

GLUCOCORTICOIDS are potent inhibitors of inflammation and endotoxic shock. This probably occurs through an inhibition of the synthesis of pro-inflammatory cytokines as well as of many of their toxic activities. Therefore, endogenous glucocorticoids (GC) might represent a major mechanism in the control of cytokine mediated pathologies. GC inhibit the synthesis of cytokines in various experimental models. Adrenalectomy or GC antagonists potentiate TNF, IL-1 and IL-6 production in LPS treated mice. GC inhibit the formation of arachidonic acid metabolites and the induction of NO synthase. They also inhibit various activities of cytokines including toxicity, haemodynamic shock and fever. Adrenalectomy sensitizes to the toxic effects of LPS, TNF and IL-1. On the other hand, GC potentiate the synthesis of several cytokine induced APP by the liver. Since many of these proteins have anti-toxic activities (antioxidant, antiprotease etc.) or bind cytokines, this might well represent a GC mediated protective feedback mechanism involving the liver. Not only do GC inhibit cytokines, but *in vivo* LPS and various cytokines (TNF, IL-1, IL-6) increase blood GC levels through a central mechanism involving the activation of the HPA. Thus, this neuroendocrine response to cytokines constitutes an important immunoregulatory feedback involving the brain.

**Key words:** Cytokines, Endotoxic shock, Glucocorticoids, Inflammation, Neuroendocrine control

## Glucocorticoids as cytokine inhibitors: role in neuroendocrine control and therapy of inflammatory diseases

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### Introduction

Glucocorticoids (GC) are effective in the treatment of a variety of inflammatory and autoimmune diseases and in these fields much of current attention is focused on cytokines. This review discusses the effects of GC on the production and actions of cytokines in order to obtain a better understanding of how the anticytokine action of GC is involved in their pharmacological activity. This review focuses on the cytokines primarily involved in the regulation of inflammatory processes, IL-1, IL-6, IL-8 and TNF.

Most studies of pharmacological modulation of cytokines have used animal models of endotoxaemia. In fact, endotoxin (lipopolysaccharide, LPS) is a potent and widely used inducer of cytokine production *in vivo* and on cultured cells, and its toxic effects are antagonized by inhibitors or antagonists of IL-1 or TNF.<sup>1–3</sup>

The role of GC in the control of cytokine mediated effects of LPS has been demonstrated by two different approaches: removal of endogenous GC (by adrenalectomy or GC-receptor antagonists), or administration of exogenous GC. Adrenalectomy increases sensitivity to the lethal action of LPS<sup>4,5</sup> and identical results have been obtained with the GC receptor antagonist mifepristone (RU38486).<sup>6,7</sup>

Treatment with GC markedly protects against LPS toxicity.<sup>8–10</sup> Susceptibility to the lethal action of LPS<sup>11</sup> and TNF<sup>12</sup> varies with the circadian rhythm; however, the role of endogenous GC is far from being established. Biochemically, GC inhibit the LPS induced production of inflammatory mediators, such as arachidonic acid metabolites and nitric oxide (NO). It is therefore important to define which of these actions are due to inhibition of cytokine production and which might involve a direct inhibition of the cytokines' action.

### Inhibition of cytokine production

*Exogenous glucocorticoids:* Most of the *in vitro* studies focused on IL-1 and TNF, whose induction is suppressed by various GC (Table 1). IFN $\gamma$  can partly overcome GC suppression of TNF production *in vitro* by mouse peritoneal macrophages.<sup>26</sup> In contrast, IL-4 enhances the inhibitory action of GC on IL-1, TNF and prostaglandins (PG) E<sub>2</sub> production by human monocytes.<sup>27</sup> However, GC had no inhibitory effects when phorbol myristate acetate (PMA) was used as a stimulus for TNF, IL-1 or IL-8 production.<sup>17,21,28</sup>

The inhibitory effect of GC on IL-1 production may proceed through the inhibition of IL-1 gene transcription and a decrease in the stability of

Table 1. Inhibition of proinflammatory cytokine production by glucocorticoids *in vitro*

Cytokine	Inducer	References
IL-1	LPS, <i>S. aureus</i> , IL-1	13-15
TNF	LPS, anti-IgG	16, 17
IL-6	LPS, IL-1, TNF	18, 19
IL-8	LPS, IL-1, TNF, cAMP	19-21
IL-2	IL-1	22
GM-CSF	IL-1, TNF	19, 23
G-CSF	IL-1, TNF	23, 24
MCP-1	IL-1	25

IL-interleukin; TNF, tumour necrosis factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; MCP-1, monocyte chemoattractant protein-1.

IL-1 mRNA.<sup>29</sup> The fact that GC did not inhibit PMA induced IL-1 might be explained by postulating that PMA has a stabilizing effect on IL-1 mRNA.<sup>28</sup> The inhibitory effect of GC on IL-1 $\beta$  gene expression was reversed by inhibitors of protein synthesis.<sup>29</sup> This has some analogy with other anti-inflammatory activities of GC that require the synthesis of lipocortins.<sup>30</sup>

Cytokines often induce each other, in a cascade fashion, and GC inhibit IL-1 and TNF induction of various cytokines (Fig. 1). In mice or rats treated with LPS or anti-CD3 antibodies GC inhibited the production of circulating TNF, IL-1, IL-6 and IFN $\gamma$ .<sup>31-34</sup> TNF seems to be more sensitive to GC inhibition *in vivo* than IL-1 or IL-6.<sup>35,36</sup>

GC inhibit TNF and IL-6 induced by stimuli other than LPS. Dexamethasone (DEX) inhibited TNF induction in mice after partial hepatectomy,<sup>37</sup> and IL-1 in a rat model of zymosan induced

pleurisy.<sup>38</sup> It also lowered serum IL-6 levels in adjuvant arthritis in rats.<sup>39</sup>

In human volunteers giving an injection of LPS, GC inhibited IL-6 and TNF production.<sup>40,41</sup> DEX, administered to IL-2 treated cancer patients<sup>42</sup> or to patients undergoing cardiopulmonary bypass,<sup>43</sup> reduced the TNF production observed in these conditions.

*Ex vivo* studies on cells from patients with sarcoidosis,<sup>44</sup> Crohn's disease<sup>45</sup> or rheumatoid arthritis<sup>46</sup> found decreased IL-1, IL-6 and IL-8 production after GC treatment.

*Effects of adrenalectomy or glucocorticoid antagonists:* The studies mentioned above employed exogenous GC. More direct evidence of the inhibitory effect of endogenous GC comes from studies where animals were adrenalectomized (ADX) or treated with GC antagonists. Adrenalectomy sensitizes to the lethal action of infections, LPS,<sup>4,5</sup> turpentine<sup>47</sup> or complete Freund's adjuvant.<sup>48</sup> This was related to increased production of TNF and IL-1.<sup>49</sup>

GC might be important in switching off TNF production and, in fact, in ADX mice injected with LPS, TNF levels remained elevated up to 5 h, whereas in sham-operated mice they returned to zero by 3 h.<sup>50</sup> This prolonged induction was not associated with higher peak TNF levels. In another study, however,<sup>51</sup> ADX mice had higher peak (1.5 h) TNF levels, but the kinetics of TNF induction was similar to that of intact mice, returning to zero within 4 h. Unpublished data from our laboratory agree with the latter report.

Production of IL-1 was also increased *ex vivo*, in peritoneal macrophages from ADX rats.<sup>52</sup> The authors' group reported that intracerebroventricular (i.c.v.) injection of IL-1 in rats induced high circulating levels of IL-6, and this effect was potentiated by adrenalectomy.<sup>53</sup> The data on ADX animals were confirmed by using RU38486 which is reported to increase LPS toxicity and induction of TNF and IL-6.<sup>6,7</sup> RU38486 also increased mortality in a mouse model of septic peritonitis.<sup>54</sup>

## Effects on cytokine receptors

Glucocorticoids increase the expression of IL-1 receptors in B-lymphocytes, fibroblasts, and some cell lines<sup>55,56</sup> but not in T-lymphocytes, large granular lymphocytes or monocytes. While this increase in IL-1 receptors might seem paradoxical, in view of the anti-inflammatory action of GC, it could result in a change in IL-1 distribution *in vivo*, where IL-1 might be soaked up by some cells rather than others.

This was also suggested in the case of IL-6 whose receptor is markedly decreased by GC in monocytes but not in hepatocytes. However, GC appeared to

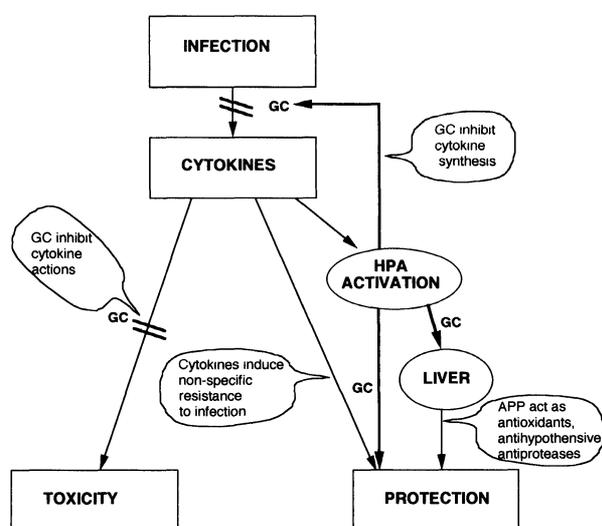


FIG. 1. Dual role of cytokines in infection and inflammation. Stimulation of neuroendocrine system, by increasing endogenous GC, inhibits cytokine production and potentiates cytokine induced protective responses. The protective mechanism involving stimulation of APP synthesis by the liver is depicted.

be essential for the induction of hepatocyte IL-6 receptors by IL-1 and IL-6 itself, and it was suggested that monocytes are normally involved in binding trace amounts of IL-6, thus preventing its interaction with the hepatocyte.<sup>57</sup>

Information on TNF receptors is scant; DEX reduced the number of 75 kDa TNF receptors on U937 cells<sup>58</sup> but did not affect the number of TNF binding sites on mouse hepatocytes in DEX treated mice.<sup>59</sup>

## Effects on cytokine actions

Cytokines have a variety of actions on different cells, resulting in various pathological effects associated with infective or inflammatory diseases.<sup>60</sup> The effects of anti-inflammatory agents, including GC and non-steroidal anti-inflammatory drugs, on the activities of TNF and IL-1 have been amply documented. Here the effect of GC on various activities of cytokines, *in vivo* and *in vitro* is reviewed.

In general, GC inhibit the pro-inflammatory and toxic effects of cytokines. These effects belong mainly to IL-1 and TNF, whose role as mediators of the mortality associated with Gram-negative septicaemia has been demonstrated by the protective effect of specific IL-1 and TNF inhibitors.<sup>2,3,6</sup> On the other hand, GC have been reported to potentiate the induction of acute phase proteins (APP).

### *Effects on inflammation:*

**Arachidonate metabolism.** Prostaglandins and other arachidonic acid oxygenation products are major mediators of inflammation. Their production is stimulated by IL-1,<sup>61</sup> and this was suggested to be an important mechanism in the inflammatory and pyrogenic action of IL-1.

Through GC induced lipocortin, GC inhibit the activity and synthesis of PLA<sub>2</sub>,<sup>62</sup> the enzyme that provides free arachidonic acid for PG synthesis. IL-1, TNF and IFN $\gamma$  induce PG synthesis by stimulating PLA<sub>2</sub> activity, and GC could inhibit this.<sup>63-65</sup> This suggests that the inhibitory effect of GC is at the level of PLA<sub>2</sub>, since arachidonic acid induced PG production was not reduced.<sup>63</sup> Furthermore, GC inhibit the *de novo* synthesis of cyclooxygenase induced by IL-1, TNF or LPS.<sup>66-68</sup>

PLA<sub>2</sub> is not implicated only in the inflammatory action of cytokines but also in the tumoricidal activity of TNF. GC inhibit the cytotoxic activity of TNF on tumour cells *in vitro*<sup>69,70</sup> as well as its tumoricidal activity *in vivo*<sup>71</sup> and it was suggested this was due to inhibition of PLA<sub>2</sub>. Interestingly, this activity of GC seems not to be mediated by lipocortin.<sup>72</sup>

**Chemotaxis and adherence.** Pretreatment with DEX abolished the neutrophil migration induced by injection of IL-8 or IL-1 in rats or mice<sup>73-75</sup> thus

suggesting that GC may directly inhibit IL-8 chemotactic activity, in addition to suppressing IL-1 induced IL-8 production. The inhibitory effect of GC on IL-1 induced chemotaxis seems to be mediated by the induction of lipocortin which, in fact, inhibits IL-1 induced chemotaxis, and anti-lipocortin antibodies abolished the inhibitory action of GC.<sup>62</sup> Contrasting indications were obtained on the effect of GC on cytokine induced expression of the adhesion molecule ICAM-1.<sup>76,77</sup>

**Nitric oxide pathway.** Nitric oxide has been identified as a major mediator of shock and inflammation. Its production is increased by LPS, TNF, IL-1 and IFN $\gamma$  through the induction of NO synthase.<sup>78</sup> GC inhibited this induction by cytokines and LPS<sup>79,80</sup> while not affecting its enzymatic activity.<sup>81</sup>

**Toxic, behavioural and catabolic effects:** The most impressive evidence for a protective role of endogenous GC against the toxic effects of cytokines comes from studies reporting that ADX mice are sensitized to the lethal effects of IL-1 and TNF;<sup>52,82</sup> thus their increased sensitivity to LPS is not only due to increased cytokine production (as discussed above) but also to increased sensitivity to their actions. Similar results have been obtained with RU38486.<sup>83</sup> Furthermore, DEX protected against the lethal effect of a high dose of TNF in intact mice without affecting its clearance.<sup>59,71</sup>

The well-known haemodynamic effects of GC might also be important in protecting against the toxicity of IL-1 and TNF, which cause a marked and often lethal hypotension.<sup>84</sup>

GC might regulate other physiological responses to infection too. For instance, ADX rats are more susceptible to LPS induced fever<sup>85</sup> and GC attenuated the sleep response to bacterial infection in rabbits.<sup>86</sup> However, it is not clear whether the effects of GC in these models are due to inhibition of the production of cytokines or of their action.

Another well-known central effect of IL-1 and TNF is anorexia. Contrasting results were reported; one paper reported that DEX pre-treatment blocked the suppression of food intake induced by i.c.v. IL-1 administration in rats,<sup>87</sup> while another showed that IL-1 induced anorexia was less pronounced in ADX rats.<sup>88</sup>

**Effects on acute phase proteins:** Induction of hepatic APP is part of a reorientation of the liver metabolism which includes an increase in the synthesis of APP and a decrease in negative acute phase reactants. GC are important for the induction of several APP, and are required for the production of fibrinogen by cultured hepatocytes stimulated with crude leukocytic extract.<sup>89</sup> The permissive action of GC was also reported *in vivo* where inflammatory stimuli caused little or no induction of angiotensinogen,<sup>90</sup> haptoglobin<sup>47</sup> and  $\alpha_2$ -macrofetoprotein<sup>91</sup> in ADX

animals. Among the various cytokines, those that play a key role as hepatocyte stimulating factors include IL-6, leukaemia inhibitory factor (LIF) and oncostatin M (OM). Induction of most APP in hepatoma cells stimulated *in vitro* with recombinant preparations of these cytokines was potentiated by GC.<sup>92-94</sup>

Induction of APP could be part of the protective feedback response to infection and inflammation. Some APP have activities that might be 'protective', either by binding cytokines, like  $\alpha_2$ -macroglobulin;<sup>95</sup> by maintaining blood pressure, like angiotensinogen;<sup>90</sup> or acting as antioxidants or proteinase inhibitors. The protective role of APP is elegantly demonstrated by Xia and Samols<sup>96</sup> who showed that transgenic mice overexpressing rabbit C-reactive protein were protected against LPS or IL-1/TNF induced lethality.

As mentioned above, some 'normal liver proteins' behave as negative acute phase reactants, including albumin and cytochrome P-450. While this can be explained on the basis of cell economy, depression of cytochrome P-450 may have a functional role. In fact, cytochromes of the P-450 family are also implicated in steroidogenesis and TNF inhibited ACTH induced steroidogenic cytochrome P-450, resulting in decreased GC production.<sup>97</sup> This effect might limit the increase in blood GC by TNF described below. It must also be noted that cytochromes of the P-450 family are implicated in the metabolism of arachidonic acid, thus suggesting another possible involvement in the regulation of inflammation.

### Effect of cytokines on glucocorticoid receptors and action

Glucocorticoids are not only cytokine inhibitors but, the other way round, cytokines may counteract some effects of GC. As early as 1976, Moore *et al.*<sup>98,99</sup> showed that GC induction of some enzymes was inhibited by LPS; they identified a macrophage product that was termed GAF (glucocorticoid antagonizing factor). LPS also downregulates hepatic GC receptors,<sup>100</sup> an effect that is tissue specific since LPS had the opposite effect in macrophages.<sup>101</sup> Although the molecular structure of GAF has never been identified it is conceivably one of the several activities of IL-1, IL-6, TNF or other known cytokines. In this respect, it is interesting to note that IL-1 decreases hepatic GC receptors thus inhibiting the induction of phosphoenolpyruvate carboxykinase.<sup>102</sup>

### Cytokine activation of the hypothalamus-pituitary-adrenal axis

Inflammation and injection of LPS induce a rise in blood GC, due to activation of the hypothalamus-

pituitary-adrenal axis (HPA).<sup>103</sup> LPS induced GC secretion *in vivo* is inhibited by selective depletion of macrophages, suggesting that macrophage derived cytokines mediate the effect of LPS.<sup>104</sup> In fact, treatment of mice with IL-1 increased blood ACTH and GC levels<sup>105</sup> and anti-IL-1 receptor antibodies blocked LPS induced ACTH release.<sup>106</sup> While an earlier work reported that TNF had no such effect, TNF and IL-6 also increased blood GC, although they were less potent than IL-1.<sup>107,108</sup>

Although in different experimental models *in vitro*, IL-1 and IL-6 directly stimulated the release of ACTH from pituitary cells,<sup>109,110</sup> the increase of blood GC observed *in vivo* seems mainly due to a stimulation of hypothalamic cells to release CRF.<sup>111</sup> IL-1 induced GC was associated with increased CRF levels in the pituitary portal vessels and anti-CRF antibodies inhibited IL-1 induced GC, thus indicating that IL-1 exerts this effect on the hypothalamus.<sup>112,113</sup>

A series of papers focused on the role of PG in IL-1 activation of the HPA. The cyclooxygenase inhibitor, indomethacin, inhibited CRF release *in vitro*<sup>114</sup> as well as activation of the HPA *in vivo*.<sup>115,116</sup>

Stress induced activation of the HPA is downregulated by a feedback mechanism, and inhibited by DEX pre-treatment. In comparison, IL-1 induced HPA activation is less sensitive to the inhibitory effect of DEX. As a possible explanation for this difference, it was reported that IL-1 decreases hippocampal GC receptors thus desensitizing them to DEX effects.<sup>117</sup>

*HPA in the regulation of immunity, autoimmunity and inflammation:*

*Immunity.* Since GC are potent inhibitors of cytokine production, cytokine activation of HPA might obviously constitute a negative feedback mechanism that regulates their production.<sup>105</sup> To support this theory, it was reported that hypophysectomized animals produce more IL-1, IL-6 and TNF.<sup>49,53</sup> Activation of HPA by i.c.v. injected IL-1 resulted in suppression of spleen macrophage IL-1 production *ex vivo*, which was not observed in ADX mice.<sup>118</sup>

Another effect of central administration of IL-1 is to lower the peripheral cellular immune response in terms of natural killer cell activity, lymphocyte response to mitogens and IL-2 production.<sup>119,120</sup> These effects were blunted by anti-CRF antibodies and were less pronounced in ADX animals, indicating that HPA is to some extent involved.

*Autoimmune diseases.* Experimental allergic encephalomyelitis (EAE) is a demyelinating disease induced by immunization to myelin basic protein, and is used as an animal model for multiple sclerosis. Recent data have indicated a pathogenetic role of TNF in this disease, as demonstrated by the

protective effect of anti-TNF antibodies.<sup>121</sup> The role of endogenous GC in the susceptibility to the disease has been reviewed by Mason.<sup>122</sup> EAE activates the HPA as revealed by the increase in serum GC. ADX rats do not recover spontaneously from EAE, and adrenalectomy increases the mortality rate in this animal model. Rat strains that are genetically resistant to the development of EAE have more marked HPA activation to stressing stimuli, and adrenalectomy can render them normally susceptible to EAE. These data on the HPA regulation of EAE provide a rationale for the use of GC in the therapy of multiple sclerosis.

**Inflammation.** Since GC are potent anti-inflammatory agents, HPA activation may also function to limit inflammatory processes. TNF and IL-1 were reported to have anti-inflammatory action in carrageenan or dextran induced hind paw oedema in rats.<sup>123</sup> This was due to the IL-1 and TNF induced rise in GC, and was not observed in ADX rats.

Lewis rats, which are genetically prone to streptococcal cell wall (SCW) induced arthritis, had markedly impaired ACTH and GC responses to SCW or IL-1.<sup>124</sup> On the other hand, RU38486 induced susceptibility to SCW arthritis in normal rats. Thus genetic susceptibility to arthritis might be related to a defective HPA responsiveness to cytokines.

## Glucocorticoid therapy in cytokine mediated pathologies

In view of their potent anti-cytokine action, GC might theoretically constitute drugs of choice in the therapy of cytokine mediated pathologies, i.e. those where a pathogenetic role of cytokines has been demonstrated in animal models by the protective action of anti-cytokine antibodies. The earliest works of passive immunization of mice against TNF showed that this cytokine is the key mediator of mortality induced by LPS or Gram-negative sepsis.<sup>2,3</sup> As mentioned above, GC has a strong protective effect in mice treated with lethal doses of LPS<sup>8-10</sup> and septic shock was an indication for the use of high GC doses.<sup>125</sup>

However, in clinical trials GC did not reduce mortality in septic shock patients, and their indication for use in this condition was withdrawn by the FDA.<sup>126,127</sup> This discrepancy between animal and clinical studies might have various reasons. For instance, in most studies GC were administered to animals before or concomitantly with LPS, a situation that is quite different from a septic patient. Furthermore, in septic shock patients, Gram-negative sepsis is often associated with Gram-positive infection,<sup>128</sup> and in mice where poly-

microbial sepsis was induced by caecal ligation and puncture, anti-TNF antibodies and GC tended to increase mortality.<sup>129,130</sup> These data indicate the existence of a complex pathway where one must consider the balance between the pathogenetic, toxic activities of cytokines and their protective actions against infection.<sup>131</sup>

A different picture emerges on the role of TNF and IL-1 in the pathogenesis of meningitis,<sup>132,133</sup> where animal studies have shown a protective effect of GC. In meningitis patients, antibiotic therapy would result in bacterial cell lysis and consequent liberation of LPS which would trigger the cytokine cascade.<sup>134</sup> It is therefore a current therapeutic approach, supported by clinical trials, to administer DEX 30 min before antibiotics to inhibit cytokine production, thus preventing an important component of the pathology.

Thus, glucocorticoids inhibit cytokines at multiple sites. However, in most animal models they are effective when given as pre-treatments, they aspecifically inhibit the synthesis of all cytokines, and they are also potent immunosuppressive agents. This limits their effectiveness in the therapy of cytokine mediated pathologies where a balance of toxic versus protective effects of cytokines is likely to exist.

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