Glucocorticoids and the Th1/Th2 Balance

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ABSTRACT: Evidence accumulated over the last 5–10 years indicates that glucocorticoids (GCs) inhibit the production of interleukin (IL)-12, interferon (IFN)-γ, IFN-α, and tumor necrosis factor (TNF)-α by antigen-presenting cells (APCs) and T helper (Th)1 cells, but upregulate the production of IL-4, IL-10, and IL-13 by Th2 cells. Through this mechanism increased levels of GCs may systemically cause a selective suppression of the Th1–cellular immunity axis, and a shift toward Th2-mediated humoral immunity, rather than generalized immunosuppression. During an immune response and inflammation, the activation of the stress system, and thus increased levels of systemic GCs through induction of a Th2 shift, may actually protect the organism from systemic "overshooting" with Th1/pro-inflammatory cytokines and other products of activated macrophages with tissue-damaging potential. However, conditions associated with significant changes of GCs levels, such as acute or chronic stress or cessation of chronic stress, severe exercise, and pregnancy and postpartum, through modulation of the Th1/Th2 balance may affect the susceptibility to or the course of infections as well as autoimmune and atopic/allergic diseases.

KEYWORDS: glucocorticoids; stress; interleukin-12; interleukin-10; Th1 cells; Th2 cells; autoimmunity; allergy; inflammation; rheumatoid arthritis; multiple sclerosis

INTRODUCTION

The T helper (Th)1/Th2 balance is critically skewed, one way or the other, in several common human diseases, such as acute and chronic infections, autoimmunity, and atopy/allergy.[1–4] These diseases frequently develop and progress in settings of hyperactivity or hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis.[5–9] Studies in the 1970s and the 1980s revealed that glucocorticoids (GCs), the end products of HPA axis activity, inhibit lymphocyte proliferation and cytotoxicity, and the secretion of TNFα, IL-2, and IFN-γ.[10,11] These observations, in the context of the broad clinical use of GCs, initially led to the conclusion that GCs are, in general, immunosuppressive. Recent evidence indicates, however, that systemically GCs cause selective suppression of the Th1–cellular immunity axis and a shift toward Th2-mediated humoral immunity, rather than generalized immunosuppression. This

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new concept helps explain some well-known, but often contradictory, effects of GCs on the immune system and on the onset and course of certain infectious, autoimmune, and atopic/allergic diseases. This new understanding is briefly outlined below.

THE TH1/TH2 PARADIGM: ROLE OF TH1 AND TH2 CYTOKINES

The immune system is classified into innate (or non-specific, natural) and adaptive (or specific, acquired) immunity. Innate immunity provides a rapid, non-specific host response against different bacteria, viruses, or tumors that precedes the adaptive immunity. Moreover, innate immunity also has an important role in determining the nature of downstream adaptive immune responses. Thus, immune responses are regulated by antigen-presenting cells (APC)—monocytes/macrophages, dendritic cells (DCs), and by natural killer (NK) cells— which are components of innate immunity, and by the recently described Th lymphocyte subclasses Th1 and Th2, which are components of adaptive (acquired) immunity. Th1 cells primarily secrete IFN-γ, IL-2, and TNFα, which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines, primarily IL-4, IL-10, and IL-13, which promote humoral immunity.[1–3] Naive $CD4^+$ (antigen-inexperienced) Th0 cells are clearly bipotential and serve as precursors of Th1 and Th2 cells. IL-12, produced by APC—monocytes/macrophages and DCs—is the major inducer of Th1 differentiation and hence cellular immunity. IL-12 also synergizes with IL-18 to induce the production of IFN-γ by natural killer (NK) cells. Thus, IL-12 in concert with IL-18, IFN-α, and IFN-γ promote the differentiation of Th0 toward the Th1 phenotype. IL-1, IL-12, TNFα, and IFN-γ stimulate the functional activity of T cytotoxic cells (Tc), NK cells, and activated macrophages, which are the major components of cellular immunity. The type 1 cytokines IL-12, TNFα, and IFN-γ also stimulate the synthesis of nitric oxide (NO) and other inflammatory mediators that drive chronic delayed-type inflammatory responses. Because of these synergistic roles in inflammation, IL-12, TNFα, and IFN-γ are considered the major pro-inflammatory cytokines.[1–3] Th1 and Th2 responses are mutually inhibitory. Thus, IL-12 and IFN-γ inhibit Th2 cells' activities, while IL-4 and IL-10 inhibit Th1 responses. IL-4 and IL-10 promote humoral immunity by stimulating the growth and activation of mast cells and eosinophils (Eo), the differentiation of B cells into antibody-secreting B cells, and B cell immunoglobulin switching to IgE. Importantly, these cytokines also inhibit macrophage activation, T cell proliferation, and the production of pro-inflammatory cytokines.[1–3] Therefore, the Th2 (type 2) cytokines IL-4 and IL-10 are the major anti-inflammatory cytokines.

SYSTEMIC EFFECTS OF GCs

Previous studies have shown that GCs suppress the production of TNFα, IFN-γ, and IL-2 *in vitro* and *in vivo* in animals and humans.[5,11] Recent evidence indicates that GCs systemically suppress the Th1–cellular immunity axis and mediate a Th2 shift by suppressing APC- and Th1- and upregulating Th2-cytokine production. Thus, GCs act through their classic cytoplasmic/nuclear receptors on APCs to sup-

press the production of the main inducer of Th1 responses, IL-12 *in vitro* and *ex vivo*.[12,13] Because IL-12 is extremely potent in enhancing IFN-γ and inhibiting IL-4 synthesis by T cells, the inhibition of IL-12 production may represent a major mechanism by which GCs affect the Th1/Th2 balance. Thus, GC-treated monocytes/macrophages produce significantly less IL-12, leading to a decreased capacity of these cells to induce IFN-γ production by antigen-primed $CD4^+$ T cells. The same treatment of monocytes/macrophages is also associated with an increased production of IL-4 by T cells, probably resulting from disinhibition from the suppressive effects of IL-12 on Th2 activity.[14] Furthermore, GCs potently downregulate the expression of IL-12 receptors on T and NK cells. This explains why human peripheral blood mononuclear cells stimulated with immobilized anti-CD3 lose their ability to produce IFN-γ in the presence of GCs.[15] Thus, although GCs may have a direct suppressive effect on Th1 cells, the overall inhibition of IFN-γ production by these cells appears to result mainly from the inhibition of IL-12 production by APCs and from the loss of IL-12 responsiveness of NK and Th1 cells. GCs also suppress the production of IL-18 (which synergizes with IL-12 to promote Th1 responses) in LPS/IL-2-stimulated peripheral blood mononuclear cells (PBMCs), although the inhibition seems to be incomplete even at high concentrations.[16] This is consistent, however, with an observation that in GC-responsive patients with Graves' ophthalmopathy the GCs treatment results in decreased IL-18 serum concentrations as compared to the pretreatment values.[17] GCs also inhibit the production of IFN-γ, another cytokine that synergizes with IL-12 to promote Th1 responses—in PBMCs of healthy adult volunteers stimulated with Newcastle disease virus (NDV), GCs reduce the IFN-α release by 50 to 60%.[18]

GCs also have a direct effect on Th2 cells by upregulating their IL-4, IL-10, and IL-13 production.[13,19] GCs have no effect on the production of the potent anti-inflammatory cytokine IL-10 by monocytes[12,20]; yet, lymphocyte-derived IL-10 production appears to be upregulated by GCs. Thus, rat $CD4^+$ T cells pretreated with dexamethasone exhibit increased levels of mRNA for IL-10.[21] Similarly, during experimental endotoxemia or cardiopulmonary bypass, or in multiple sclerosis patients having an acute relapse, the treatment with GCs is associated with an increased plasma IL-10 secretion.[20,22,23] This might have resulted from a direct stimulatory effect of GCs on T cell IL-10 production and/or from the disinhibition of the restraining inputs of IL-12 and IFN-γ on monocyte/lymphocyte IL-10 production.

LOCAL VERSUS SYSTEMIC EFFECTS

The systemic Th2-inducing properties of GCs may not pertain to certain conditions or local responses in specific compartments of the body. Thus, steroid treatment results in a significant increase in the number of $IL\text{-}12^+$ cells with concurrent reduction in the number of $IL\text{-}13^+$ expressing cells in bronchial biopsy specimens of subjects with asthma. Interestingly, this occurs only in steroid-sensitive but not steroid-resistant asthmatic subjects.[24] This may reflect only a redistribution of cells, but the number of $IL\text{-}4^+$ cells in the bronchial and nasal mucosa is also reduced by prednisone treatment.[25,26] Furthermore, the synthesis of transforming growth factor (TGF)-β, another cytokine with potent anti-inflammatory activities, is enhanced by GCs in human T cells but suppressed in glial cells,[27] and low concentra-

tions of dexamethasone can indeed activate alveolar macrophages, leading to increased LPS-induced IL-1β production.[28]

In contrast to the abovementioned inhibitory effect of GCs on the production of IL-18 by LPS/IL-2-stimulated PBMCs,[16] in cultured unstimulated PBMC and promonocytic cell lines, prednisolone upregulates IL-18 transcription in parallel with increasing the IL-18 protein release into cell culture supernatants.[29] It is highly likely that GCs downregulate IL-18 production in activated macrophages but upregulate IL-18 production in resting, non-activated cells. In this context it is an interesting observation that Cushing's patients that have high cortisol levels have also markedly elevated levels of IL-18.[30]

CRH/SP–Mast Cell–Histamine Interactions

As the primary regulator of corticotropin (ACTH) secretion from the pituitary and thus, glucocorticoid secretion from the adrenal gland, corticotropin-releasing hormone (CRH) modulates immune/inflammatory reactions through receptor-mediated actions of GCs on their target immune tissues, effects that are in general anti-inflammatory. CRH, however, is also secreted peripherally at inflammatory sites (peripheral or immune CRH), where it exerts mostly pro-inflammatory activities.[31] Immunoreactive CRH is identified locally in tissues from patients with rheumatoid arthritis (RA), autoimmune thyroid disease (ATD), and ulcerative colitis. CRH in early inflammation is of peripheral nerve rather than immune cell origin.[31,32] Peripheral CRH has vascular permeability–enhancing and vasodilatory actions. An intradermal CRH injection induces a marked increase of vascular permeability and mast cell degranulation, mediated through CRH type 1 receptors.[33] It appears that the mast cell is a major target of immune CRH. Substance P (SP) and peripheral CRH, which are released from sensory peptidergic neurons, are two of the most potent mast cell secretagogues.[33–36] Thus, peripheral CRH and SP activate mast cells via a CRH type 1 and NK1 receptor–dependent mechanism leading to release of histamine and other contents of the mast cell granules that subsequently may cause vasodilatation, increased vascular permeability, and other manifestations of inflammation.

CLINICAL IMPLICATIONS

Intracellular Infections

A major factor governing the outcome of infectious diseases is the selection of Th1- versus Th2-predominant adaptive responses during and after the initial invasion of the host. Since the major catecholamines (CAs), epinephrine (EPI) and norepinephrine (NE), also systemically induce a Th2 shift,[4,37] stress-induced—and hence a GC- and CA-induced—Th2 shift may have a profound effect on the susceptibility of the organism to an infection, and/or may influence its course. Thus, stress has a substantial effect on the defense system where cellular immunity mechanisms have a primary rule.

Cellular immunity, and particularly IL-12 and IL-12-dependent IFN-γ secretion in humans, seems essential in the control of mycobacterial infections.[38] In the 1950s, Thomas Holmes (cf. Ref. 7) reported that individuals who had experienced stressful life events were more likely to develop tuberculosis and less likely to recover from

it. Although it is still a matter of some speculation, stress hormone–induced inhibition of IL-12 and IFN-γ production, and the consequent suppression of cellular immunity, may amply explain the pathophysiologic mechanisms of these observations.

Helicobacter pylori infection is the most common cause of chronic gastritis that in some cases progresses to peptic ulcer disease. The role of stress in promoting peptic ulcers has been recognized for many years.[39,40] Thus, increased systemic stress hormone levels, in concert with an increased local concentration of histamine, induced by inflammatory or stress-related mediators, may skew the local responses toward Th2 and thus may allow the onset or progression of a *Helicobacter pylori* infection.

HIV^+ patients have IL-12 deficiency, while disease progression has been correlated with a Th2 shift. Progression of HIV infection is also characterized by increased cortisol secretion in both the early and late stages of the disease. Thus, increased glucocorticoid production, probably triggered by the chronic infection, was recently proposed to contribute to HIV progression.[41] In another recent study, Kino and colleagues found that one of the HIV-1 accessory proteins, Vpr, acts as a potent coactivator of the host glucocorticoid receptor rendering lymphoid cells hyperresponsive to GCs.[42] The extracellular Vpr also enhances the suppressive actions of the ligand-activated glucocorticoid receptor on IL-12 secretion by human monocytes/macrophages.[43] Through this effect, Vpr may contribute to the suppression of innate and cellular immunities of HIV-1–infected individuals and AIDS patients. Thus, on the one hand, stress hormones suppress Th1 and cellular immunity responses, while, on the other hand, retroviruses may increase the sensitivity of lymphoid cells to the suppressive effects of GCs.

In a recent study, an association was demonstrated between stress and the susceptibility to common cold among 394 persons who had been intentionally exposed to five different upper respiratory viruses. Psychological stress was found to be associated in a dose-dependent manner with an increased risk of acute infectious respiratory illness, and this risk was attributed to increased rates of infection rather than to an increased frequency of symptoms after infection.[44] Thus, stress hormones, through their selective inhibition of cellular immunity, may play substantial roles in the increased risk of an individual to acute respiratory infections caused by common cold viruses. In addition, stress hormones–induced Th2 can compromise the host's cellular immune response and trigger herpes simplex viral reactivation.[45]

Atopy/Allergy

Allergic diseases, such as asthma, seasonal and perennial allergic rhinitis, eczema, and IgE-mediated food allergy, are characterized by dominant Th2 responses—an overproduction of IL-4, IL-5, IL-9, and IL-13, histamine and a shift to IgE production.[46,47] Interestingly, elevations in IL-13 appear to be more associated with asthma than with atopy. An impaired IL-12 production coupled to an overproduction of IL-13 by alveolar macrophages may underlie to a great extent the Th2-biased response in asthma.[24,47] The effects of stress and GCs on atopic/allergic reactions are complex, at multiple levels, and can be in either direction.[4,48,49] Stress episodes preceding the development of the disease through induction of the Th2-potential may increase the susceptibility of the individual.[49] When the disease is already established, stress may induce a Th2 shift and also can activate the CRH–mast cell–histamine axis

(see above) and, thus may facilitate or sustain atopic reactions; however, these effects can be antagonized by the effects of stress hormones on the mast cell.[4] GCs and CAs (through β_2-adrenergic receptors [ARs]) suppress the release of histamine by mast cells, thus abolishing its pro-inflammatory, allergic, and bronchoconstrictor effects. Consequently, reduced levels of epinephrine and cortisol in the very early morning could contribute to nocturnal wheezing and have been linked to high circulating histamine levels in asthmatics.[50] This may also explain the beneficial effect of GCs and β_2-agonists in asthma. It is noteworthy that infusion of high doses of adrenaline, however, causes a rise in circulating histamine levels that may be due to an α-adrenergic-mediated increase in mediator release (cf. Ref. 50). Thus, severe acute stress associated with high EPI concentrations and/or high local secretion of CRH could lead to mast cell degranulation. As a result, a substantial amount of histamine could be released, which consequently would not antagonize, but rather amplify the Th2 shift through H2 receptors, while in parallel, by acting on H1 receptors, it could initiate a new episode or exacerbate a chronic allergic condition.

GCs alone or in combination with β_2-AR-agonists are broadly used in the treatment of atopic reactions, and particularly asthma. *In vivo*, *ex vivo*, and *in vitro* exposure to GCs and β_2-agonists result in a reduction of IL-12 production, which persists at least several days.[12,14,51] Thus, glucocorticoid and/or β_2-AR-agonist therapy is likely to reduce the capacity of APC to produce IL-12, to greatly suppress type 2 cytokine synthesis in activated, but not resting T cells, and to abolish eosinophilia.[14] If, however, resting, (cytokine-uncommitted) T cells are subsequently activated by APCs preexposed to GCs and/or β_2-AR agonists, enhanced IL-4 production, but limited IFN-γ synthesis, could be induced.[14] Thus, while in the short term, the effect of GCs and β_2-AR agonists may be beneficial, their long-term effects might be to sustain the increased vulnerability of the patient to the allergic condition. This is further substantiated by the observations that both GCs and β_2-AR agonists potentiate the IgE production *in vitro* and *in vivo*.[52,53]

Th1-Related Autoimmunity

Several autoimmune diseases are characterized by common alterations of the Th1 versus Th2 and pro- versus anti-inflammatory cytokine balance. In rheumatoid arthritis (RA), multiple sclerosis (MS), type 1 diabetes mellitus, and autoimmune thyroid disease (ATD) the balance is skewed toward Th1 and an excess of IL-12 and TNFα production, whereas Th2 activity and the production of IL-10 appear to be deficient. This appears to be a critical factor that determines the proliferation and differentiation of Th1-related autoreactive cellular immune responses in these disorders.[54] A hypoactive stress system may facilitate or sustain the Th1 shift in Th1-mediated autoimmunity.[4,55,56] Animal studies and certain clinical observations support this hypothesis. Thus, Fischer rats, which have a hyperactive stress system, are extremely resistant to experimental induction of Th1-mediated autoimmune states, including collagen- and adjuvant-induced arthritis and experimental allergic encephalomyelitis (EAE). Conversely, Lewis rats, which exhibit a hypoactive stress system, are extremely prone to develop the abovementioned experimentally induced Th1-mediated disease models.[57,58] Recent studies suggest that suboptimal production of cortisol is involved in the onset and/or progression of RA.[6,59,60] Patients with RA have "inappropriately normal" or low cortisol and CA levels in the setting of severe,

chronic inflammation, characterized by increased production of TNFα, IL-1, and IL-6. This may actually facilitate or sustain the pro-inflammatory shift in this disease. Whether this abnormality is primary or secondary has not been established.[59] Clinical observations also indicate that RA and MS frequently remit during pregnancy but exacerbate, or have their onset, in the postpartum period. Recent evidence suggests that a cortisol-, NE-, and 1,25-dihydroxyvitamin D3–induced inhibition and subsequent rebound of IL-12 and TNFα production may represent a major mechanism by which pregnancy and postpartum alter the course of or susceptibility to RA and MS.[9]

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