH. In turn, ACTH targets the cortex of the adrenal glands to release cortisol into the bloodstream. Once in circulation, cortisol can be converted to the inactive form, cortisone, by 11β-hydroxysteroid dehydrogenase type 2 [5]. Conversely, 11β-hydroxysteroid dehydrogenase type 1 converts cortisone to cortisol. Glucocorticoids exert their effects by binding to their receptor; the GR. GR is expressed in virtually all cell types and tissues. Thus, GR signalling plays an important role in the modulation of a large number of biological functions in immune cells and in several organs and tissues, including the brain, liver, heart, lungs, adipose tissue, reproductive system, stomach and muscle [5].

Glucocorticoid therapy was first introduced by Dr. Philip Hench in the 1940s for the treatment of rheumatoid arthritis. Since then, glucocorticoids have commonly been prescribed to treat inflammatory disorders, including asthma, allergic rhinitis, ulcerative colitis, and several other dermatological, ophthalmic, neurological and autoimmune diseases. Despite their therapeutic benefits, glucocorticoid use, in traditional high doses >5 mg/day, is associated with severe side effects, including diabetes, hypertension, glaucoma, muscle atrophy and growth retardation. However, the magnitude of the positive or negative effects of glucocorticoids will depend on the dose, duration of the treatment, glucocorticoid receptor (GR) levels, and cell- and tissue-specific glucocorticoid signal transduction [6].

The host inflammatory response is a primary defence mechanism engaged immediately following injury or infection which is necessary to restore homeostasis following successful elimination of the injurious agent, ultimately leading to resolution and tissue repair. Although categorically distinct, the innate (the relatively non-specific immediate host defence system that provides a rapid reaction to infection and tissue damage) and adaptive (the more slowly acquired, highly antigen-specific response) immune systems interact and often overlap during an inflammatory response. Indeed, although acute inflammation is largely mediated by the innate immune system, the adaptive immune system often plays a major role in chronic inflammatory disease, with dysregulated lymphocyte responses [7].

Inflammation is initiated at the site of injury by resident cells, particularly mast cells and resident macrophages, which release pro-inflammatory mediators including bioactive amines, lipid mediators and cytokines—typically TNF-α and IL-1 [8]. These cause vasodilation, increased capillary permeability (humoral response) and leukocyte emigration into injured tissues (cellular response), resulting in the hallmark pain, heat, redness and swelling of inflammation as well as generating a chemotactic gradient to guide and activate recruited cells to the site of injury [9]. Although specific characteristics depend on the immune exposure (e.g. irritant vs pathogen), the recruitment process and activation of inflammatory cells are common. Activated granulocytes, crucial to contain microbial infection, are rapidly

***Corresponding author:** Angelica Merlot, Department of Pathology, University of Sydney, Australia, E-mail: Angelica.Merlot@gmail.com

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attracted to the inflamed site, and followed by monocyte emigration from blood vessels and subsequent maturation into macrophages. Once at the inflamed site, neutrophils undergo constitutive apoptosis, functionally isolating them from the inflammatory environment by loss of stimulated chemotaxis, phagocytosis, degranulation and respiratory burst, whilst at the same time, facilitating safe removal of their potentially histologic contents by macrophages [10]. Foreign antigens are taken up by antigen presenting cells; particularly dendritic cells, but also macrophages, that then migrate to draining lymph nodes where they instruct the adaptive immune system (T and B lymphocytes), shaping the subsequent immune response. As the inflammatory response progresses and evolves, mononuclear cells predominate and resolution normally ensues [11]. Successful resolution of acute inflammation is an active and highly regulated process and dependent on mechanisms engaged early in the inflammatory response that programme the trajectory and form of the subsequent resolution. Persistence of the initiating stimulus invariably leads to chronic inflammation, with the typical dysregulation between destructive inflammatory and excessive healing responses seen in diseases such as arthritis, atherosclerosis and asthma [12].

Glucocorticoids inhibit many of the initial events in an inflammatory response. They also promote the resolution of inflammation although the mechanisms by which they do so have received less attention than those associated with suppression of the initial response [13]. Acutely, glucocorticoids inhibit the vasodilation and increased vascular permeability that occurs following inflammatory insult and they decrease leukocyte emigration into inflamed sites, effects that require new protein synthesis. They also alter leukocyte distribution/trafficking, death/survival and, importantly, alter cellular differentiation programmes, thus shaping the subsequent response [14].

The anti-inflammatory actions of glucocorticoid-induced genes have been recently reviewed. Briefly, as well as DUSP1 and IκB, this class of genes includes IL-10, a potent immunomodulatory and anti-inflammatory cytokine, Glucocorticoid-induced leucine zipper (GILZ), a protein whose mechanism of action is unclear but which interacts with, and inhibits the function of, NFκB and AP-1 and annexin AI (AnxA1), a calcium-dependent phospholipid binding protein [15]. GILZ knockout mice have not been reported, but AnxA1-deficient mice show defective glucocorticoid suppression of inflammation in carrageenin-induced oedema, zymosan-induced peritonitis and antigen-induced arthritis. IL-10-deficient mice develop autoimmune disease and chronic inflammation, but effects of glucocorticoids in these mice have not been reported [16]. However, IL-10 has been implicated in negative regulation of corticosterone synthesis, acting at the adrenal gland, providing a plausible homeostatic mechanism to terminate HPA axis activation once inflammation is resolving. Like IL-10, administration of AnxA1 can mimic a subset of the effects of glucocorticoids (although in T cells, AnxA1 effects may be opposite to those of glucocorticoids). Similarly, ectopic expression of GILZ in T cells and dendritic cells can mimic some of the effects of glucocorticoid. Indeed, some of the effects of both IL-10 and AnxA1 may even be mediated by GILZ, although as IL-10, AnxaA1 and GILZ all alter differentiation or activation state of immune cells such conclusions remain tentative [17].

The last 2 decades have produced a wealth of information on the importance of pre-receptor steroid metabolism. By interconverting active glucocorticoids and inert 11-keto metabolites (cortisone, 11-dehydrocorticosterone), 11β-HSD modulates intracellular access of glucocorticoid to receptors [18]. Type 2 11β-HSD (11β-HSD2) inactivates glucocorticoids in vivo, thus protecting the otherwise non-selective MR from occupation by glucocorticoids. In contrast, because 11β-HSD1 reactivates glucocorticoids, it increases intracellular glucocorticoid concentration. In addition to cortisone (the natural metabolite), certain synthetic steroids (notably prednisone/prednisolone) are also substrates for the 11β-HSD enzymes. The reaction direction of 11β-HSD1 is dictated by its association with hexose-6-phosphate dehydrogenase (H6PD), which couples glucose-6-phosphate oxidation to NADP reduction, generating NADPH co-factor to drive 11β-HSD1 reductase activity. 11β-HSD1 has attracted a lot of recent attention as a potential therapeutic target for metabolic disease, with inhibitors currently under clinical development [19]. Overexpression of 11β-HSD1 in adipose tissue is associated with obesity in both humans and rodents and in transgenic mice, additionally causes hypertension and insulin resistance. Conversely, inhibition of, or deficiency in 11β-HSD1 reduces hyperglycemia and improves insulin sensitivity in non-insulin dependent diabetes in humans and rodents. Selective inhibition of 11β-HSD1 also prevented progression of atherosclerosis in Apoe−/− mice and lowered levels of circulating MCP-1, a cytokine that recruits monocytes to sites of injury. It will be important to determine the extent to which these pro-inflammatory effects of 11β-HSD1 are due to its dysregulation in adipose tissue and possibly other tissues in metabolic disease [20].

Transcriptional repression by GR has always been the subject of debate, as alluded to above, including the extent to which it is dependent or independent of direct GR DNA binding. However, it is agreed that gene activation requires DNA binding by GR. Much of the early work on GR transcriptional activation was based around a consensus GR binding site, comprising two 6 bp "half sites" arranged in an inverted repeat (palindrome) separated by a 3 bp spacer, derived from comparisons of around 20 GR binding sites in promoters including the MMTV-LTR Subsequent work has confirmed this but additionally shown GR-mediated gene regulation to be much more complex recent unbiased screen of GR binding sites coupled with transcriptome analysis showed that genes activated by glucocorticoid had GR bound within a median distance of 11 kb from the transcription start site whereas repressed genes had GR bound a median of 146 kb from the transcription start site, suggesting that repression occurs independently of promoter-proximal GR binding [21]. In silico prediction, genome scanning, chemically directed sequence-specific disruption of GR binding and chromatin immunoprecipitation experiments have shown that sequences that match the GR consensus do not necessarily bind GR in cells and that disruption of GR binding to the conserved half site sequence 5′-WGWWCW-3′ (where W = A/T) only affects a minority of glucocorticoid-regulated genes, both repressed and activated. It has long been clear that many GR binding sites (core sites) are embedded in "composite" glucocorticoid responsive units. Core GR binding sites vary considerably around the consensus although the precise sequence in and immediately around the core GR binding site in a gene (the glucocorticoid responsive unit) is highly conserved between species [22].

Moreover, actual occupancy by GR is influenced by post-translational modification and depends on cell-specific factors [23]. Thus, efficient glucocorticoid regulation depends on concomitant binding by other transcription factors at composite elements, to the extent that GR may "tether" at some promoters, retained principally by protein–protein interactions rather than direct interactions with DNA. Given that GR homodimerisation, at least of the isolated DNA binding domain, only occurs on DNA binding, then monomers of GR may bind to divergent sequences at composite response elements or by tethering to other transcription factors. Thus, the context of the GR binding site is crucial with the outcome – repression, activation or even

specificity (MR vs GR) – dependent on the cell-specific complement of transcription factors. Whether and how GR contacts DNA might be critical. The GR DNA binding sequence itself acts as an allosteric regulator of GR function, dictating the pattern of regulation that ensues following GR binding. DNA binding induces conformational changes in the dimerisation interface that expose otherwise silent transcriptional activation surfaces. These conformational changes are exquisitely sensitive to the DNA sequence, with single base pair differences differentially affecting GR conformation and transcriptional regulation. Further complexity is revealed at the level of chromatin, where GR binding is highly dynamic and invariably occurs at either constitutive or hormone inducible nuclease accessible sites (regions of "open" chromatin) at which the requirement for chromatin remodelling complexes differs. These dynamic and gene-specific differences in chromatin remodelling by GR are likely to be highly cell-specific and could underlie the complex kinetics of glucocorticoid responses, where glucocorticoid responsive genes may exhibit alternate activation and repression, with poor correlation in some cases between GR binding to response elements and target gene response. Elucidating the nature of GR interactions with target genes, especially in the immune system, will be crucial to understanding their anti-inflammatory effects, but the challenge will be to establish these actions in physiologically relevant settings.

## Discussion

Synthetic glucocorticoids, especially dexamethasone, have higher affinity, greater bioavailability (unlike the natural hormones, most bind poorly or not at all to corticosteroid binding globulin) and are poorly metabolised, thus they persist in plasma much longer than endogenous glucocorticoids (cortisol, corticosterone). Moreover, the endogenous hormones are released from the adrenal gland in both a circadian and a highly pulsatile manner (in). Recent work from the laboratories of Gordon Hager and Stafford Lightman has shown that this pulsatile release of glucocorticoids is coupled to a highly dynamic pattern of GR-mediated transcriptional bursts, driven by rapid recycling of GR occupancy of chromatin binding sites in response to the hormonal pulses in vivo as well as in vitro. This pulsatility did not occur with constant administration of hormone, nor did it happen with synthetic ligands, including dexamethasone, which failed to cause significant ultradian cycling of GR on chromatin and consequently failed to couple fluctuations in hormone levels with transcriptional response. Thus, transcriptional output can be profoundly altered by synthetic GR ligands or even with natural hormones if not administered in the natural pattern. Moreover, basal levels of glucocorticoids in vivo exert tonic effects [24]. Thus, macrophages elicited by thioglycollate in the peritoneum of adrenalectomised rats behaved very differently to macrophages from sham operated rats, with much greater TNFα secretion and NO production in the unstimulated state, which could only be marginally increased by LPS/IFNγ stimulation.

## Conclusion

Cytokines themselves are potent activators of the HPA axis, and may permanently programme endogenous glucocorticoid secretion when elevated in early life. Importantly, when the HPA axis is activated, not only is plasma cortisol elevated (corticosterone in rodents), but so is plasma cortisone (11-dehydrocorticosterone in rodents), itself intrinsically inert due to poor binding to GR, but which is available in plasma (it shows negligible binding to corticosteroid binding globulin) and which can be readily enzymatically converted inside cells to the active steroid by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Many aspects of the anti-inflammatory actions of glucocorticoids have not been covered here. However, it is clear that the field is at an exciting stage. The next few years should provide a big step forward in our understanding of how these important hormones exert their effects, with concomitant advances in the clinical treatment of inflammatory disease.

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## Conflict of Interest

None

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