Immunology 1985 **56** 359

Glucocorticoids inhibit IgE receptor expression on the human monocyte cell line U937

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Accepted for publication 24 April 1985

Summary. Cells of a human monocyte-like cell line (U937) were analysed for IgE Fc receptors ($Fc_\varepsilon R$) before and after glucocorticoid treatment. Specific binding of human myeloma IgE (Sha) was measured by ^{125}I-labelled IgE, and by fluorescein-labelled IgE monitored by flow cytometry. Treatment of cells with dexamethasone or other steroids with glucocorticoid activity caused a significant decrease in $Fc_\varepsilon R$ expression. The inhibition was dose dependent, with a half-maximal effect at 20 nM dexamethasone, a concentration which is near to the dissociation constant of glucocorticoid receptors for dexamethasone. Inhibition of $Fc_\varepsilon R$ was significant beginning 8 h following glucocorticoid treatment and reached a plateau at 24 hr. The K_a for IgE binding was similar for control and dexamethasone-treated cells, while the number of IgE binding sites was decreased by 50–60%. Culture supernatants from dexamethasone-treated U937 cells which were concentrated 10-fold and depleted of free steroid did not affect $Fc_\varepsilon R$ expression. These results demonstrate that glucocorticoids can directly decrease the number of $Fc_\varepsilon R$. This effect could participate in the glucocorticoid-induced suppression of IgE-mediated allergic reactions.

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Abbreviations: BPB, *p*-bromophenacyl bromide; ETYA, eicosatetraynoic acid; FBS, fetal bovine serum; $Fc_\varepsilon R$, Fc receptor for IgE; $Fc_\gamma R$, Fc receptor for IgG; FITC, fluorescein isothiocyanate; IM, indomethacin; NGDA, nordihydroguarietic acid; PBS-BSA, Dulbecco's phosphate-buffered saline containing 2 mg/ml bovine serum albumin.

INTRODUCTION

The presence of Fc receptors for IgE ($Fc_\varepsilon R$) on basophils and on mast cells is well established. $Fc_\varepsilon R$ are also found on monocytes (Melewicz & Spiegelberg, 1980; Melewicz, Plummer & Spiegelberg, 1982), macrophages (Capron *et al.*, 1977; Boltz-Nitulescu, Plummer & Spiegelberg, 1982), on a subpopulation of lymphocytes (Gonzales-Molina & Spiegelberg, 1977; Yodoi & Ishizaka, 1979) and on the human monocyte cell line U937 (Anderson & Spiegelberg, 1981), but the biological importance of these receptors is not understood. Indirect evidence, however, suggests that $Fc_\varepsilon R$ of mononuclear phagocytes may play a role in allergic diseases: IgE-dependent cytotoxicity by blood mononuclear cells, as well as the number of monocytes bearing $Fc_\varepsilon R$, is increased in patients with severe atopy (Melewicz & Spiegelberg, 1980; Melewicz *et al.*, 1981), and murine macrophages have been shown to respond to immune complexes of IgE with the release of leukotriene C_4 and other arachidonic acid metabolites (Rouzer *et al.*, 1982).

Glucocorticoids, among their many immunosuppressive and anti-inflammatory actions, are therapeutic in allergic reactions. While it has been shown by

Melewicz *et al.* (1981) that in atopic patients receiving corticosteroid therapy the percentage of $Fc_\varepsilon R$-positive lymphocytes is much lower than that in non-treated patients, there are no definitive reports of direct glucocorticoid-specific inhibition of $Fc_\varepsilon R$ expression. Glucocorticoids have been shown to decrease the number of Fc receptors for IgG (Schreiber *et al.*, 1975; Crabtree, Munck & Smith, 1979), and we have previously reported that γ-interferon increases $Fc_\varepsilon R$ expression on U937 cells, an action which is opposed by dexamethasone (Náray-Fejes-Tóth & Guyre, 1984). In order to determine whether the beneficial effects of glucocorticoids in atopic diseases might be, at least in part, mediated through a direct action on the expression of $Fc_\varepsilon R$, we investigated further the effect of glucocorticoids on the IgE receptors of the human monocyte cell line, U937. Since some glucocorticoid-specific effects on the immune system have recently been described as being mediated through a glucocorticoid-induced protein, lipocortin (Hattori *et al.*, 1983a; Hirata & Iwata, 1983), we also investigated whether the glucocorticoid effect on $Fc_\varepsilon R$ is dependent on such an extracellular mediator.

MATERIALS AND METHODS

Cell line

U937 cells, obtained from Dr P. Ralph (Memorial Sloan Kettering Institute, Rye, NY), were maintained at cell density of $3–5 \times 10^5$/ml in 75-cm^2 flasks (Costar, Cambridge, MA) in RPMI-1640 medium (KC Biological, Lenixa, KS) supplemented with 10% fetal bovine serum (Sterile Systems Inc. Logan, UT), and 50 μg/ml gentamicin (Schering, Kenilworth, NJ). Dexamethasone and other steroids were dissolved in ethanol and diluted in RPMI-1640 to the concentrations required, so that the final concentration of ethanol was always less than 0·1%.

Isolation and labelling of immunoglobulins

Human myeloma IgE (Sha) was kindly provided by Dr O. R. McIntyre (Dartmouth Medical School, Hanover, NH) and was purified and labelled as described in detail elsewhere (Náray-Fejes-Tóth & Guyre, 1984).

Analysis of $Fc_\varepsilon R$

Measurement of $Fc_\varepsilon R$ was performed by two methods: (i) using FITC-labelled human IgE and monitoring specific (saturable) cell-bound fluorescence by flow cytometry, and (ii) by the binding of ^{125}I-labelled human IgE. In both cases, the ligand was centrifuged at 100,000 ***g*** for 1 hr prior to use to remove aggregates.

Flow cytometry. For this method, 2×10^6 U937 cells were incubated in 60 μl of RPMI-1640, 10% FBS with 200 nM FITC-labelled IgE in the presence or absence of 20 μM non-labelled IgE (Sha) at 37° for 2 hr. Cells were then washed with ice-cold Dulbecco's phosphate-buffered saline containing 2 mg/ml bovine serum albumin (PBS-BSA) and resuspended in PBS-BSA. Cell-bound fluorescence was determined by cytofluorography using an Ortho System 50 H with 488 nm laser excitation. The method of Titus *et al.* (1982) was used to verify that surface immunofluorescence was linearly correlated with saturable binding of radiolabelled IgE.

Scatchard binding assays. For this method, 10^6 cells were incubated in 60 μl of RPMI-1640, 10% FBS with 12 serial 1:2 dilutions of ^{125}I-labelled IgE (final concentrations from 2 μM to 0·5 nM). Additional tubes were run containing 100-fold excess of unlabelled IgE. The samples were incubated at 37° for 2 hr, then 50 μl of each were pelleted in 400 μl tubes (BioRad, Richmond, CA) through 200 μl of 84% silicone oil (Contour Chemical, Woburn, MA):16% light paraffin oil (Fisher, Fair Lawn, NJ) by centrifugation in a Beckman microfuge B for 2 min at 11,000 ***g***. The tubes were cut above the cell pellet with a razor blade, and the cell-bound and free radioactivities were measured by a Searle gamma-counter at an efficiency of 70%. Specific IgE-binding was calculated by subtracting radioactivity measured in samples incubated with cold IgE from those incubated without cold IgE. Data were analysed according to Scatchard (1949) using the computer program developed by Munson & Rodbard (1980). The ratio of specific/non-specific binding of ^{125}I-IgE was 1·1/1; 4·5/1 and 7·9/1 at concentrations of 5×10^{-7}; $6{\cdot}25 \times 10^{-8}$ and $7{\cdot}8 \times 10^{-9}$ M labelled IgE, respectively, for control cells. This ratio was 0·6/1; 2·23/1 and 3·7/1 at the same concentrations of labelled IgE as above, respectively, for dexamethasone-treated cells (200 nM for 24 hr).

Both FITC-labelled and ^{125}-labelled IgE-binding assays showed high specificity for IgE, since several human myeloma IgGs (Arr, Pig, Str), even at 1000-fold excess concentration, did not compete with labelled IgE, while two myeloma IgEs (Bat, Sha) did compete (Náray-Fejes-Tóth & Guyre, 1984).

$Fc_\gamma R$ were measured by flow cytometry as described in detail previously (Guyre, Morganelli & Miller, 1983).

Assay for factors in U937 supernatants which influence IgE binding

U937 cells were cultured in the presence or absence of 50 nM dexamethasone for 48 hr, then the medium was aspirated and the FITC-labelled IgE binding capacity of the cells was measured as described above. Media from control and dexamethasone-treated cells were vacuum-dialysed against 200 volumes of RPMI-1640 using a dialysis membrane with a pore size of 6000–8000 μ. [^{3}H]dexamethasone was added to the supernatants, and the efficiency of dialysis was monitored by measuring radioactivity in the samples. Vacuum-dialysis resulted in a 10-fold concentration and a reduction of dexamethasone concentration greater than 99·5%. Fresh U937 cells were cultured in RPMI-1640 plus 10% FBS with 10% of vacuum-dialysed medium of dexamethasone-treated or non-treated cells for 24 hr, then the cells were assayed for $F_\varepsilon R$ by flow cytometry.

Surface markers defined by monoclonal antibodies

The monoclonal antibodies listed in Table 3 were used to evaluate the effect of dexamethasone on other surface determinants of U937 cells besides Fc receptors. U937 cells (10^6 in 20 μl) were mixed with human IgG (Sigma, final concentration of 0·7 mg/ml) to saturate $Fc_\gamma R$, and 20 μl of the solution of the appropriate monoclonal antibody, and incubated for 1 hr at 0–4°. The cells were then washed twice with PBS-BSA, resuspended in 20 μl of FITC-labelled goat anti-mouse immunoglobulin (Boehringer, Indianapolis, IN, final concentration 4 μg/ml), and incubated at 0–4° for a further 60 min. After this, cells were washed with PBS-BSA and analysed on the Cytofluorograf System 50 H.

Competition for glucocorticoid receptors

U937 cells (5×10^6 in 0·1 ml) were incubated in RPMI-1640 with [^{3}H]dexamethasone (40 nM final concentration, specific activity 38 Ci/mmole; NEN) at 37° for 30 min in the presence or absence of competing unlabelled steroid (1 μM final concentration). After incubation, the cells were washed three times with 1 ml of medium, pelleted by centrifugation, and the tip of the tube was cut, placed in 5 ml of Hydrofluor (National Diagnostics, Somerville, NJ) and counted for radioactivity.

RESULTS

Pretreatment of U937 cells with dexamethasone caused a significant reduction in the specific IgE binding to Fc receptors. Figure 1 shows the cytofluorographic analysis of 10,000 cells, indicating a uniform

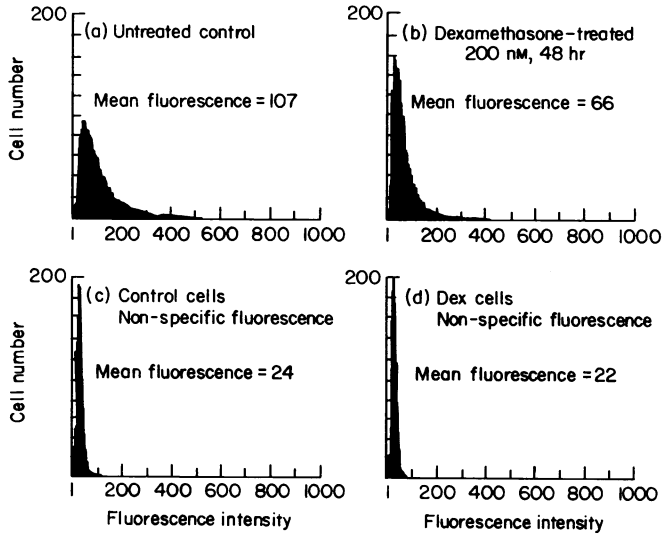

Figure 1. Flow cytometric analysis of $Fc_\varepsilon R$ inhibition by dexamethasone. U937 cells were incubated with or without 200 nM dexamethasone for 24 hr, then washed, and the binding of FITC-labelled IgE was measured by flow cytometry. (a) shows the fluorescence histogram for control cells, mean fluorescence intensity (MIF) = 107. (b) shows dexamethasone-treated cells, MFI = 66. For both cultures, the MFI due to autofluorescence was 20, and the MFI due to autofluorescence plus non-specific binding was less than 25. (c) control cells, (d) dexamethasone-treated cells.

decrease in IgE binding for the entire cell population following 24 hr treatment with dexamethasone. Figure 2 illustrates the time-course of the effect of 200 nM dexamethasone. Maximal effect (~60% reduction in IgE binding) was observed after 24 hr. No significant changes in cell size, cell cycle or proliferation could be detected as a consequence of glucocorticoid treatment during this period (data not shown). Figure 3 shows that the effect of dexamethasone was dose related, the half-maximal response being at 20 nM, a concentration at which dexamethasone half saturates the glucocorticoid receptors of U937 cells.

In order to determine whether dexamethasone decreased IgE binding by reducing the number of $Fc_\varepsilon R$ or its affinity for IgE, Scatchard analyses of ^{125}I-labelled IgE binding by control cells and cells pretreated with 200 nM dexamethasone were performed. Data in Table 1 demonstrate that there was a significant decrease in the number of $Fc_\varepsilon R$ following glucocorticoid treatment, and that the equilibrium dissociation constant for IgE did not change. Values of receptor number and dissociation constant for IgE in control cells are very similar to those found earlier by Anderson & Spiegelberg (1981) using the same cell type and the same ligand.

The response was specific for glucocorticoids, since only steroids with known glucocorticoid activity decreased the number of $Fc_\varepsilon R$ (Table 2). Also, there was a good correlation ($r = 0{\cdot}983$) between competition for binding to glucocorticoid receptors and the inhibitory effect on $Fc_\varepsilon R$.

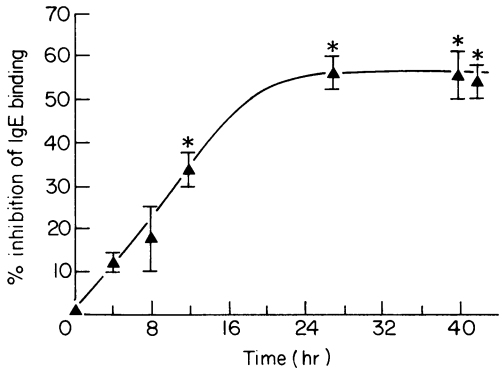

Figure 2. Time-course of dexamethasone inhibition of $Fc_\varepsilon R$ expression on U937 cells. Cells were incubated with or without 200 nM dexamethasone for different periods of time, then the binding of FITC-IgE was measured by flow cytometry. Specific binding of FITC-IgE to control cells did not change during this period of incubation. Values are means ± SEM of three separate experiments. In each experiment, three cultures were analysed separately and the SD values were always less than 10% of the mean. *P* values refer to differences from the control cultured for the same period of time. (*$P < 0{\cdot}01$.)

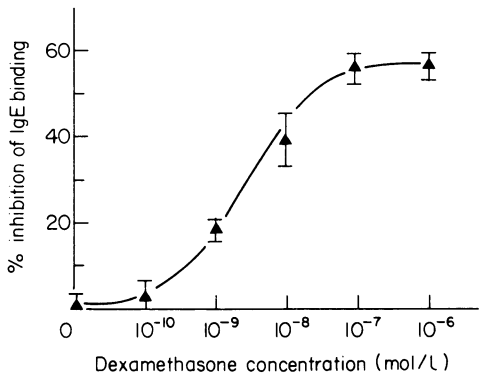

Figure 3. Dose-dependency of $Fc_\varepsilon R$ inhibition by dexamethasone. U937 cells were incubated with 0–1 μM dexamethasone for 40 hr, then the binding of FITC-IgE was measured by flow cytometry. Values are means ± SEM of three independent experiments.

Table 1. Number and K_d of $Fc_\varepsilon R$ in control and dexamethasone-treated U937 cells

Treatment	K_d for IgE (nM)	$Fc_\varepsilon R$ number/cell
None	27·8 ± 5·5	76,400 ± 7951
200 nM dexamethasone for 40 hr	21·5 ± 6·9	30,200 ± 3116*

Values are means ± SEM of four experiments. Scatchard binding assays were performed as described in the Materials and Methods.
*$P < 0{\cdot}01$.

Table 2. Steroid specificity of $Fc_\varepsilon R$ inhibition and glucocorticoid receptor binding in U937 cells

Steroid (1 μM)	% inhibition	
	Binding of IgE	Binding of [^{3}H]-dexamethasone
Dexamethasone	56	85
Triamcinolone acetonide	54	95
Hydrocortisone	40	76
Corticosterone	31	60
Cortisone	5	10
Progesterone	15	20
Oestradiol	3	5
Dihydrotestosterone	6	4
Aldosterone	1	10

U937 cells were incubated with or without different steroids for 40 hr, then $Fc_\varepsilon R$ expression was measured by flow cytometry. Binding of [^{3}H]dexamethasone (40 nM) by untreated U937 cells was assayed in the presence or absence of various steroids (1 μM) as decribed in the Materials and Methods.

In further experiments, the specificity of glucocorticoid-induced inhibition was investigated by measuring the binding of monoclonal antibodies to other cell surface determinants following dexamethasone administration. These assays showed that, of the determinants studied, only Fc receptors, including both for IgE and IgG, were inhibited by dexamethasone (Table 3).

IgE binding of U937 cells did not change after incubation for up to 16 hr with either one of the following inhibitors of arachidonic acid metabolism: 10 μM *p*-bromophenacyl bromide (BPB); 10 μM nordihydroguarietic acid (NDGA); 10 μM eicosatetraynoic acid (ETYA); 100 μM indomethacin (IM). IgE binding was 96·5%, 98·0%, 97·0% and 103·2% of control for BPB, NDGA, ETYA and IM, respectively.

In order to investigate whether the effect of dexamethasone was mediated via some steroid-induced protein (such as macrocortin or lipomodulin), the supernatant of U937 cells treated with 50 nM of dexamethsone was concentrated 10-fold and depleted of free dexamethasone by vacuum dialysis. U937 cells were then cultured with dialysed supernatants of control and dexamethasone-treated cells. Although 50 nM dexamethasone decreased $Fc_\varepsilon R$ number by about 45%, the dexamethasone-free supernatant of dexamethasone-treated cells did not bring about any changes in IgE binding.

DISCUSSION

Although the therapeutic effect of long-term glucocorticoid treatment in atopic diseases is well-established,

Table 3. Dexamethasone effect on the binding of myeloma proteins and monoclonal antibodies (MoAbs)* to U937 cells

Marker	Specificity	Mean fluorescence	
		Control	Dexamethasone-treated†
IgE	$Fc_\varepsilon R$	188	92‡
IgG	$Fc_{\gamma M}R$	69	33‡
P3 (control MoAb)	Unknown	15	14
HLA ABC MoAb	HLA antigen	134	180
3G8 MoAb	$Fc_{\gamma N}R$	24	25
M1 MoAb	Monocyte	140	150
B 3/25 MoAb	Transferrin receptor	44	43
Ta-1 MoAb	T cell and monocyte	38	29
AML 201 MoAb	B_2-microglobulin	199	170

* Sources of monoclonal antibodies were as follows: P3 and AML-201, gifts of Dr Michael Fanger, Dartmouth Medical School, Hanover, NH; 3G8, gift of Dr Jay Unkeless, Rockefeller University, New York, NY; HLA-ABC, Bethesda Research Laboratories Inc., Rockville, MD; LEU-M1, Becton-Dickenson Inc., Mountain View, CA; B3/25 and TA-1, Hybritech Inc., La Jolla, CA.

† U-937 cells were cultured with or without 200 nM dexamethasone for 40 hr, washed three times with serum-free medium, and then assayed as described in the Materials and Methods.

‡ $P < 0{\cdot}01$.

the exact mechanism of their anti-allergic action is not well understood. It has been suggested that inhibition of histamine release from basophils may contribute to the anti-inflammatory action of steroids (Schleimer, Lichtenstein & Gillespie, 1981). Another possibility is that glucocorticoid treatment decreases the number or affinity of $Fc_\varepsilon R$ on cells participating in allergic reactions. Indeed, it has been shown by Spiegelberg *et al.* (1979) and by Yodoi, Hirashmima & Ishizaka (1981) that, under certain conditions, glucocorticoids decrease the percentage of $Fc_\varepsilon R$-bearing cells. However, from these previous studies it was not clear whether corticosteroids suppressed the *de novo* $Fc_\varepsilon R$ synthesis, caused a redistribution of lymphoid cells, or, in the case of *in vitro* experiments with rat lymphocytes, caused lysis of $Fc_\varepsilon R$-positive cells, thus changing the composition of the cell population. Yodoi *et al.* (1981) suggested that dexamethasone treatment changed the biological activity of IgE binding factors produced by lymphocytes.

Our results demonstrate that glucocorticoids inhibit the expression of $Fc_\varepsilon R$ on a human monocyte cell line directly. We used an established cell line, thus excluding indirect effects which might be due to the production of lymphocyte-derived factors, or changes in cell subpopulations. Furthermore, we measured $Fc_\varepsilon R$ by both ^{125}I-IgE and FITC-IgE binding. Radioligand binding enabled us to determine the binding affinity and receptor density averaged over 10^6 cells per assay point, while flow cytometric analysis allowed us to make independent measurements of *each* of 10,000 cells analysed per treatment in each experiment. We have, therefore, determined that the entire population of U937 cells bears $Fc_\varepsilon R$, and that dexamethasone reduced $Fc_\varepsilon R$ number on the entire population of cells, not on a subpopulation (Fig. 1).

The finding that half-maximal inhibition of $Fc_\varepsilon R$ expression was found at a concentration of dexamethasone which corresponds with the K_d of glucocorticoid receptors in U937 cells (Paavonen, Anderson & Kontula, 1980) strongly suggests that this effect is a glucocorticoid receptor-mediated process. The inhibition of $Fc_\varepsilon R$ expression was specific in two ways: (i) only steroids with high affinity for glucocorticoid receptors had an effect; and (ii) among the eight different cell surface markers investigated, only the Fc receptor which binds monomeric IgG ($Fc_{\gamma M}R$) and the $Fc_\varepsilon R$ were significantly reduced by dexamethasone. The Fc receptor which is commonly expressed on neutrophils ($Fc_{\gamma N}R$) was monitored using the monoclonal antibody 3G8. $Fc_{\gamma N}R$ was expressed at a very low level on U937 cells and was unaffected by dexamethasone. Our results confirm and extend the finding of Crabtree *et al.* (1979) who demonstrated a dexamethasone-induced decrease in the number of $Fc_{\gamma M}R$ on HL-60 cells, which form another human cell line.

The exact mechanism of action of glucocorticoids on $Fc_\varepsilon R$ expression cannot be deduced from the present experiments. However, it is unlikely that glucocorticoids affect $Fc_\varepsilon R$ by a direct membrane effect, since physiological concentrations of glucocorticoids reduce IgE binding. Membrane stabilizing effects are not glucocorticoid-specific, and generally require 1000–10,000 times higher concentrations of hormone. Moreover, the slow time-course of changes argues against a direct effect on the cell membrane. Previously, it has been reported that very high concentrations of steroid hormones inhibited IgG binding on monocytes (Schreiber *et al.*, 1975). It appears that this latter effect was probably mediated through a direct action on the cell membrane, since not only glucocorticoids but also mineralocorticoids and sex steroids were found to be inhibitory at concentrations between 10^{-4} M and 10^{-3} M, with a half-maximal effect seen after 15 min.

Glucocorticoid-induced inhibition of immune functions such as NK activity may be mediated via lipomodulin (Hattori *et al.*, 1983a; Hirata & Iwata, 1983). Theoretically, it is possible that the glucocorticoid-induced reduction of $Fc_\varepsilon R$ expression is mediated through the decreased synthesis of some arachidonic acid metabolites (prostaglandins or lipoxygenase products). However, in our case this seems to be unlikely, since the number of $Fc_\varepsilon R$ on U937 cells was unaffected by the following compounds: *p*-bromophenacyl bromide, a phospholipase A_2 inhibitor (Vallee *et al.* 1979); indomethacin, which is a well-known cyclo-oxygenase-inhibitor, and by ETYA and nordihydroguarietic acid which inhibit both cyclo-oxygenase and lipoxygenase pathways. Prostaglandin E_2 at concentrations up to 1 μM failed to increase IgE binding (it was 98–107% that of control cells), suggesting that the effect of glucocorticoids was probably not mediated by inhibition of phospholipase activity. Hattori, Hoffman & Hirata (1983b) have demonstrated that dexamethasone induces both lipomodulin production and differentiation of U937 cells. In our studies, however, it seems unlikely that a lipocortin-like mediator plays a role in glucocorticoid inhibition of $Fc_\varepsilon R$, since supernatants from dexamethasone-treated cells had no effect on $Fc_\varepsilon R$ expression. The reason for this apparent

discrepancy is probably because, in our experiments, inhibition of $Fc_\varepsilon R$ expression was found after treatment with physiological doses of glucocorticoids for 24 hr; in the experiments of Hattori *et al.* (1983b), induction of lipomodulin required treatment with very high doses of dexamethasone for 6 days.

It has been suggested that, in atopy, elevated circulating levels of IgE might increase the number of $Fc_\varepsilon R$-positive mononuclear cells (Melewicz *et al.*, 1981). This would enhance the possibility of binding of IgE-immune complexes to monocytes which, in turn, could lead to increased production of LTC_4 and other vasoactive substances. The direct inhibition of $Fc_\varepsilon R$ expression on a human mononuclear phagocyte, reported here, demonstrates a mechanism which might lead to decreased production of the postulated mediators of anaphylactic and allergic reactions.

ACKNOWLEDGMENTS

We are grateful to Dr Allan Munck for his helpful suggestions, to Dr M. W. Fanger for some of the human IgE preparations, and to R. Miller for her excellent assistance with flow cytometric studies. This work was supported by U.S.P.H.S. Grants AM 03535 and AM 33100, and by the Core Grant of the Norris Cotton Cancer Centre (CA 23108). A. Náray-Fejes-Tóth was supported by an American Cancer Society Eleanor Roosevelt International Cancer Fellowship awarded by the International Union Against Cancer. The flow cytometer was the generous gift of the Fannie E. Rippel Foundation.

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