

Corticosteroid modulation of human, antigen-specific Th1 and Th2 responses

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Corticosteroids are potent antiinflammatory agents that modulate human T-lymphocyte responses. Controversy remains as to their possible differential effects on Th1 and Th2 subsets. This study explores the kinetics and efficacy of these agents in human, antigen-driven peripheral blood mononuclear cells (PBMCs) and in nontransformed, antigen-specific Th1 and Th2 clones. Ragweed- and tetanus toxoid-driven proliferative responses of PBMCs from dually sensitized individuals were downregulated equally by dexamethasone (inhibitory concentration of 50% [IC₅₀] = 3×10^{-9} and 2×10^{-9} mol/L, respectively). The addition of dexamethasone as late as 36 hours after ragweed stimulation still resulted in more than 75% inhibition of the proliferative response, whereas the efficacy of dexamethasone was less than 50% when added 24 hours after tetanus toxoid stimulation. Antigen-induced gene expression for proinflammatory cytokines (IL-4, IL-5, IL-13, and interferon- γ) from PBMCs was also downregulated by dexamethasone. Proliferation of antigen-specific Th1 and Th2 clones was inhibited by several corticosteroids (hydrocortisone < budesonide < dexamethasone; IC₅₀ = 10^{-6} to 10^{-8} mol/L), but no significant differences between Th1 and Th2 clones were evident. IC₅₀ values in the clones were 10-fold greater than in PBMCs. Gene expression and protein secretion for IL-4, IL-13, and interferon- γ were downregulated in a concentration-dependent manner by each of the corticosteroids in Th1 and Th2 clones. These data suggest that Th1 and Th2 responses are equally affected by corticosteroids. (*J Allergy Clin Immunol* 1997; 100:400-7.)

Key words: Human, Th1/Th2, IL-4, IL-13, interferon- γ , corticosteroids

Corticosteroids are potent antiinflammatory agents widely used in the management of allergic disease.¹ Corticosteroid administration produces multiple immunomodulatory effects, including downregulation of cytokine production by T helper lymphocytes.²⁻⁹ One mechanism by which corticosteroids may alter T-cell cytokine expression involves translocation of the corticosteroid/

Abbreviations used

APCs:	Antigen-presenting cells
IC ₅₀ :	Inhibitory concentration of 50%
IFN:	Interferon
PBMCs:	Peripheral blood mononuclear cells
RT-PCR:	Reverse-transcription polymerase chain reaction
RW:	Ragweed pollen extract
TT:	Tetanus toxoid

corticosteroid receptor complex to the nucleus and subsequent induction of the I κ B α gene. The I κ B α protein binds the transcription factor NF- κ B in the cytoplasm, preventing its translocation to the nucleus and activation of proinflammatory cytokine gene expression.¹⁰⁻¹² This regulation of cytokine production modulates effector functions of T cells and thereby influences the host immune response.

On the basis of their patterns of cytokine secretion and effector functions, human CD4⁺ T cells may be divided into two subsets.¹³ Th1 cells produce IL-2 and interferon- γ (IFN- γ) and promote delayed-type hypersensitivity reactions. Th2 cells, important in atopy and asthma, secrete IL-4, IL-5, and IL-10. IL-13 is produced by both T helper cell subsets and may serve to exacerbate allergic inflammation.^{14, 15} IL-4 and IL-13 share certain functional properties; however, IL-13 is able to independently induce class switching and IgE secretion from human B cells.¹⁶ In addition, IL-13 enhances expression of CD23 and major histocompatibility complex class II and may act as a monocyte chemoattractant.¹⁷ Therefore reduction of IL-13 production should be a key component of antiinflammatory drug design. To date, no studies on the pharmacologic regulation of IL-13 have been published.

Corticosteroids have been hypothesized to exert differential effects on Th1 and Th2 cells; however, previous studies conducted with peripheral blood mononuclear cells (PBMCs) or T-cell lines have provided conflicting results.^{2-4, 18} We herein present the first comprehensive study of the effects of corticosteroids on proliferation and cytokine generation in antigen-stimulated human PBMCs and nontransformed, antigen-specific human Th1 and Th2 clones. We describe for the first time the effects of corticosteroids on antigen-induced IL-13 gene expression and secretion. Our data argue against signif-

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Supported by grants AI07290 and AI34002 of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and a Research Fellowship Award from the American Lung Association.

Received for publication Oct. 21, 1996; revised Mar. 18, 1997; accepted for publication May 6, 1997.

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icant differential regulation of Th1 and Th2 responses by corticosteroids.

METHODS

Selection of subjects

Subjects were allergic volunteers associated with the Johns Hopkins Asthma and Allergy Center who showed positive epicutaneous skin test responses to a 100,000 allergen unit (AU) stock of short ragweed extract (ALK Laboratories Inc., Milford, Conn.). All subjects had a history of upper and/or lower airway symptoms induced by ragweed. Subjects had received tetanus immunizations within the preceding 3 years and had not received any medications for the month preceding study; none of the subjects had undergone immunotherapy.

PBMC isolation and derivation of antigen-specific T-lymphocyte clones

Human PBMCs were isolated by gradient centrifugation on Ficoll-Paque (Pharmacia Inc., Piscataway, N.J.) and resuspended in RPMI (BioWhittaker, Walkersville, Md.) supplemented with 1% penicillin/streptomycin and 5% human AB serum (Gibco/BRL, Gaithersburg, Md.), as previously described.^{19,20} The cells were either used directly or irradiated for use as antigen-presenting cells (APCs). Platelet contamination of these preparations was less than 1%; viability determined by trypan blue exclusion was uniformly greater than or equal to 99%.

The antigen-specific T-cell clones used in this study were derived as previously described.²¹ Briefly, PBMCs from an asthmatic subject with epicutaneous skin test reactivity to short ragweed (*Ambrosia artemisiifolia*) and short ragweed-specific IgE equal to 1761 ng/ml, as determined by RAST, were cultured in the presence of short ragweed antigen (RW) at 10 μ g/ml. This primary culture was followed by successive, bi-weekly stimulations of the antigen-specific T cells with a major short ragweed antigen, Amb a 1, in the presence of autologous APCs. The resulting antigen-specific T-cell line was cloned and subcloned by using the limiting dilution technique. Proliferative responses restricted to Amb a 1 confirmed antigen specificity. All T-cell clones were CD3⁺CD4⁺CD8⁻CD45RO⁺ as determined by flow cytometry. Cytokine profiles were determined by both reverse-transcription polymerase chain reaction (RT-PCR) and ELISA for cytokines secreted into culture supernatants; on the basis of these data, phenotypic assignment to Th0, Th1, or Th2 was made.²¹

Proliferation assays

Proliferation assays were performed as previously described.^{19,21} Briefly, either 2×10^5 PBMCs or 2×10^4 clonal T cells with 1.5×10^5 APCs were cultured in the presence of antigen in 96-well flat-bottom plates. Antigens were used at concentrations previously determined to be optimal: 10 μ g/ml for ragweed and 0.1 IF/ml for tetanus toxoid (TT). Culture conditions were designated by the presence of varying concentrations of one of three corticosteroids: dexamethasone, budesonide, or hydrocortisone (Sigma Chemical Co., St. Louis, Mo.). For PBMC kinetics experiments, antigen was preincubated with the cells for the indicated times before addition of corticosteroids; for all other assays, antigen and corticosteroids were added simultaneously. Negative (media alone) and positive (antigen only) controls were performed with each culture. No exogenous cytokine was used in these assays. All conditions were performed in triplicate and incubated for 72 hours at 37°C with 5% CO₂. Each culture was pulsed with 1 μ Ci of tritiated

thymidine, incubated for an additional 20 hours, harvested onto glass fiber filters in a multichannel cell harvester (Cambridge Technologies Inc., Watertown, Mass.), and counted for 1 minute in an automated beta counter (Beckman Instruments Inc., Fullerton, Calif.). Viability in these cultures, as determined by trypan blue exclusion, remained uniformly greater than or equal to 99% in the presence of the corticosteroids.

Gene expression assays

Cytokine gene expression was determined as previously described.^{20,22} Briefly, either 5×10^6 PBMCs or 2×10^5 clonal T cells with 3×10^6 APCs were cultured in the absence and presence of antigen with or without corticosteroids. Antigen and corticosteroids were added simultaneously, and no exogenous cytokine was used. Ragweed was used at 10 μ g/ml; TT was used at 0.1 IF/ml. After a 12-hour incubation in polypropylene tubes, the cells were pelleted, washed, and subjected to RNA isolation by the RNeasy[®] technique, according to the manufacturer's instructions (Tel-Test Inc., Friendswood, Texas). Diethylpyrocarbonate-treated water without sodium dodecylsulfate was used for the final resuspension step, and RNA was stored at -80°C. Semiquantitative RT-PCR was performed with 5 mmol/L magnesium and oligo dT priming by using the Gene Amp kit (Perkin Elmer Cetus, Norwalk, Conn.) and cytokine-specific primer pairs designed in our laboratory and made at the DNA Core Facility of the Johns Hopkins University. All PCR products were visualized by ethidium bromide-stained gel electrophoresis and photographed.

Cytokine protein secretion assays

Cytokine protein secretion was assessed by ELISA with Cytoscreen Immunoassay kits (Biosource, Int., Camarillo, Calif.) according to the manufacturer's instructions, with World Health Organization standards provided by the company. Culture supernatants were collected after a 12-hour incubation and stored at -20°C until assayed. Dilutions of samples, when necessary, were performed in culture medium. All standards and samples were tested in duplicate. Most samples were used at two different dilutions and compared for internal consistency.

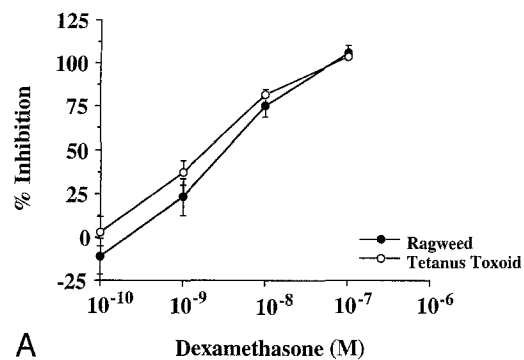
Statistical analysis

Mean and standard error values, as well as *t* test comparisons, were derived by using StatView (BrainPower, Inc., Calabasas, Calif.) on a Macintosh Classic computer. Probability (*p*) values are paired and one-tailed. Percent inhibition for each condition was calculated on the basis of inhibition relative to stimulated, drug-free mean counts, corrected in every case for background counts with media alone. IC₅₀ values represent the concentration of drug at 50% inhibition.

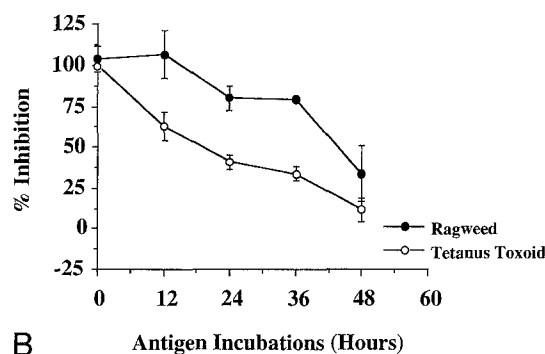
RESULTS

PBMC proliferation in the presence of corticosteroids

Fig. 1, A shows the proliferative responses of human PBMCs stimulated with RW or TT, each in the presence of dexamethasone. When added simultaneously with antigen, dexamethasone produced a clear concentration-dependent inhibition for both antigens (IC₅₀ = 3 nmol/L and 2 nmol/L for RW and TT, respectively); no significant differences between the antigens could be discerned. Fig. 1, B, shows the efficacy of dexamethasone 10⁻⁷ mol/L, added at various times after stimulation with



A



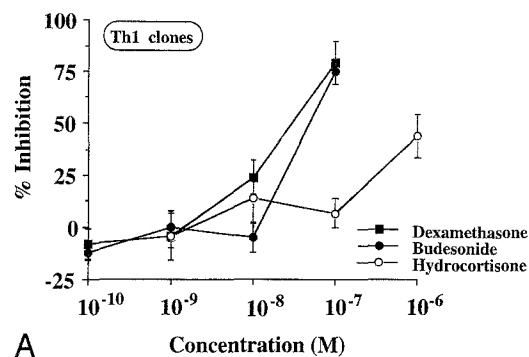
B

FIG. 1. Modulation of RW- and TT-stimulated PBMC proliferation by dexamethasone. **A**, Dose-response data are shown for simultaneous addition of antigen and steroid. Data are presented as percentage of inhibition $\pm$ SEM relative to stimulated, steroid-free cultures, subtracted for background with media alone. Background and stimulated mean counts per minute $\pm$ SEM were: 1323 ± 109 and 6120 ± 1848 for RW and 1482 ± 166 and $14,003 \pm 3229$ for TT. $N = 9$ individual experiments for RW and 7 for TT from six different subjects. **B**, Efficacy of 10^{-7} mol/L dexamethasone added at various times after stimulation of PBMC cultures with RW or TT is shown. Data are presented as percentage of inhibition $\pm$ SEM relative to stimulated, steroid-free cultures, subtracted for background with media alone at each time point. $N = 3$ individual experiments at each time point from three different subjects.

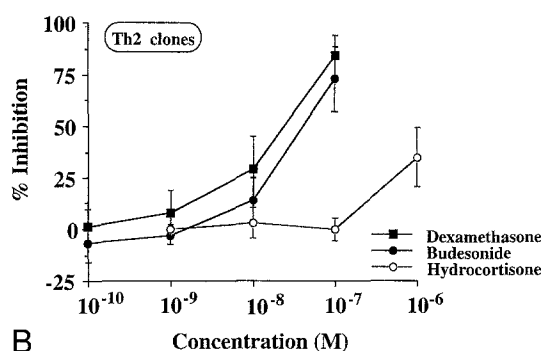
RW or TT, on antigen-driven proliferation. In the RW-driven system, dexamethasone continued to inhibit proliferation by more than 50% even when added 36 hours after antigen exposure. In the TT-driven system, however, the percent inhibition declined rapidly with increased antigen incubation time, such that significant differences in efficacy were evident at 12, 24, and 36 hours ($p = 0.03$, 0.02 , and 0.03 , respectively). Similar results were obtained with lower concentrations of dexamethasone (data not shown). Preincubating cells with dexamethasone before antigen stimulation did not significantly increase the inhibitory activity of dexamethasone (data not shown).

Th1 and Th2 clonal proliferation in the presence of corticosteroids

Fig. 2 shows the proliferative responses of Amb a 1-specific Th1 (Fig. 2, A) and Th2 (Fig. 2, B) clones in



A



B

FIG. 2. Modulation of antigen-driven Th1 and Th2 proliferation by corticosteroids. RW-specific T-cell clones were stimulated in the presence of various concentrations of each of three corticosteroids: dexamethasone, budesonide, and hydrocortisone. Data are presented as percentage of inhibition $\pm$ SEM relative to stimulated, steroid-free cultures, subtracted for background with media alone. Background and stimulated mean counts per minute $\pm$ SEM for Th1 clones were: 4450 ± 1659 and $80,145 \pm 34,522$ in dexamethasone assays; 2785 ± 1449 and $77,933 \pm 26,367$ in budesonide assays; and 1449 ± 652 and $58,516 \pm 29,298$ in hydrocortisone assays. Background and stimulated mean counts per minute $\pm$ SEM for Th2 clones were: 2523 ± 1913 and $45,201 \pm 14,653$ in dexamethasone assays; 3918 ± 2104 and $83,232 \pm 28,915$ in budesonide assays; and 2873 ± 1817 and $37,065 \pm 10,077$ in hydrocortisone assays. $N = 5$ individual experiments with Th1 clones and 4 individual experiments with Th2 clones.

the presence of three different steroids. In this system dexamethasone and budesonide showed strong and equivalent inhibition of both Th1 and Th2 cell proliferation at 10^{-7} mol/L; however, their efficacy diminished rapidly, and at 10^{-8} mol/L there was little effect. Hydrocortisone also affected Th1 and Th2 clones equally, but with less potency than dexamethasone or budesonide. In the Th1 clones, IC_{50} values were 30 nmol/L and 70 nmol/L for dexamethasone and budesonide, respectively, and greater than $1 \mu\text{mol/L}$ for hydrocortisone; in the Th2 cells, IC_{50} values were 20 nmol/L and 30 nmol/L for dexamethasone and budesonide, respectively, and again greater than $1 \mu\text{mol/L}$ for hydrocortisone. Clonal lymphocyte proliferation was 10-fold less responsive to dexamethasone than was proliferation in PBMC cultures.

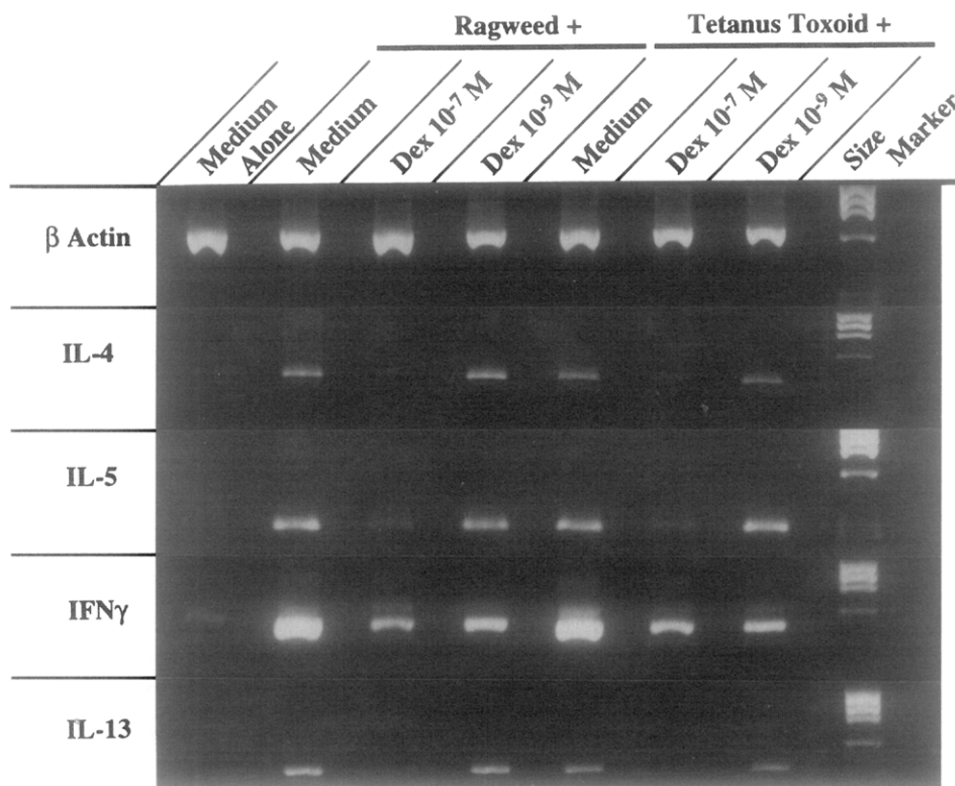


FIG. 3. Modulation of cytokine gene expression by dexamethasone in RW- and TT-stimulated PBMCs. Representative RT-PCR amplification products for IL-4, IL-5, IFN- γ , and IL-13 are shown for each of seven different PBMC culture conditions from a single experiment. Adequate normalization of RNA was confirmed by equivalent β -actin gene expression at subsaturating cycle number (row 1). The DNA size marker is shown in lane 8. $N = 3$ individual experiments in three different subjects. *Dex*, Dexamethasone.

Cytokine gene expression in PBMCs and T-cell clones in the presence of corticosteroids

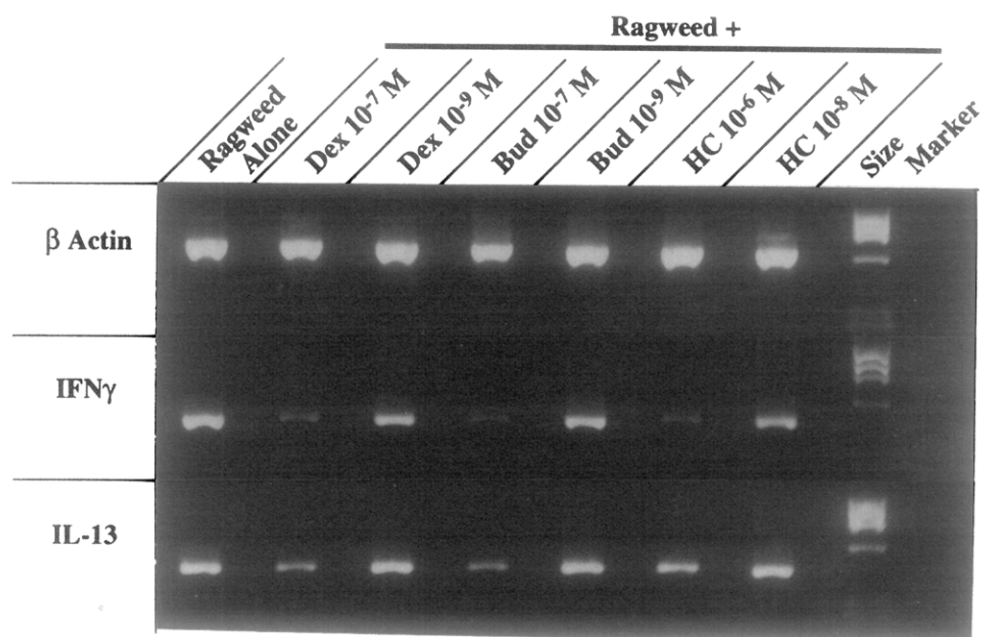
Fig. 3 shows the influence of high (10^{-7} mol/L) and low (10^{-9} mol/L) concentrations of dexamethasone on gene expression for IL-4, IL-5, IFN- γ , and IL-13 in PBMCs stimulated with either RW or TT. β -Actin- and cytokine-specific RT-PCR amplification products from one representative subject are shown; the same results were obtained in three separate experiments in three different subjects. Adequate normalization of RNA for semiquantitative analysis was confirmed by the equality of RT-PCR amplification products at subsaturating cycle number for β -actin gene expression (Fig. 3, top row). Unstimulated PBMCs expressed minimal message for proinflammatory cytokines (column 1). Expression of all four cytokines was strongly downregulated or eliminated in the presence of 10^{-7} mol/L dexamethasone (columns 3 and 6, respectively for RW and TT), as compared with positive controls (columns 2 and 5, respectively for RW and TT); 10^{-9} mol/L dexamethasone caused little or no inhibition of cytokine gene expression (columns 4 and 7, respectively, for RW and TT). This effect was similar for both RW and TT.

Fig. 4 shows the influence of high and low concentrations of three different corticosteroids on cytokine gene expression from Th1 and Th2 clones, respectively. β -Actin-

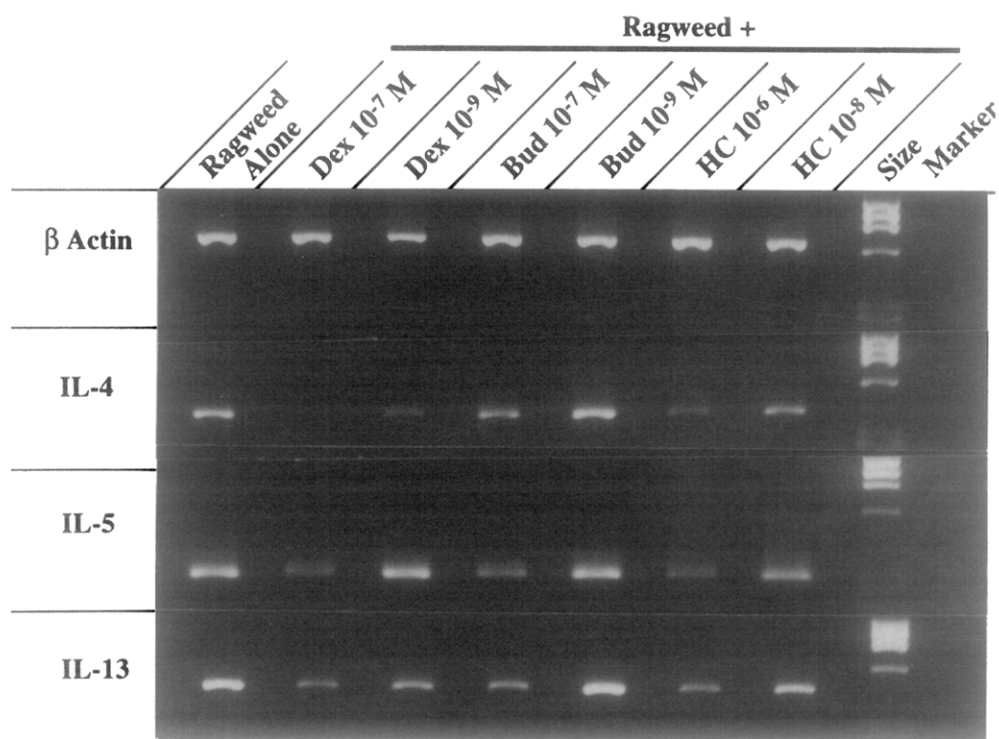
and cytokine-specific RT-PCR amplification products from one representative experiment are shown; the same results were obtained in three separate experiments. Adequate normalization of RNA for semiquantitative analysis was again confirmed by the equality of RT-PCR amplification products at subsaturating cycle number for β -actin gene expression (Fig. 4, top rows). Neither unstimulated T-cell clones nor stimulated irradiated APCs expressed message for proinflammatory cytokines (data not shown). Similar to the data from PBMCs, Th1 and Th2 clones each showed strong downregulation of gene expression for their respective cytokines when cultured with high concentrations of corticosteroids (columns 2, 4, and 6); little effect was observed with low concentrations of corticosteroids (columns 3, 5, and 7). IL-13 gene expression from both Th1 and Th2 clones was downregulated by high concentrations of corticosteroids, and differential efficacy between Th1 and Th2 clones was not evident.

Regulation of IL-4, IFN- γ , and IL-13 production from Th1 and Th2 clones by corticosteroids

Figs. 5 and 6 show the influence of high, medium, and low concentrations of three different corticosteroids on cytokine protein secretion from Th1 and Th2 clones. Fig. 5 shows IFN- γ (A) and IL-4 (B) secretion from Th1 and



A



B

FIG. 4. Modulation of cytokine gene expression in RW-stimulated Th1 (**A**) and Th2 (**B**) clones by corticosteroids. Representative RT-PCR amplification products for IFN- γ and IL-13 in Th1 clones and IL-4, IL-5, and IL-13 in Th2 clones are shown for each of seven different culture conditions from a single experiment. Adequate normalization of RNA was confirmed by equivalent β -actin gene expression at subsaturating cycle number (row 1). The DNA size marker is shown in lane 8. $N = 3$ individual experiments with Th1 clones and 3 individual experiments with Th2 clones. *Dex*, Dexamethasone; *Bud*, budesonide; *HC*, hydrocortisone.

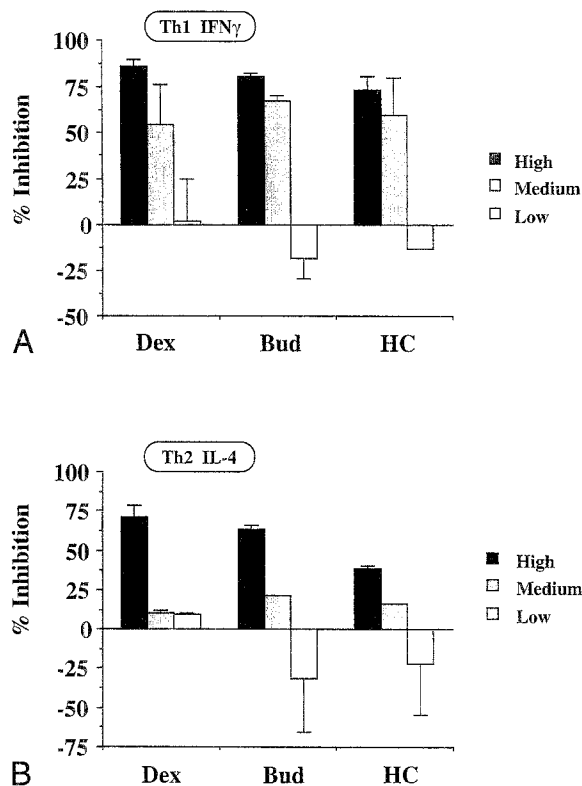


FIG. 5. Dose-dependent modulation of cytokine production by corticosteroids in Th1 and Th2 clones. Secretion of IFN- γ by Th1 clones (A) and IL-4 by Th2 clones (B) in the presence of each of three corticosteroids is shown. For dexamethasone and budesonide, the high dose was 10^{-7} mol/L, the medium dose was 10^{-9} mol/L, and the low dose was 10^{-10} mol/L. For hydrocortisone, the high dose was 10^{-6} mol/L, the medium dose was 10^{-8} mol/L, and the low dose was 10^{-9} mol/L. Data are presented as percentage of inhibition $\pm$ SEM relative to stimulated, steroid-free control cultures. Mean IFN- γ production from stimulated Th1 controls = 6147 ± 3084 pg/ml; mean IL-4 production from stimulated Th2 controls = 872 ± 193 pg/ml. Dex, Dexamethasone; Bud, budesonide; HC, hydrocortisone.

Th2 clones, respectively. All three steroids produced similar concentration-dependent inhibition of IFN- γ production from the Th1 clones. Compared with IFN- γ production from the Th1 clones, a significantly lower sensitivity to inhibition was evident in IL-4 production from the Th2 clones for budesonide 10^{-7} mol/L and hydrocortisone 10^{-6} mol/L ($p = 0.02$ and 0.03 , respectively). Differences in IFN- γ and IL-4 production in cultures with lower concentrations of corticosteroids were not significant (p uniformly > 0.1). Fig. 6 shows IL-13 secretion from Th1 (A) and Th2 (B) clones; equivalent concentration-dependent inhibition for all three corticosteroids was evident (p uniformly > 0.3).

DISCUSSION

Modulation of cytokine production in T lymphocytes has long been hypothesized to be one of the primary mechanisms by which corticosteroids suppress immune responses. The description of Th1 and Th2 phenotypes in human CD4 $^{+}$ T-cell populations led naturally to the

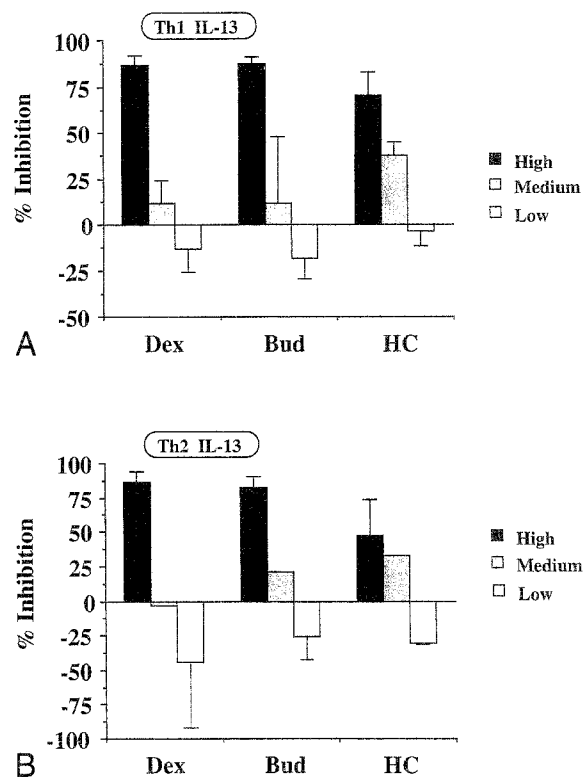


FIG. 6. Dose-dependent modulation of IL-13 production by corticosteroids in Th1 and Th2 clones. Secretion of IL-13 by Th1 (A) and Th2 (B) clones in the presence of each of three corticosteroids is shown for the same culture conditions indicated in Fig. 5. Data are presented as percentage of inhibition $\pm$ SEM relative to stimulated, steroid-free cultures. Mean IL-13 production from stimulated controls = 688 ± 102 pg/ml for Th1 clones and $3531 \pm 1,119$ pg/ml for Th2 clones. Dex, Dexamethasone; Bud, budesonide; HC, hydrocortisone.

question of whether corticosteroids might differentially regulate cytokine production in these subsets. Previous studies in this area have provided conflicting results.^{2-4, 6-7, 18} Using PBMCs, Brinkmann et al.⁴ demonstrated IL-4 enhancement and IFN- γ inhibition with corticosteroid treatment, whereas Snijdwint et al.² showed downregulation of both IL-4 and IFN- γ with more pronounced effects on IL-4. However, cellular activation in these studies was achieved with free or plate-bound monoclonal antibodies; the relevance of these systems to APC and antigen-driven Th1 and Th2 phenotypic responses is unclear. Moreover, the mixed cell populations used in these experiments allowed for the possibility of corticosteroid effects on other cell types, further complicating interpretation of their results. Other investigators have used clonal cell populations to study this question. Schmidt et al.³ showed that a transformed murine Th2-type line (D10.G4.1) was significantly more sensitive to corticosteroids than a human Th1-type line (Jurkat). In contrast, Snijdwint et al.² found that both Th1- and Th2-type cytokines were suppressed equally in a study of human Th0 clones

stimulated with monoclonal antibodies and mitogen. Once again, the relevance of these data to APC and antigen-driven human Th1 and Th2 phenotypic responses is unclear. We and others have shown that mitogenic stimulation of phenotypically specific CD4⁺ T-cell clones (human or murine) will result in nonphenotypically selective (Th0-type) cytokine generation; subsequent restimulation with antigen and APCs will restore phenotypic specificity.^{21, 23} Thus mitogen stimulation appears to obviate phenotypic specificity; moreover, mitogen stimulation is clearly less physiologic than antigen stimulation. This study is the first comprehensive analysis of corticosteroid modulation in human, antigen-stimulated PBMCs and nontransformed, antigen-specific Th1 and Th2 clones. Our results indicate that in antigen-stimulated T cells, corticosteroids strongly and equally suppress both Th1 and Th2 responses. Although an effect on accessory cell function by corticosteroids in this study system cannot be ruled out, the use of irradiated autologous PBMCs as APCs militates against this. Moreover, results from preincubation and washout experiments with corticosteroids by using PBMCs subjected to an adherence-based separation protocol were essentially the same as those presented in this article, suggesting a direct effect on T cells (data not shown).

Although corticosteroids are effective downregulators of both Th1 and Th2 responses, certain differences between the Th1 and Th2 phenotypes and between different antigens were evident in this study. First, downregulation of IFN- γ secretion was more sensitive to high concentrations of budesonide or hydrocortisone than was secretion of IL-4. However, this difference in IFN- γ and IL-4 production was not significant for lower concentrations of these corticosteroids or any concentrations of dexamethasone, and there were no differences in the downregulation of IL-13 between Th1 and Th2 clones cultured with any of these three corticosteroids. Whether these differences reflect subtle biologic differences between T-cell phenotypes or differential sensitivity of transcriptional promoters for these two cytokines to corticosteroids is unclear; however, similarities at the level of cytokine gene expression with semi-quantitative RT-PCR argue against the latter possibility. Moreover, we have performed studies of the time course of cytokine generation; IL-4 can be detected after 3 to 4 hours, is significantly elevated at 6 hours, reaches plateau by 12 hours, then declines rapidly after 24 hours; IFN- γ follows a similar pattern, whereas IL-13 reaches plateau slightly later and remains elevated (data not shown). The kinetics, as well as antigen concentration, APC-to-target cell ratios, and other culture parameters were all optimized before this study was performed.

Second, the kinetics of corticosteroid modulation were different in RW- and TT-stimulated proliferative responses of PBMCs. Dexamethasone suppressed RW-driven proliferation significantly better than TT-driven proliferation when added up to 36 hours after stimulation. This observation could be due to the fact that these two antigens target different populations of responder

cells, which may have distinct pharmacologic sensitivities; differences in the activation processes triggered by the two antigens might cause differences in the timing of the proliferative responses.²⁴ The general ability of corticosteroids to downregulate an inflammatory response after antigen stimulation is consistent with clinical observations; however, the finding of differential efficacy may have implications in designing optimal corticosteroid dosing schedules for various immunologic diseases.

A number of other conclusions may be drawn from these data. First, IL-13 generation by T cells is downregulated by corticosteroids; moreover, corticosteroids downregulate IL-13 production equally from Th1 and Th2 cells. Because IL-13 has several known proinflammatory actions, downregulation of IL-13 should be an important component of antiinflammatory drug efficacy.¹⁶ To our knowledge, this is the first report of the efficacy of corticosteroids on the regulation of antigen-driven IL-13 production from lymphocytes. These observations may have important implications in the design of therapeutic strategies targeting chronic allergic inflammation.

Finally, antigen-driven proliferation of PBMCs was inhibited by corticosteroids at concentrations 10-fold lower than those required for T-cell clones. This finding confirms those of Snijdwint et al.² and Brinkmann et al.,⁴ who suggested that corticosteroids may be less efficacious in downregulating memory responses than naive responses. In chronic inflammatory diseases, in which T cells may be continually activated by the persistence of antigen in the body, the reduced efficacy of corticosteroids on memory responses could have particularly serious clinical implications. These data neither confirm nor refute the hypothesis of differential efficacy on memory and naive phenotypes; however, they do confirm the findings of these other investigators. Although the general mechanisms of corticosteroid action are beginning to be understood, the potential mechanism for differential efficacy on memory and naive cells remains unclear.

In conclusion, proliferation and cytokine generation from antigen-driven PBMCs and nontransformed, antigen-specific human Th1 and Th2 clones were strongly inhibited by several corticosteroids. Our data argue against significant differential efficacy of corticosteroids on Th1 and Th2 responses.

We thank Ms. Jane M. White, Ms. Maria Stockton-Thompson, Mr. John Brummet, Officer Dennis Smith, Ms. Sonya Meeker, and Dr. James Ellis for their support and assistance during these experiments.

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