Interleukin 1 Stimulates Its Own Receptor Expression on Human Fibroblasts through the Endogenous Production of Prostaglandin(s)

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Abstract

The regulation of interleukin 1 receptor (IL 1R) expression on human dermal fibroblasts was investigated. On exposure to IL 1 for 3 h at 37°C, the capacity of fibroblasts to bind ^{125}I-labeled human recombinant IL 1 alpha (^{125}I-IL 1α) was reduced by 75%. The IL 1 binding capability of the fibroblasts was restored to control levels by 16 h after removal of unbound IL 1, and then increased to about twofold over that of control cells by 48 h. This later enhancement of IL 1 receptor expression after IL 1 treatment was abolished by indomethacin. Addition of exogenous (PGE_1 and PGE_2, also analogues of AMP, or forskolin increased the specific binding of ^{125}I-IL 1α to fibroblasts. Scatchard analysis indicated that PGE_2 increased the number of IL 1R from $\sim 1.6 \times 10^3$ to 5.4×10^3 per cell without change in the binding affinity. These data suggest that the later IL 1-induced up-regulation of IL 1R is mediated by IL 1 stimulation of endogenous prostaglandin production. The combination of PGE_2 and prednisolone increased the number of IL 1R on fibroblasts in an additive manner.

Introduction

The availability of recombinant murine and human IL 1 has facilitated studies of the cell surface receptor for IL 1 on various responsive cells. Dower et al. first reported the expression of specific receptors for IL 1 on a variety of both human and murine cell types (1). We have also demonstrated the presence of high-affinity receptors for IL 1 on an EBV-transformed human B lymphocyte cell line and have shown that the receptors for IL 1α and IL 1β are identical (2). The regulation of IL 1 receptor (IL-1R) expression on various cell types remains largely unexplored and provides a potentially crucial locus of control of IL 1 activity. We have reported that IL 1 rapidly down-regulates IL 1 receptor expression on the human large granular lymphocyte YT cell line (3). We have also demonstrated that glucocorticoid hormones (GC) markedly increased the number of IL 1 receptors on several cell types including human peripheral B lymphocytes, human dermal fibroblasts, and YT cells without alteration in the binding affinity (4).

In this study, we have similarly observed that IL 1 rapidly initially down-regulates IL 1 receptor expression on human dermal fibroblasts. However, thereafter, IL 1 up-regulates IL 1 receptor expression through IL-1-induced endogenous production of prostaglandin(s) on human dermal fibroblasts. Exogenously added PGE_2 and prednisolone also enhanced IL 1R expression by fibroblasts and PBMC in an additive manner. Consequently, these data suggest that the in vivo expression of IL 1 receptors may be up-regulated both by prostaglandins and glucocorticoids that are produced in response to administration of IL 1.

Methods

Reagents. Prednisolone, PGE_1, PGE_2, 8-Bromoadenosine 3′:5′-cyclic monophosphate (8-Br cAMP), N^6,2′-*O*-dibutyryladenosine-3′:5′-cyclic monophosphate (dibutyryl cAMP), N^2,$O^{2'}$-dibutyryl guanosine-3′:5′-cyclic monophosphoric acid (dibutyryl cGMP), and forskolin were purchased from Sigma Chemical Co. (St. Louis, MO). Cycloheximide (CH) and actinomycin D (Act. D) were also obtained from Sigma Chemical Co. Purified, carrier-free human recombinant IL-1α was a generous gift from Dr. M. Yamada (Dainippon Pharmaceutical Co., Osaka, Japan).

Cell culture. Human dermal fibroblasts (CRL 1507; American Type Culture Collection, Rockville, MD) were maintained in DME (Advanced Biotechnologies Inc., Silver Spring, MD) supplemented with 10% FCS (Hyclone Laboratories, Logan, UT), 2 mM of L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin at 37°C in 5% CO_2. Fibroblasts (7×10^5 cells; passages 8–30) were plated in 35-mm-diam dishes (3506, Costar, Cambridge, MA) containing 3 ml of medium. After 2 d, the medium was replaced with 3 ml of new medium at 37°C containing various reagents as described. Prostaglandins were dissolved in 95% ethanol, forskolin was dissolved in DMSO, and cAMP was dissolved in Dulbecco's PBS and all were then added to the culture media to yield the indicated final concentration. An equivalent volume of ethanol or DMSO was added to control cultures. PBMC were freshly isolated by Ficoll-Hypaque gradient centrifugation and were resuspended at a density of 5×10^5 cells per ml in RPMI 1640 medium (Advanced Biotechnologies, Inc.) with 10% FCS.

Preparation of iodinated IL 1. Human recombinant IL 1α was labeled with ^{125}I using the Bolton-Hunter reagent (2,200 Ci/mmol, monoiodinated; New England Nuclear, Boston, MA) for 1 h on ice as previously described (4). After stopping the reaction with 0.5 ml of 0.5 M glycine in 0.1 M borate buffer, pH 8.5, ^{125}I-IL 1α was separated from free iodine by chromatography on a Sephadex G-25 column (Pharmacia Fine Chemicals, Piscataway, NJ). The labeling efficiency of IL 1 was $\sim 5 \times 10^7$ cpm of ^{125}I/μg of IL 1α.

Receptor binding assay. After treatment with various reagents, fibroblasts were transferred to 0.5 ml of binding medium (DME supplemented with 1 mg/ml BSA and 10 mM Hepes buffer). ^{125}I-IL 1α (14 ng/ml) was incubated with cells in the presence or absence of unlabeled IL 1α at a concentration of 2 μg/ml. After a 1-h incubation at 4°C, the cells were rinsed four times with cold DME and solubilized in 0.5 ml of 0.1 N NaOH containing 2% Na_2HCO_3 and 1% SDS. The total cell-associated radioactivity was determined by counting this volume in a gamma counter. PBMC were harvested after treatment with various

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1. *Abbreviations used in this paper:* Act. D, actinomycin D; CH, cycloheximide; GC, glucocorticoid hormones; IL 1R, interleukin 1 receptor.

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reagents, and the specific binding activity of ^{125}I-IL 1α to PBMC was determined as described elsewhere (4).

Measurement of PGE_2 levels. PGE_2 concentrations in culture media were determined by RIA using a PGE_2 ^{125}I-RIA kit (NEK 020A10; New England Nuclear).

Treatment with metabolic inhibitors. The cells were cultured with 3.5 μg/ml CH or 1.5 μg/ml Act. D in the presence of prednisolone (1×10^{-6} M) or PGE_2 (1×10^{-6} M) or 8-Br cAMP (1×10^{-3} M). After 12 h of culture, the effects of the metabolic inhibitor on the induction of IL 1 receptor were measured. The viability of the treated cells was not changed as compared with the control cells as measured by trypan blue dye exclusion test.

Results

Biphasic effects of IL 1 on IL 1 receptor expression. We examined the effect of IL 1 on IL 1R expression on normal human dermal fibroblasts. Fibroblasts in a confluent state were preincubated for 3 h at 37°C in the presence or absence of human recombinant IL 1α (100 U/ml). The cells were washed extensively to remove unbound IL 1, and were subsequently incubated in fresh medium at 37°C. Fig. 1 demonstrates the total binding of ^{125}I-IL 1α to fibroblasts at different times after IL 1 treatment. Under these conditions, IL 1 initially down-regulated IL 1R on the surface of fibroblasts as observed in a human large granular lymphocyte cell line, YT cells, and other cell types (3, 5). In this study, pretreatment with 100 U/ml IL 1 (5 ng) reduced the binding of ^{125}I-IL 1α to fibroblasts by 75%. The binding of labeled IL 1 recovered to ~ 60% of control by 6 h, and returned to control levels by 16–20 h. IL 1-untreated control cells showed moderately reduced binding after 24 h of incubation. The binding of ^{125}I-IL 1α to IL 1-pretreated cells progressively increased over control levels with 24 and 116% increases over control level at 30 and 48 h, respectively, and returned to control levels by day 3.

Because the enhancement of IL 1 binding occurred relatively slowly, it was hypothesized to be an indirect effect mediated by the production(s) of such as prostaglandins by IL 1-treated fibroblasts (6, 7). We therefore tested the effect of indomethacin on the restoration of IL 1R expression. Cells incubated with 2×10^{-6} M indomethacin after IL 1 pretreatment, showed reduced ^{125}I-IL 1 binding activity. Treatment with indomethacin largely inhibited the late phase of up-regulation of IL 1R expression. Indomethacin itself did not decrease the IL 1 binding activity of control cells (data not shown). As shown in Table I, we also can demonstrate the production of PGE_2 by fibroblasts in response to IL 1 and the block of PGE_2 production by indomethacin. Under the condition of this experiment, the cell number and viability of down-regulated cells remained the same as for control cells (Table 1). These data suggest that the later IL 1-induced up-regulation of IL 1R is mediated by endogenous production of prostaglandins.

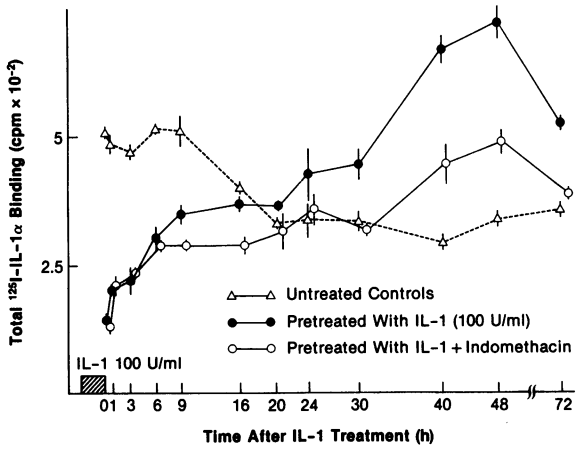

Figure 1. Biphasic effects of IL 1 on IL 1R expression of fibroblasts. Human dermal fibroblasts (confluent state in 35-mm culture dish) were pretreated with IL 1α (100 U/ml) for 3 h at 37°C and washed to remove unbound IL 1. Subsequently, the cells were incubated in fresh medium at 37°C with or without indomethacin (2×10^{-6} M) for the indicated period. The specific binding of ^{125}I-IL 1α to fibroblasts was determined as described in Methods. Each binding activity represents the mean (and indicated SD) of triplicate measurements. The data shown here represent three independent experiments.

Effect of prostaglandins on specific ^{125}I-IL 1α binding. Human dermal fibroblasts were exposed to PGE_2 (1×10^{-6} M) to determine the effect of exogenously added PGE on IL 1R expression. Fig. 2 illustrates the mean of triplicate measurements of specific ^{125}I-IL 1α binding at various times. The specific binding increased gradually with time after exposure to PGE_2. The maximal effect appeared after 18–24 h of exposure, and thereafter binding declined toward control levels. Next fibroblasts were treated with different doses of PGE_1 and PGE_2 for 24 h. Fig. 3 demonstrates that PGE_1 and PGE_2 increased the binding of ^{125}I-IL 1α in a dose-dependent manner. A concentration of 10^{-8} M PGE (which can be produced by fibroblasts) augmented IL 1R expression significantly and maximal effects were obtained with 1×10^{-7}–1×10^{-6} M of prostaglandins. Scatchard analysis was performed using fibroblasts treated with PGE_2 (1×10^{-6} M) and prednisolone (1×10^{-6} M) for 24 h to determine whether the increased binding could be accounted for by an increase in the number of high-affinity receptors. As illustrated in Fig. 4, treatment with PGE_2 or another IL 1R up-regulator, prednisolone increased the number of ^{125}I-IL 1α binding sites on fibroblasts without any alteration in binding affinity. Receptor numbers increased from 1.6×10^3 by control cells, to 5.4×10^3 for PGE_2 treated cells, and to 5.7×10^3 for prednisolone-treated cells. Fibroblasts treated with the combination of PGE_2 (1×10^{-6} M) and prednisolone (1×10^{-6} M), expressed 11×10^3 receptors per cell. There was no significant change in the binding affinity of control and treated cells ($4–6 \times 10^{-10}$ M). Thus, PGE_2 and GC both increased expression of high affinity receptors for IL 1 on fibroblasts, and the combination of PGE_2 and GC had an additive effect on IL 1R expression.

Induction of IL 1R expression on PBMC by PGE_2 and glucocorticoids. To determine whether PGE_2 up-regulates IL 1R on other cell types, PBMC were exposed to PGE_2 or prednisolone for 6 h at 37°C. Cells were subsequently harvested and the specific binding activity of ^{125}I-IL 1α was determined. As shown in Table II, both PGE_2 and prednisolone also increased ^{125}I-IL Iα binding of PBMC as well as of fibroblasts. Indomethacin did not inhibit the induction of IL 1R expression on PBMC by either exogenously added PGE_2 or GC.

Induction of IL 1R expression on fibroblasts by forskolin and AMP. As prostaglandins are known to stimulate adenylate cyclase, we examined the role of adenylate cyclase on IL 1R expression on fibroblasts. Fibroblasts were treated for 24 h with different doses of forskolin, an activator of the catalytic subunit of adenylate cyclase (8). As shown in Fig. 5 *A*, treat-

Table I. Effect of IL 1 on IL 1 Receptor Expression, PGE_2 Production, and Replication of Human Fibroblasts

Pretreatment	Cultured for 48 h in	Cell number at 48 h	^{125}I-IL 1 bound	PGE_2 in culture media
		×10⁵/well	*cpm/well*	*M*
None	MEM + 10% FCS	5.16±0.14	433±23	7.2×10^{-10}
IL 1 (*100 U/ml*)	MEM + 10% FCS	5.14±0.28	735±37	2.1×10^{-8}
IL 1 (*100 U/ml*) and indomethacin (2×10^{-6} *M*)	MEM + 10% FCS + 2×10^{-6} M indomethacin	5.27±0.35	518±14	1.9×10^{-9}

Fibroblasts were cultured in conditions as described for Fig. 1.

ment with forskolin markedly enhanced the specific binding of ^{125}I-IL 1α to fibroblasts in a dose-dependent manner, and maximal effects were obtained with 1×10^{-5} M of forskolin. We also evaluated the effect of analogues of cAMP on IL 1R induction. Fibroblasts treated with high concentrations of dibutyryl cAMP or 8-Br cAMP (1×10^{-3} M) for 24 h also showed augmentation of IL 1R expression (Fig. 5 *B*). In contrast, dibutyryl cGMP did not increase specific binding of labeled IL 1α to fibroblasts. The combination of prednisolone with either forskolin or cAMP analogues also increased IL 1R expression in an additive manner (data not shown). These data suggest that prostaglandins-induced up-regulation of IL 1R expression was mediated by adenylate cyclase and accumulation of intracellular cAMP.

Effect of metabolic inhibitors on prostaglandin and glucocorticoid-induced IL 1R expression. To determine whether prostaglandins- and GC-induced IL 1R expression required de novo synthesis of new receptor, we analyzed the effects of metabolic inhibitors, CH, and Act. D. Fibroblasts were treated with 3.5 μg/ml CH or 1 μg/ml Act. D in the presence or absence of prednisolone (1×10^{-6} M), PGE_2 (10^{-6} M), or 8-Br cAMP (1×10^{-3} M) for 12 h. These metabolic inhibitors abolished the up-regulation of IL 1R expression without reducing cell viability over a 12-h period (Fig. 6). These data suggest that prostaglandins- and GC-induced IL 1R up-regulation required both protein and RNA synthesis.

Discussion

Down-regulation of receptors by their ligands is commonly observed for hormones and cytokines including epidermal growth factor (EGF) (9), insulin (10), and IFN (11). Rapid down-regulation of IL 1R expression by IL 1 has also been reported for the human LGL cell line YT (3), the murine T cell line, EL4, and the fibroblast cell line, Swiss 3T3, (5). We previously reported that a brief, 3-h incubation of YT cells with IL 1 down-regulates IL 1R expression and IL 1 binding returns to normal levels by 16 h at 37°C after removal of IL 1 from the culture media. Similarly, exposure of normal human fibroblasts to IL 1 initially down-regulates IL 1R, and is followed by up-regulation of IL 1R expression. The phenomenon of ligand-dependent induction of specific receptors has been demonstrated to occur at the level of transcription or at the protein level in the case of EGF (12, 13), growth hormone (14), prolactin (15), insulin (16), and IL 2 (17). On the other hand, the synthesis of the receptor for low density lipoprotein has been reported to be inhibited by ligand binding (18). The basis for the effect of IL 1 on IL 1R gene expression remains to be established.

Many reports have demonstrated the regulatory role of cAMP on gene expression (19–23). For example, forskolin and cAMP analogues enhanced the expression of low- and high-affinity IL 2 receptors on YT cells and T cell lines (24). Both

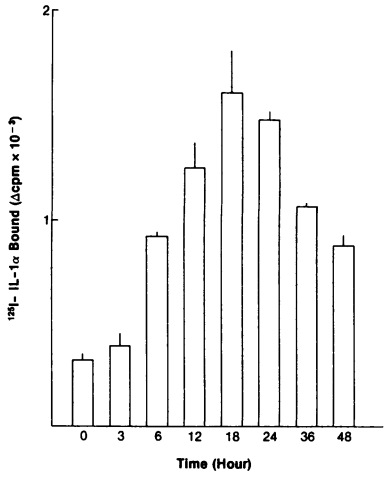

Figure 2. Time course of ^{125}I-IL 1α binding to PGE_2-treated fibroblasts. Fibroblasts (confluent state in 35-mm culture dish) were incubated with PGE_2 (1×10^{-6} M) as indicated. The specific ^{125}I-IL 1α binding at 14 ng/ml of ^{125}I-labeled ligand to treated cells was determined. Nonspecific binding, defined as the amount of ^{125}I-IL 1α bound to cells in the presence of 2 μg/ml of human recombinant IL 1α, was subtracted from total binding to yield specific binding.

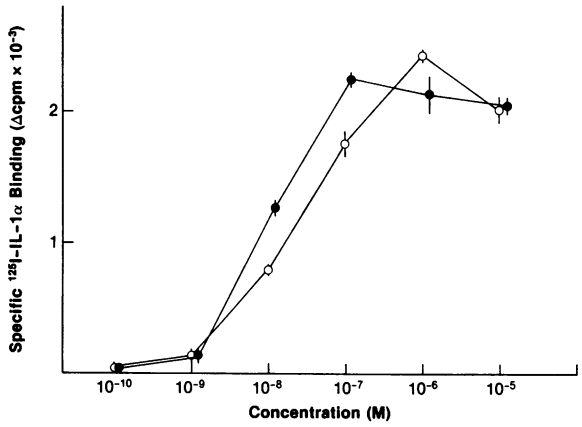

Figure 3. Effects of prostaglandins on specific ^{125}I-IL 1α binding on human fibroblasts. Fibroblasts were incubated in culture media in the presence of varying concentrations of PGE_1 and PGE_2. After culture for 24 h at 37°C, specific binding of ^{125}I-IL 1α was determined. The level of background binding was 483±19 cpm, which was subtracted from the data shown here. ●, PGE_1; ○, PGE_2.

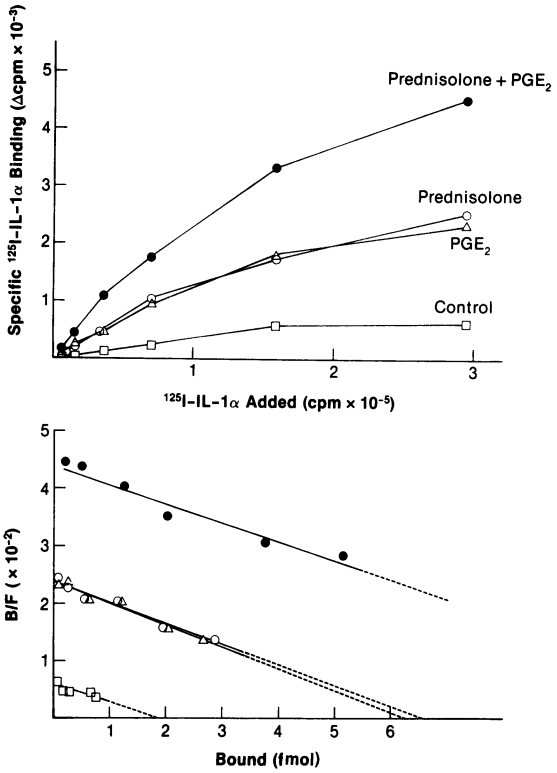

Figure 4. Specific binding of ^{125}I-IL 1α to fibroblasts and Scatchard plot analysis. Fibroblasts (7×10^5/35-mm culture dish) were incubated in culture media (□), in the presence of 1×10^{-6} M of PGE_2 (△) or 1×10^{-6} M of prednisolone (○) or the combination of PGE_2 and prednisolone (●) for 24 h. Subsequently, the cells were incubated with various dilutions of ^{125}I-IL 1α (4.9×10^7 cpm/μg) for 1 h at 4°C. Nonspecific binding was estimated in the presence of 140 times excess of cold recombinant IL 1α.

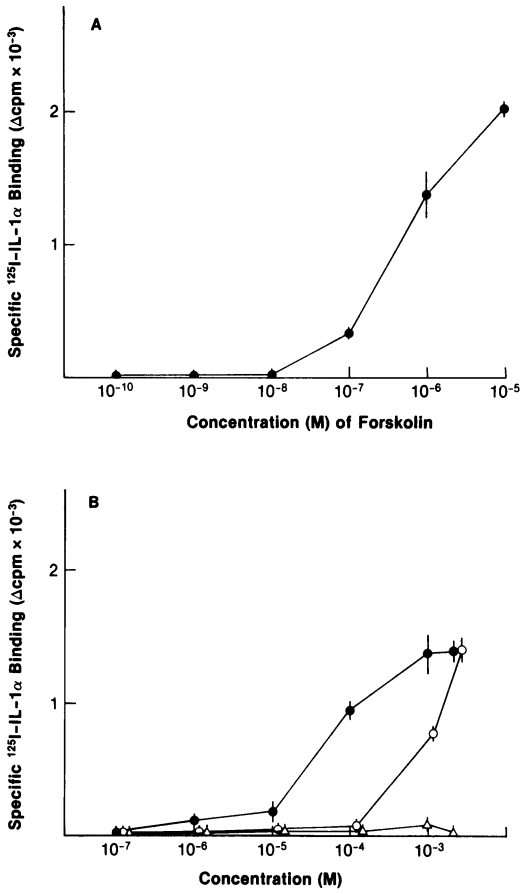

Figure 5. Effects of forskolin and cAMP on specific ^{125}I-IL 1α binding on fibroblasts. The cells were incubated at 37°C with various concentrations of (*A*) forskolin or (*B*) several analogues of cAMP. After incubation for 24 h, specific binding of ^{125}I-IL 1α was determined. The background binding of 483±11 and 311±15 cpm for the forskolin experiment and the cAMP analogues experiment, respectively were subtracted from the data shown here. ●, dibutyryl cAMP; ○, 8-Br cAMP; △, dibutyryl cGMP.

cAMP-dependent protein kinase (A-kinase) and calcium-phospholipid dependent protein kinase (C-kinase) (25) can also activate IL 2R expression in the course of lymphocyte activation. However, phorbol esters, potent activators of C-kinase, could not modulate IL 1R expression on fibroblasts, PBMC, and YT cells (data not shown), arguing against the involvement of C-kinase system in up-regulating IL 1R expression. Since forskolin, a reversible activator of adenylate

Table II. Effects of PGE_2 and Glucocorticoid on the Induction of IL 1 Receptor Expression by PBMC

Treatment	^{125}I-IL 1 bound
	cpm mean±SD/10^7 cell
Medium alone	266±71
Indomethacin (2×10^{-6} *M*)	328±32
PGE_2 (10^{-6} *M*)	1,529±67
PGE_2 + indomethacin	1,472±183
Prednisolone (10^{-6} *M*)	4,763±143
Prednisolone + indomethacin	5,019±296

PBMC (1×10^7 cells) were cultured for 6 h at 37°C with PGE_2 (10^{-6} M) or prednisolone (10^{-6} M) with or without indomethacin (2×10^{-6} M). Cells were subsequently harvested and specific binding of ^{125}I-IL 1 was determined as described in Methods.

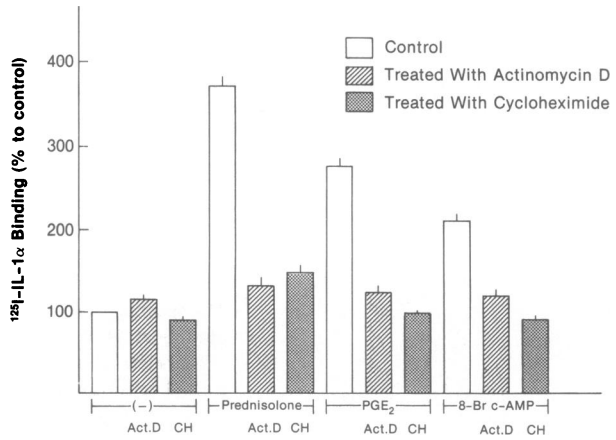

Figure 6. Effects of metabolic inhibitors on the induction of IL 1R expression by glucocorticoid, PGE_2, and cAMP. Fibroblasts were incubated with 3.5 μg/ml CH or 1 μg/ml Act. D for 12 h in the presence or absence of prednisolone (1×10^{-6} M), PGE_2 (1×10^{-6} M), or 8-Br cAMP (1×10^{-3} M). Bars, mean percent (and indicated SD) of the total ^{125}I-IL 1α binding to untreated control cells. □, control; ▨, treated with Act. D; □, treated with CH.

cyclase, and analogues of cAMP-induced IL 1R expression on fibroblasts, the A-kinase system is probably involved in IL 1-induced IL 1R expression.

We have previously reported the up-regulation of IL 1R expression by GC on selected cell types (human peripheral B lymphocytes and fibroblasts, but not on T lymphocytes, monocytes, or neutrophils (4). The induction of de novo synthesis of IL 1R on B cells by GC is rather unexpected, because GC are well known to suppress both IL 1 production (26, 27) and effects of IL 1 on T cells (28), which presumably contribute to the suppressive effects of GC on inflammation and immunity. However, it has also clearly documented that GC stimulates in vitro polyclonal immunoglobulin production by PBMC (29), which may be based on the induction of functional IL 1R on B cells (4). These divergent effects of GC led us to propose that GC may use this mechanism to favor humoral immunity at the expense of cell-mediated immunity (4).

Prostaglandins appear to have analogous effects to GC on IL 1R expression. PG induce two- to threefold increases in the expression of IL 1R on fibroblasts and sixfold increases on PBMC. However, prostaglandins, like GC, also suppress the production of IL 1 (30), inhibit the effects of IL 1 on T lymphocytes (31), suppress Ia antigen expression of macrophages (26), inhibit macrophage cytotoxicity (32), and reduce cellular immune reactions. In contrast, conflicting data have been reported concerning the effect of PGE_2 on B lymphocytes. Although prostaglandins suppress B cell proliferation (33), both PGE_2 and cAMP analogues were reported to be able to synergize effectively with IL 1 and IL 2 to induce B cell maturation and antibody production (34). Thus, prostaglandins, by inducing IL 1R on B lymphocytes, may also favor humoral immunity at the expense of cellular immunity.

The interactions of prostaglandins and IL 1 on fibroblasts are also complex. Prostaglandin mediates some of the effects of IL 1 on some cell types. For example, we have previously reported that the augmentation of human monocyte cytotoxicity by IL 1 is mediated by endogenous production of PGE (35). IL 1 stimulation of plasminogen activator production by human synovial fibroblasts is also said to be mediated by endogenous PGE production (36). In addition to mediating some of the effects of IL 1, PGE can also further promote the effects of IL 1 indirectly by inducing expression of IL 1 receptors on fibroblasts. The physiological role of IL 1 receptor induction on fibroblasts may be to promote wound healing.

Multiple interactions can potentially occur between IL 1, prostaglandins, and GC in vivo. Administration of IL 1 induces increased serum cortisol levels (37). IL 1 also induces the production of prostaglandins by many cell types (35). Inhibition of prostaglandin and IL 1 production by GC may counteract some of these effects. We have shown that both PGE and GC induce IL 1R expression by fibroblasts and PBMC. Since PGE and GC induce IL 1R expression in an additive manner and indomethacin did not block GC-induced IL 1R expression, the pathways are probably distinct. Overall, these data suggest that IL 1, prostaglandins, and GC can influence each others' production and effects in both an agonistic and antagonistic manner.

Acknowledgments

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