Inhibition of Th1 Immune Response by Glucocorticoids: Dexamethasone Selectively Inhibits IL-12-Induced Stat4 Phosphorylation in T Lymphocytes

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Inhibition of Th1 Immune Response by Glucocorticoids: Dexamethasone Selectively Inhibits IL-12-Induced Stat4 Phosphorylation in T Lymphocytes

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Glucocorticoids are widely used in the therapy of inflammatory, autoimmune, and allergic diseases. As the end-effectors of the hypothalamic-pituitary-adrenal axis, endogenous glucocorticoids also play an important role in suppressing innate and cellular immune responses. Previous studies have indicated that glucocorticoids inhibit Th1 and enhance Th2 cytokine secretion. IL-12 promotes Th1 cell-mediated immunity, while IL-4 stimulates Th2 humoral-mediated immunity. Here, we examined the regulatory effect of glucocorticoids on key elements of IL-12 and IL-4 signaling. We first investigated the effect of dexamethasone on IL-12-inducible genes and showed that dexamethasone inhibited IL-12-induced IFN-γ secretion and IFN regulatory factor-1 expression in both NK and T cells. This occurred even though the level of expression of IL-12 receptors and IL-12-induced Janus kinase phosphorylation remained unaltered. However, dexamethasone markedly inhibited IL-12-induced phosphorylation of Stat4 without altering its expression. This was specific, as IL-4-induced Stat6 phosphorylation was not affected, and mediated by the glucocorticoid receptor, as it was antagonized by the glucocorticoid receptor antagonist RU486. Moreover, transfection experiments showed that dexamethasone reduced responsiveness to IL-12 through the inhibition of Stat4-dependent IFN regulatory factor-1 promoter activity. We conclude that blocking IL-12-induced Stat4 phosphorylation, without altering IL-4-induced Stat6 phosphorylation, appears to be a new suppressive action of glucocorticoids on the Th1 cellular immune response and may help explain the glucocorticoid-induced shift toward the Th2 humoral immune response. The Journal of Immunology, 2000, 164: 1768–1774.

Glucocorticoids are widely used in the therapy of inflammatory, autoimmune, and allergic diseases. As the end-effectors of the hypothalamic-pituitary-adrenal (HPA) axis, endogenous glucocorticoids also play an important role in restraining the cellular immune response in several experimental inflammatory diseases in rats and mice (2, 3). Although glucocorticoids generally suppress innate immunity, their action on the cellular and humoral immune responses is more complex (4). Thus, the cellular immune response (delayed-type hypersensitivity) is strongly suppressed by glucocorticoids, whereas the humoral or allergic immune response is poorly inhibited or even enhanced (5–7). This is accompanied by a glucocorticoid-induced shift from Th1 to Th2 cytokine secretion (8–11). Indeed, pre-exposure of CD4+ lymphocytes to glucocorticoids increased the secretion of Th2-type cytokines, such as IL-4, IL-13, and IL-10, while it suppressed the secretion of Th1-type cytokines, such as IFN-γ and TNF-α (9). Similarly, glucocorticoids caused a marked reduction of IL-12 secretion by human monocytes and, hence, a decreased capacity to produce IFN-γ and an increased ability to induce IL-4 secretion by T cells (10).

The differentiation of naive CD4+ T cells into Th1 and Th2 cell types is influenced by cytokines produced early in response to the Ag triggering the immune response (12, 13). Specifically, IL-12 promotes Th1 cell differentiation, which leads to cell-mediated immunity, while IL-4 promotes Th2 cell differentiation, which drives allergic and humoral-mediated immunity. The Th1 and Th2 immune responses in large measure depend upon the activation of transcription factors Stat4 and Stat6, respectively (14). Stat4 knockout mice have a deficient cellular immune response, while Stat6 knockout mice have an impaired humoral immune response (15–18).

Understanding the regulatory effects of glucocorticoids on cytokine signaling would help to further clarify how these hormones influence Th1 cellular and Th2 humoral immune responses. Recently, it was reported that glucocorticoids suppressed the Th1 immune response by inhibiting the responsiveness of activated PBMC to IL-12, through down-regulation of the IL-12R β1- and β2-chain expression (19). Here, we report that glucocorticoids decrease IL-12 responsiveness through another mechanism, namely inhibition of Stat4 phosphorylation. This novel mechanism contributes to the immunosuppressive action of glucocorticoids on the Th1 cellular immune response and the associated shift toward the Th2 humoral immune response.
Materials and Methods

Cytokines, Abs, and cells

The following reagents were purchased: recombinant human IL-12 and IL-4 (R&D Systems, Minneapolis, MN), anti-phosphotyrosine Ab (4G10) (Upstate Biotechnology, Lake Placid, NY), polyclonal rabbit anti-Stat4 and anti-Stat6 Ab (Santa Cruz Biotechnology, Santa Cruz, CA), and polyclonal rabbit anti-Jak2, anti-Jak1, and anti-Tyk2 Ab (Upstate Biotechnology). Polyclonal rabbit anti-Jak3 and anti-Stat5a Abs were produced as previously described by this laboratory (20). Human IL-2 was provided by Dr. C. Reynolds (National Cancer Institute, Frederick, MD). NK3.3 were provided by Dr. J. Kornbluth (Arkansas Cancer Research Center, Little Rock, AR). NIH3T3 were provided by the American Type Culture Collection (Manassas, VA). PBMC from healthy donors were isolated by Ficoll-Paque gradient centrifugation, activated with PHA (2 µg/ml) for 72 h and cultured for an additional day in the presence of IL-2 (40 IU/ml), as described previously (21, 22). Cell viability, as determined by trypan blue exclusion, thymidine incorporation, and FACS (annexin V/PI) analysis (Trevigen, Gaithersburg, MD), was not affected by dexamethasone treatment.

IFN-γ ELISA

NK3.3 cells and T lymphocytes (5 × 10^6/ml) were rested in 1% FCS medium for 4 h, pretreated with 10^{-7} M of dexamethasone for various times, and then stimulated with IL-12 (20 ng/ml) for 10 h. The cell cultures were centrifuged, and the supernatant was removed and stored at -20°C. IFN-γ was measured using a specific immunosassay (R&D Systems) according to the manufacturer’s instructions.

RNase protection assay

NK3.3 cells and T lymphocytes were rested for 4 h, pretreated with dexamethasone at 10^{-7} M for various times, and then stimulated with IL-12 (20 ng/ml) for 4 h. RNA extraction was performed (RNAgent; Promega, Madison, WI), and mRNA expression was evaluated by RNase protection. RNase protection assay was performed as follows: 32P-labeled RNA probes were synthesized using SP6 RNA polymerase or T7 RNA polymerase for the IFN regulatory factor (IRF)-1 probe and the multiprobe template set (Riboquant; PharMingen, San Diego, CA). DNA was digested with DNase I (Boehringer Mannheim, Indianapolis, IN), and RNA probes were extracted with phenol/chloroform and precipitated with ethanol. Labeled RNA probes were hybridized overnight with target RNA (5 µg) at 56°C and were digested with T1 RNase (Life Technologies, Gaithersburg, MD). The protected mRNA fragment was extracted with phenol and chloroform, precipitated with ethanol, resolved on a 6% denaturing polyacrylamide gel, and subjected to autoradiography. Gene transcripts were identified by the length of the protected fragments. Equal loading of RNA was estimated from the amounts of protected fragments of two housekeeping genes, L32 and GAPDH.

Immunoprecipitation and immunoblotting

NK3.3 cells and T lymphocytes were pretreated with different concentrations of dexamethasone for various times, resuspended in 1 ml of serum-free medium (2 × 10^6 NK3.3 cells, 5 × 10^6 T cells), and stimulated with either IL-12 (20 ng/ml) or IL-4 (20 ng/ml). Following stimulation, cells were washed once in PBS and lysed on ice in a buffer containing 0.5% Triton X-100, 50 mM Tris-HCl, pH 7.5, 300 mM NaCl, 2 mM EDTA, 200 µM NaVO_4, 10 µg/ml aprotinin, 10 µg/ml leupeptin, and 2.5 mM p-nitrophenyl p-guanidinobenzoate on ice for 30 min. Immunoprecipitation with anti-Stat or Jak Abs and subsequent SDS-PAGE were performed as described previously (21, 22). Cell viability, as determined by trypan blue exclusion, thymidine incorporation, and FACS (annexin V/PI) analysis (Trevigen, Gaithersburg, MD), was not affected by dexamethasone treatment.

Transfection experiments

NIH3T3 cells were seeded in six-well plates (1.8 × 10^4 per well). Eighteen hours later, the cells were transfected, using lipofectamine (Life Technologies), according to the manufacturer’s protocol. The cells were transfected for 8 h with the following plasmids: pκGAS-luciferase (kindly provided by Dr. Richard Pine, Public Health Research Institute, New York, NY) (0.2 µg), CMV-β-galactosidase (0.2 µg), and, as indicated, with pEF-BOS-IL-12R β1 (0.2 µg), pEF-BOS-IL-12R β2 (kindly provided by Dr. Uli Gubler, Roche Nutley, NJ) (0.6 µg), pCDNA3-Stat4 (kindly provided by Dr. J Ihle, St. Jude Children’s Hospital, Memphis, TN) (0.2 µg), and pCDNA3-Tyk2 (0.2 µg). The transfected cells were pretreated with 10^{-7} M dexamethasone (6 h), washed once, and then stimulated with IL-12 (10 ng/ml), where indicated, for another 6 h. Cells were lysed, and luciferase and β-galactosidase activities were determined using the Dual-Light Kit according to manufacturer’s instruction (Tropix, Bedford, MA). The results were normalized for each sample by dividing luciferase activity by β-galactosidase activity. The results are representative of three independent experiments performed in triplicate.

Results

Dexamethasone inhibits IL-12-induced IFN-γ and IRF-1 expression

IL-12-dependent production of IFN-γ is an important step in the generation of a cell-mediated immune response. As shown in Fig. 1A, IL-12 induced IFN-γ secretion in NK3.3 cells (lanes 1 and 2),
and dexamethasone pretreatment (10−7 M) was found to block this induction (lanes 3 and 4). The inhibition of IL-12-induced IFN-γ secretion was observed after 6 h of dexamethasone pretreatment and was maximal after 18 h. To better characterize the kinetics of inhibition, we analyzed the levels of IFN-γ mRNA expression. As is evident in Fig. 1B, stimulation of NK3.3 with IL-12 for 4 h resulted in increased IFN-γ expression (lanes 1 and 2). Notably, 6 h and 18 h of dexamethasone pretreatment nearly completely blocked the IL-12-induced IFN-γ expression in NK3.3 cells (lanes 3 and 4). This result was also confirmed in T lymphocytes (data not shown).

To determine whether this was a general effect or limited to the IFN-γ gene, we next analyzed the expression of another gene important for Th1 differentiation, IRF-1 (Fig. 1C). We and others have recently reported that IL-12 up-regulates IRF-1 expression (lanes 1 and 2) (23, 24). Interestingly, 6 and 18 h of pretreatment with dexamethasone substantially reduced IRF-1 expression (lanes 3 and 4). Equal amounts of GAPDH and L32 transcripts confirmed that equal amounts of RNA were used (Fig. 1, B and C).

**Dexamethasone does not alter the level of expression of IL-12 receptors**

To understand the possible mechanism of the decreased responsiveness to IL-12 by dexamethasone, we first examined whether dexamethasone influenced IL-12R (β1- and β2-chains) expression in NK 3.3 cells. Dexamethasone was previously shown to decrease IL-12 receptor expression in peripheral blood mononuclear cells stimulated with immobilized anti-CD3 for 3 days (19). We evaluated the IL-12R (β1- and β2-chains) expression after shorter incubations with dexamethasone (Fig. 2A). Treatment with dexamethasone from 1 to 18 h did not alter the levels of these cytokine receptors (lanes 1–6). We also analyzed IL-4R (α- and the common γ-chains) expression; it remained unchanged by dexamethasone treatment (Fig. 2B, lanes 1–6). These results underscore the specific decrease in expression of IFN-γ and IRF-1. Equal amounts of GAPDH and L32 transcripts confirmed that equal amounts of target RNA was used. Similar results were also obtained in T lymphocytes (data not shown).

**Dexamethasone does not inhibit IL-12 or IL-4-induced Jak phosphorylation.** NK3.3 cells were untreated (lanes 1 and 2) or treated with dexamethasone (10−7 M) at indicated times (lanes 3 and 4). Cells were stimulated with IL-12 (20 ng/ml) for 20 min (lanes 2–4), lysed, and immunoprecipitated with anti-Jak2 (upper panel) or anti-Tyk2 (lower panel) and then subjected to immunoblotting with anti-phosphotyrosine (top) and anti-Jak2 or anti-Tyk2 (bottom). IL-4-induced Jak phosphorylation was also analyzed the effect of dexamethasone treatment on IL-4 signaling, namely activation of Jak1 and Jak3. As shown in Fig. 3A, IL-4 induced phosphorylation of Jak2 and Tyk2 within 20 min (lane 2) (22). However, preincubation of the cells with dexamethasone (10−7 M) for 6 or 18 h had no effect on the phosphorylation of Jak2 and Tyk2 (Fig. 3A, lanes 3 and 4). The levels of Jak1 and Tyk2 protein were also unchanged, as determined by reblotting with Abs to Jak2 and Tyk2. Thus, neither the phosphorylation nor the protein expression of Jak2 and Tyk2 were modulated by dexamethasone treatment. We also analyzed the effect of dexamethasone treatment on IL-4 signaling, namely activation of Jak1 and Jak3. As shown in Fig. 3B, IL-4 induced phosphorylation of these kinases within 20 min (lane 2). Preincubation of the cells with dexamethasone (10−7 M) for 6 or 18 h had no effect on the phosphorylation of these kinases (Fig. 3B, lanes 3 and 4). The levels of Jak1 and Jak3 protein were also unchanged, as determined by reblotting with the relevant Abs.

**Dexamethasone inhibits IL-12-induced phosphorylation of Stat4**

Once Jaks are activated, they phosphorylate cytokine receptors allowing the recruitment and phosphorylation of Stat proteins, which...
in turn dimerize, translocate to the nucleus, and activate gene transcription (14). IL-12-dependent regulation of the IFN-γ and IRF-1 genes is thought to be mediated by Stat4. Therefore, we next examined whether dexamethasone could affect IL-12-induced Stat4 phosphorylation. As previously shown, stimulation of NK3.3 cells with IL-12 (20 ng/ml) resulted in Stat4 phosphorylation (Fig. 4; A, lanes 2 and 5; B and C, lane 2; C, lanes 2 and 5) (21). Interestingly, pretreatment with dexamethasone (10^{-7} M) inhibited IL-12-induced Stat4 phosphorylation (Fig. 4, A, lanes 3–7). This was confirmed when a more detailed time course of inhibition was analyzed (Fig. 4B, lanes 3–6); inhibition was observed as early as 2 h. Moreover, this inhibition was evident at doses of dexamethasone varying from 10^{-10} to 10^{-7} M (Fig. 4C, lanes 3–6). This effect was mediated by the glucocorticoid receptor, as 10^{-7} M RU486, a specific glucocorticoid receptor antagonist, abrogated the inhibition of Stat4 phosphorylation (Fig. 4D, lane 3 vs 6). However, Stat4 protein levels were not altered by dexamethasone treatment; reblotting with anti-Stat4 Ab showed that its expression was unchanged (Fig. 4, A–D, lower panels).

We have previously reported that both IL-12 and IFN-α induce Stat4 phosphorylation (25). To assess whether the inhibition of Stat4 phosphorylation was specific to IL-12, we examined the effect of dexamethasone pretreatment on IFN-α-induced Stat4 phosphorylation and observed that this was also inhibited by dexamethasone pretreatment (data not shown). This was consistent with our findings that early events in IL-12 signaling (i.e., Jak activation and receptor expression) were not affected by dexamethasone.

To ascertain that dexamethasone inhibition of Stat4 phosphorylation was of general importance, we sought to determine whether it also occurred in normal human T lymphocytes. As shown in Fig.
Dexamethasone pretreatment decreases IL-12-induced IRF-1 promoter activity. NIH3T3 cells were transiently transfected with an IRF-1 promoter-reporter construct and CDNA encoding for IL-12R subunits, Stat4 and Tyk2, as indicated. The cells were cultured with or without dexamethasone (10^{-7} M) and then stimulated with IL-12 (10 ng/ml) for 6 h. Cells were lysed and analyzed for luciferase activity normalized by β-galactosidase activity. The results are representative of three independent experiments performed in triplicate.

4E, IL-12 induced Stat4 phosphorylation in activated T lymphocytes within 20 min (lane 2). Consistent with the results in the NK cell line, dexamethasone pretreatment was also found to block the IL-12-induced Stat4 phosphorylation in T cells (lanes 3 and 4).

Th2 immune responses are poorly inhibited or even enhanced by glucocorticoids (5–11). In fact, glucocorticoids increase the synthesis of Ig E by IL-4-stimulated human lymphocytes (5–7). It would then be expected that IL-4-dependent phosphorylation of Stat6 should be resistant to dexamethasone. Therefore, we next tested the specificity of the inhibition of IL-12-induced Stat4 phosphorylation in T lymphocytes, examining the effect of dexamethasone on IL-4-induced Stat6 phosphorylation. As expected, IL-4 induced Stat6 phosphorylation (Fig. 4E, lane 6). In contrast to Stat4, dexamethasone pretreatment did not affect IL-4-induced Stat6 phosphorylation (Fig. 4E, lane 7 and 8).

Dexamethasone pretreatment decreases IL-12-induced IRF-1 promoter activity.

To further characterize the specific inhibition of Stat4 activation by dexamethasone, we next examined its effect in a heterologous system using transfected NIH3T3 cells. In this model, we and others have previously shown that the IRF-1 induction by IL-12 is dependent upon Stat4 (23, 24). This system allowed us to dissect the elements involved in the IL-12 signaling pathway and to study the effect of dexamethasone.

First, IL-12 enhanced IRF-1 promoter activity (Fig. 5, lane 7); this induction was Stat4 dependent because mock-transfected cells did not show any luciferase activity after IL-12 stimulation in the absence of Stat4 (Fig. 5, lane 3). Dexamethasone pretreatment alone had no effect on IRF-1 promoter activity in mock- and Stat4-transfected cells (Fig. 5, lanes 2 and 6). However, IL-12-induced IRF-1 promoter activity was decreased after dexamethasone pretreatment (Fig. 5, lane 8).

We next examined if this decreased IRF-1 promoter activity by dexamethasone required signaling by the IL-12 receptor. Stat activation can be simply induced by overexpressing Jak kinases. Therefore, we analyzed whether this receptor-independent means of Stat4 activation was also inhibited by dexamethasone. Over-expression of Tyk2 was accompanied by a significant increased activity of the IRF-1 promoter (Fig. 5, lane 9). Similarly, dexamethasone pretreatment led to a decreased IRF-1 promoter activity (Fig. 5, lane 10). This suggested that the inhibition of Stat4 activation by dexamethasone occurred through a IL-12R-independent mechanism.

Discussion

IL-12 secretion by activated monocyte/macrophages and dendritic cells is a critical step in the development of cell-mediated immune responses. IL-12 causes NK and T cells to secrete IFN-γ and enhances the cytolytic functions of activated NK and CD8 T cells (26). IL-12 exerts its effect by inducing tyrosine phosphorylation of Jak2 and Tyk2, which in turn phosphorylate the transcription factor Stat4 (21, 22), responsible for the regulation of a number of key IL-12-inducible genes (23, 24, 26). In this study, we report that dexamethasone pretreatment inhibits Stat4 phosphorylation without altering other early steps of IL-12 signaling, namely the expression of IL-12R β1- and β2-chains and IL-12-induced Tyk2 and Jak2 phosphorylation. Simultaneously, IL-4-induced Stat6 phosphorylation remained unchanged. Thus, this study suggests that glucocorticoids, by preventing Stat4 phosphorylation, decrease IL-12 responsiveness, diminishing the induction of genes such as those of IFN-γ and IRF-1.

Several studies have shown the opposing effect of glucocorticoids on the cellular and humoral immune responses (4–7). One clear mechanism is their action on cytokine secretion; glucocorticoids inhibit the secretion of Th1 and enhance the production of Th2 cytokines (8–11). Stat4 knockout mice have an impaired Th1 immune response with decreased Th1 cytokine and enhanced Th2 cytokine secretion (16). IRF-1 knockout mice also have a deficient Th1 immune response (27). Indeed, we and others have shown that IL-12 induces IRF-1 expression through Stat4 activation (23, 24). Previous reports have suggested that glucocorticoids suppress the Th1 immune response by inhibiting IL-12 secretion by monocytes/macrophages and dendritic cells (9–11). Here, we show that glucocorticoids decrease the ability of T cells to respond to IL-12. Thus, glucocorticoids appear to block Th1 lymphocyte development by both inhibiting IL-12 secretion and Stat4-mediated IL-12 signaling. In addition, the differential action of glucocorticoids on IL-12 and IL-4 signaling might explain the observed shift of the immune response toward the Th2 humoral immune response.

A previous study reported a decreased IL-12 responsiveness by dexamethasone via down-regulation of IL-12R β1- and β2-chain expression (19). However, the authors analyzed only the long-term effect of dexamethasone on activated lymphocytes and the down-regulation of IL-12 receptors could only be shown after a 3-day culture of anti-CD3/TCR-stimulated T cells in the presence of dexamethasone. In contrast, in our study, decreased IL-12-induced Stat4 phosphorylation was observed as early as 2 h after dexamethasone pretreatment, at a time when IL-12 receptor expression was unaffected. Although these two phenomena are distinct, they
might coexist and together contribute to decreased IL-12 responsiveness in T lymphocytes. Indeed, because the down-regulation of STAT4 activation results in decreased IFN-γ secretion (Fig. 1) and IFN-γ has been demonstrated to increase expression of IL-12R β2 (28), the two observations may be directly linked.

Glucocorticoids could inhibit Stat4 phosphorylation through a number of potential mechanisms, several of which have already been identified. These include the modulation of expression or activity of different factors that play a role in the attenuation of cytokine signaling, such as phosphatases, suppressors of cytokine signaling proteins (SOCS and cytokine inhibitor Src homology 2-containing protein (CIS)), or protein inhibitors of activated Stats (PIAS). Finally, glucocorticoids might inhibit the expression of some factor that is required for the activation of Stat4. A potential negative regulation of a positive acting factor may also be envisaged, although such a factor as not been described yet.

Src homology 2 domain-containing tyrosine phosphatases like Src homology protein (SHIP)-1 and SHP-2 can attenuate cytokine and hormone signaling (29–34). Glucocorticoids might inhibit cytokine signaling by inducing or activating these or other tyrosine phosphatases (29). Presently, we cannot determine whether SHP-1 or SHP-2 associate with IL-12R β2, the subunit containing several tyrosine residues, and whether glucocorticoids affect this association, as no reagents that immunoprecipitate IL-12R β2 are currently available. However, this mechanism of action seems unlikely, granted that the inhibition of Stat4 phosphorylation by dexamethasone appears not to be IL-12R dependent. Furthermore, the lack of inhibition of IL-4-induced Stat6 phosphorylation in T cells suggests that this phosphatase may be specific for Stat4. While it is well recognized that Stat phosphorylation is specific, specific Stat phosphatases have yet to be identified.

Another alternative explanation would be the regulation of different members of the family of SOCS (also known as JAK-binding protein or STAT-induced STAT inhibitor) (35–37). For instance, IL-10 suppresses IFN-α and IFN-γ-dependent Stat1 phosphorylation, and this is accompanied by the up-regulation of SOCS-3 (38). However, the inhibition of IL-12-induced Stat4 phosphorylation without altering Jak activation argues against an involvement of SOCS; SOCS-1 is thought to bind to Jak5, inhibiting their activity (35–37). Nevertheless, the first identified inhibitor of Stat signaling, CIS, was reported not to bind to Jak5 but rather to interact with phosphotyrosine residues in the erythropoietin receptor and IL-3 βc, thereby preventing Stat phosphorylation (37, 39). Thus, CIS might be a good candidate for a steroid inducible inhibitor of Stat4 phosphorylation.

Finally, the recently described PIAS1 and -3 interact with and block Stat1 and -3 DNA-binding activities but do not alter Stat phosphorylation (40, 41). No Stat4-specific PIAS family member has been characterized as yet; moreover, PIASs without altering Stat phosphorylation may not play a role in this condition. Further studies will be needed to clarify the underlying mechanism responsible for the inhibitory action of glucocorticoids on Stat4 phosphorylation.

Activation of the HPA axis by proinflammatory cytokines results in the release of endogenous glucocorticoids, which in turn suppress innate and specific immune responses (3). The inflammatory response of streptococcus cell wall-induced arthritis in susceptible Lewis and resistant Fischer rats is inversely related to the magnitude of their HPA axis response to inflammatory mediators. Moreover, the glucocorticoid receptor antagonist RU486 renders Fischer rats susceptible to arthritis (42, 43). Also, adrenalectomy in Lewis rats with experimental allergic encephalomyelitis, a Th1 cell-mediated autoimmune disease, leads to a chronically active disease, while substitutional replacement of glucocorticoids induces recovery from the disease (44, 45). Thus, endogenous glucocorticoids might decrease susceptibility to Th1-type immune diseases by lowering T cell responsiveness to IL-12.

Glucocorticoids have been used for 50 years as potent immunosuppressants in the therapy of Th1 autoimmune and autoimmune diseases. Glucocorticoids render treated patients immunocompromised, with an increased susceptibility to intracellular infections. The ability of glucocorticoids to specifically suppress Th1 cellular immunity is well described but poorly understood. Our study suggests that glucocorticoid-mediated inhibition of Stat4 phosphorylation may represent a major underlying mechanism of the specific suppression of cellular immunity by glucocorticoids.

References


