The effect of the glucocorticosteroid, dexamethasone, on arachidonic acid (AA) release and on protein levels of p11 and cytosolic phospholipase A2 (cPLA2) was studied in two epithelial cell lines, HeLa cells and BEAS-2B cells. Dexamethasone treatment of HeLa cells and BEAS-2B cells increased cellular p11 protein and mRNA levels in a time- and dose-dependent manner. It had little effect on levels of cPLA2 protein. In order to determine if increased p11 protein expression resulted in increased interaction between p11 and cPLA2, anti-cPLA2 antibodies were used to immunoprecipitate p11-cPLA2 complexes and Western blots of the immunoprecipitate were used to detect p11. In cells treated with dexamethasone, more p11 was detected in the anti-cPLA2 immunoprecipitate compared with control cells. Dexamethasone treatment of HeLa cells prelabeled with [3H]AA decreased the release of [3H]AA under basal conditions and after stimulation with the calcium ionophore A23187 (10^{-6} M). In order to determine if altering the p11 protein levels in HeLa cells independent of glucocorticosteroid treatment could also produce an effect on [3H]AA release, cells were stably transfected with plasmids expressing either p11 antisense mRNA or p11 mRNA. Cloned HeLa cells expressing p11 antisense mRNA exhibited less cellular p11 protein compared with control cells and greater [3H]AA release compared with cells transfected with a control vector. Cloned HeLa cells stably transfected with a p11 expression vector exhibited increased p11 cellular protein and diminished [3H]AA release under basal conditions and in response to A23187. Therefore, dexamethasone alteration of epithelial cell AA release may be due in part to induction of p11 protein expression.

**Phospholipase A2s (PLA2s)** are a group of enzymes that hydrolyze the ester bond of fatty acids from the sn-2 position of glycerophospholipids. The release of arachidonic acid (AA) from membranes by PLA2 and its subsequent conversion into leukotrienes, prostaglandins, and other eicosanoids plays an important role in inflammation (1–4). The mammalian calcium-dependent PLA2s can be grouped into major classes based on their molecular mass and cellular distribution, including the low molecular mass (10–14 kDa) secreted forms (sPLA2) and the structurally unrelated high molecular mass (85 kDa) cytosolic PLA2 (cPLA2) (1, 3, 5).

To date, five different sPLA2 isozymes have been described in mammalian cells. The 14-kDa sPLA2 enzyme from synovial fluid and platelets (Group IIA) may be involved in the pathogenesis of inflammatory reactions (3, 6, 7). The 14-kDa PLA2 lacks apparent selectivity for the sn-2 fatty acids of phospholipids and requires much higher Ca^{2+} concentrations (millimolar) than normal intracellular Ca^{2+} levels (nanomolar to micromolar) for activity. The 85-kDa high molecular mass cPLA2 has higher selectivity to hydrolyze phospholipids containing AA esterified in the sn-2 position (1, 3, 5, 8–11). Its activity is regulated by phosphorylation, G-protein activation, and physiologically relevant concentrations of calcium. Because cPLA2 may play a central role in producing AA and lysophospholipid for subsequent metabolism to prostaglandins, leukotrienes, hydroxyecosatetraenoic acids, and platelet-activating factor, potent lipid mediators of inflammation, the activation of cPLA2 may play an important role in modulating the airway inflammatory response (1, 3, 5).

S-100 proteins are a family of proteins first described by Moore (12) who initially characterized a group of abundant low molecular weight (10–12 kDa) acidic proteins in neural tissue. S-100 proteins are a group of Ca^{2+}-binding proteins that are expressed in a cell type-dependent fashion. This family includes S-100a, S-100b, and p11/calpain light chain (13). p11 was described as a member of the S-100 family of EF hand type Ca^{2+}-binding proteins but does not have the ability to bind Ca^{2+} ions due to crucial amino acid deletions and substitutions in the two EF hand loops of the protein (14, 15). p11 binds to and inhibits the phosphorylation of a 36-kDa protein known as p36, also known as annexin II as well as calpain heavy chain (16, 17).

Glucocorticoids are effective in the treatment of immune and inflammatory disorders affecting the lung and other organs. One mechanism of glucocorticoid modulation of the inflammatory response is inhibition of the release of AA from cellular lipids (18, 19) and inhibition of prostaglandin H synthase-2 synthase or cyclooxygenase-2 expression in a number of tissues (20–24). The rate of eicosanoid synthesis may be regulated by the availability of free AA that can be metabolized into prostanoids and leukotrienes via the cyclooxygenase and lipoxygenase pathways. The decreased synthesis of bioactive eicosanoids may represent an important mechanism of the anti-inflammatory action of glucocorticoids. Glucocorticoids can induce annexins which might inhibit sPLA2 activity in vitro (25–30). A recent study has demonstrated that p11 can directly
interact with the COOH-terminal region of 85-kDa cPLA₂ and inhibit cPLA₂ enzyme activity (31). Therefore, it was of interest to study whether p11 plays a role in glucocorticoid induced changes in cellular arachidonic acid release.

EXPERIMENTAL PROCEDURES

Cell Culture—HeLa cells were obtained from the American Type Culture Collection (Rockville, MD) and grown in DMEM medium with 10% fetal bovine serum. BEAS-2B cells were grown in L-15 medium (BioWhittaker, Walkersville, MD) supplemented with 10% fetal bovine serum. Cells—The HeLa or BEAS-2B cells grown on 175-cm² culture flasks were treated with dexamethasone (Calbiochem) (10⁻⁷, 10⁻⁸, and 10⁻⁹ M) for 24, 36 or 48 h. For time course experiments, the culture medium was changed at the same time, and all cells were harvested at the same time. Dexamethasone (10⁻⁷ M) was added at the indicated times prior to harvesting. At the indicated times treated and control cells were rinsed three times with cold PBS. After washing, the cells were transferred to 0.5 ml of homogenization buffer; 50 mM Hepes, pH 8.0, 1 mM EDTA, 1 mM EGTA, 100 μM leupeptin, 1 mM diithothreitol, 10 mM phenylmethylsulfonyl fluoride, 0.5 mM soybean trypsin inhibitor, 15 mM aprotinin, and 0.5% Triton X-100. Cells in homogenization buffer were sonicated for 15 s three times using a microprobe. Total protein was assayed by BCA reagent (Pierce). Samples containing 20 μg of cell lysate protein were separated on 18% Tris-glycine gels (Novex, San Diego, CA) using Tris-glycine SDS running buffer. The separated proteins were electrophoretically transferred onto a nitrocellulose membrane (Novex), then blocked with 5% non-fat dry milk overnight. p11 protein expression was detected by using 1:2000 dilution of mouse-anti-p11 monoclonal antibody (Transduction Laboratories, Lexington, KY) and 1:5000 dilution horseradish-peroxidase-conjugated goat-anti-mouse IgG as secondary antibody (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA). The blot was developed using the ECL Western blotting detection system (Amer sham Pharmacia Biotech).

Immunoblot of cPLA₂ Protein—HeLa cells grown in 175-cm² flasks were treated with dexamethasone (10⁻⁷ M) with or without the glucocorticoid receptor antagonist, RU486 (10⁻⁷, 10⁻⁸, 10⁻⁹, 10⁻¹⁰, and 10⁻¹¹ M). At the end of the incubation time, crude cytosolic extracts of treated and control cells were prepared and Western blots were done as described in the experimental procedures section for immunoblot of p11 protein.

Stable Transfection of a p11 Antisense Plasmid in HeLa Cells—The HeLa cells grown on T-75-cm² cultured flasks were labeled for 18 h with 1 μCi/ml [³²P]-labeled cDNA fragment of p11 cDNA was amplified by polymerase chain reaction using the following primers: 5'-CAACCAAAATGCCATCTC-3' (101–121) and 3'-5'-CTGCTCATTTGCGTACTT-3' (400–419). The protected RNA fragment was analyzed by agarose gel electrophoresis. To construct the probe for p11 mRNA, a 320-bp probe of p11 was amplified by polymerase chain reaction using the following set of sense and antisense primers: 5' primer, 5'-ACCA-CACCCAAAATGGGATC-3' (799–823); 3' primer, 5'-AAATAAGTGCGGCGCATATAA-3' (1104–1084) (Biosynthesis Inc., Lewisville, TX). The product for cPLA₂ mRNA was cloned into the TA cloning vector (Invitrogen, San Diego, CA). Orientation of the insert was determined by DNA sequencing. The cPLA₂ and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) RNA probes were prepared by in vitro transcription using T7 polymerase with [a-³²P]-CTP. The cPLA₂ probes were prepared by in vitro transcription using SP6 polymerase with [γ-³²P]-CTP. An RPA assay kit (RPAII, Ambion, Austin Texas) was used. Hybridization was performed at 45 °C for 16 h and with 10 μg (for GAPDH) or 20 μg (for cPLA₂) and 40 μg (for p11) of total RNA. 10⁻⁷ M dexamethasone, 10⁻⁸ M p11 antisense cDNA and 10⁻⁹ M GAPDH cDNA were used. After hybridization, the unhybridized RNA was digested by addition of 1:100 diluted RNaseA/T1 mix at 37 °C for 60 min. Digestion was terminated by the addition of RNase inactivation and precipitation mixture. The protected RNA fragment was analyzed by autoradiography after separation on 6% polyacrylamide, 8 x urea gels (Novex).

Effect of RU486 on Dexamethasone-induced p11 Expression—The HeLa cells grown on 175-cm² flasks were treated with dexamethasone (10⁻⁷ M) with or without the glucocorticoid receptor antagonist, RU486 (10⁻⁷, 10⁻⁸, 10⁻⁹, 10⁻¹⁰, and 10⁻¹¹ M) for 24 h. At the end of incubation time, crude cytosolic extracts of treated and control cells were prepared and Western blots were done as described in the experimental procedures section for immunoblot of p11 protein.

Arachidonic Acid Release from Dexamethasone-treated Cells—The HeLa cells grown on T-75-cm² cultured flasks were labeled for 18 h with 1 μCi/ml [³²P]-labeled cDNA fragment of p11 cDNA was amplified by polymerase chain reaction using the following primers: 5' primer, 5'-AAATAAGTGCGGCGCATATAA-3' (1104–1084) (Biosynthesis Inc., Lewisville, TX). The protected RNA fragment was analyzed by agarose gel electrophoresis. To construct the probe for p11 mRNA, a 320-bp probe of p11 was amplified by polymerase chain reaction using the following set of sense and antisense primers: 5' primer, 5'-ACCA-CACCCAAAATGGGATC-3' (799–823); 3' primer, 5'-CTGCTCATTTGCGTACTT-3' (400–419) (Genosys Biotechnologies, Inc., The Woodlands, TX). The product for cPLA₂ mRNA was cloned into the pGEM-T Easy Vector (Promega, Madison, WI). Orientation of the insert was determined by DNA sequencing. The cPLA₂ and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) RNA probes were prepared by in vitro transcription using T7 polymerase with [α-³²P]-CTP. The cPLA₂ probes were prepared by in vitro transcription using SP6 polymerase with [γ-³²P]-CTP. An RPA assay kit (RPAII, Ambion, Austin Texas) was used. Hybridization was performed at 45 °C for 16 h and with 10 μg (for GAPDH) or 20 μg (for cPLA₂) and 40 μg (for p11) of total RNA. 10⁻⁷ M dexamethasone, 10⁻⁸ M p11 antisense cDNA and 10⁻⁹ M GAPDH cDNA were used. After hybridization, the unhybridized RNA was digested by addition of 1:100 diluted RNaseA/T1 mix at 37 °C for 60 min. Digestion was terminated by the addition of RNase inactivation and precipitation mixture. The protected RNA fragment was analyzed by autoradiography after separation on 6% polyacrylamide, 8 x urea gels (Novex).

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RESULTS

Dexamethasone Increases p11 Protein Levels in Human HeLa Cells and BEAS-2B Cells—The effect of dexamethasone treatment on human epithelial cell expression of p11 was studied by Western blot of two different epithelial cell lines, HeLa cells and BEAS-2B cells. Fig. 1A demonstrates the effect of dexamethasone treatment of HeLa cells on cellular p11 accumulation. Treatment of cells with dexamethasone (10^{-7} M) for 24–48 h resulted in a significant increase in p11 protein expression in cell lysates. In addition, treatment of cells with 10^{-7}, 10^{-9}, and 10^{-11} M dexamethasone for 24 h resulted in a dose-related increase cellular p11 protein levels (Fig. 1B). Treatment of BEAS-2B cells with dexamethasone (10^{-7} M) for 24–48 h also resulted in a significant increase in p11 protein expression in cell lysates (Fig. 1C).

Effect of Dexamethasone on Steady State Levels of p11 mRNA—Steady state levels of mRNA for p11 were measured by RPA of total cellular RNA extracted from HeLa cells that were incubated without or with dexamethasone (10^{-7} M) for 24–48 h. As shown in Fig. 2A, these cells produce p11 mRNA and the steady state level of p11 mRNA was increased by dexamethasone treatment over 24–48 h. In addition, dexamethasone in concentrations of 10^{-7} to 10^{-11} M induced a dose-related change in p11 mRNA levels (Fig. 2B).

Effect of Dexamethasone on cPLA2 Protein and mRNA Levels in HeLa Cells—The effect of dexamethasone treatment on human epithelial cell expression of cPLA2 was studied by Western blot of cell lysates. Treatment of cells with dexamethasone
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RU486 Inhibits Dexamethasone-induced p11 Protein Increases—

The results from RPA and Western blot studies indicated that dexamethasone treatment had an effect on p11 mRNA levels and protein production but little or no effect on the mRNA expression or protein level of cPLA2. In these cells, dexamethasone treatment does alter the release of [3H]-labeled AA both at base line and after exposure to the calcium ionophore A23187. Fig. 6 demonstrates that labeled AA release from dexamethasone-treated HeLa cells (HD) is lower than that from untreated HeLa cells (HC). After treatment with A23187, the release of labeled AA from dexamethasone-treated HeLa cells (HD + A) is significantly decreased compared with untreated control cells (HC + A).

Antisense Inhibition of p11 Increases AA Release—We have shown that dexamethasone increases p11 expression and inhibits PLA2 activity in vitro. It has been reported that p11 can bind to cPLA2 and inhibit cPLA2 activity in vitro. In order to study whether dexamethasone might alter cPLA2 activity in part by increasing p11 expression in human cells, we performed the following study. First, we constructed a p11 antisense plasmid and then stably transfected HeLa cells to examine the AA release in these cells. Western blot studies of cloned transformed cells showed that p11 protein production was decreased in HeLa cells which were transfected with pSor1-plcdNA3.1(+) plasmid compared with HeLa cells, which were transfected with pcDNA3.1(+) plasmid alone (Fig. 7A). There was no change in cPLA2 expression in these cells (Fig. 7B). [3H]AA release from the HeLa cells that were permanently transfected with p11 antisense plasmid was increased both at base line and

Dexamethasone Inhibits AA Release from the HeLa Cells—

In an attempt to determine if the effect of dexamethasone on p11 protein levels is mediated via a glucocorticoid receptor interaction, RU486 (10^{-7} to 10^{-12} M) was incubated with cells prior to and concomitant with the dexamethasone treatment. Treatment with RU 486 resulted in a dose-dependent inhibition of the dexamethasone-induced increases in p11 protein levels. Fig. 5 shows the effect of RU486 (10^{-10} to 10^{-12} M) on dexamethasone-induced p11 protein levels.

The results from RPA and Western blot studies indicated that dexamethasone treatment had an effect on p11 mRNA levels and protein production but little or no effect on the mRNA expression or protein level of cPLA2. In these cells, dexamethasone treatment does alter the release of [3H]-labeled AA both at base line and after exposure to the calcium ionophore A23187. Fig. 6 demonstrates that labeled AA release from dexamethasone-treated HeLa cells (HD) is lower than that from untreated HeLa cells (HC). After treatment with A23187, the release of labeled AA from dexamethasone-treated HeLa cells (HD + A) is significantly decreased compared with untreated control cells (HC + A).

FIG. 3. The effect of dexamethasone on cPLA2 protein and steady state mRNA levels. A, the effect of dexamethasone on cPLA2 protein levels in HeLa cells. Cells were grown to near confluence and then treated with dexamethasone (10^{-7} M) for 24–48 h. Cell lysates from treated and untreated cells were processed as described under “Experimental Procedures,” and 20 µg of total protein was subjected to gel electrophoresis and immunoblotting. B, the dose effect of dexamethasone on cPLA2 protein levels in HeLa cells. Cells were grown to near confluence and then treated with dexamethasone (10^{-7} to 10^{-11} M) for 24 h. Cell lysates from treated and untreated cells were processed as described under “Experimental Procedures,” and 20 µg of total protein was subjected to gel electrophoresis and immunoblotting. C, the effect of dexamethasone on cPLA2 mRNA levels. HeLa cells were treated with dexamethasone (10^{-7} M) for 24, 36, and 48 h before total RNA was extracted. Ten µg and 20 µg of the total RNA were hybridized to GAPDH and cPLA2-specific radiolabeled cRNA probes, respectively, and assayed by RPA. The protected fragments of cPLA2 (306 bp) and GAPDH were visualized by autoradiography. The result shown is representative of three separate experiments.

Dexamethasone Increases p11 Bound to cPLA2—The above results demonstrated that dexamethasone treatment increased p11 expression, but had little or no effect on cPLA2 expression. To further investigate the interaction between p11 and cPLA2 in human epithelial cells, immunoprecipitation of the p11-cPLA2 complex from HeLa cells was performed. As shown in Fig. 4, A and B, p11 was precipitated from the HeLa cell and BEAS-2B cell lysates by rabbit anti-human cPLA2 polyclonal antibody followed by the addition of Protein G Plus/Protein A-agarose beads. Immunoblots of the purified complex were developed for p11 protein. There was more p11 coprecipitated with cPLA2 after dexamethasone treatment. This result demonstrated that dexamethasone treatment resulted not only in an increase in cellular p11 protein but also in an increase in p11 bound to cPLA2.

RU486 Inhibits Dexamethasone-induced p11 Protein Increases—

In an attempt to determine if the effect of dexamethasone on p11 protein levels is mediated via a glucocorticoid receptor interaction, RU486 (10^{-7} to 10^{-12} M) was incubated with cells prior to and concomitant with the dexamethasone treatment. Treatment with RU 486 resulted in a dose-dependent inhibition of the dexamethasone-induced increases in p11 protein levels. Fig. 5 shows the effect of RU486 (10^{-10} to 10^{-12} M) on dexamethasone-induced p11 protein levels.

We have shown that dexamethasone increases p11 expression and inhibits PLA2 activity in vitro. It has been reported that p11 can bind to cPLA2 and inhibit cPLA2 activity in vitro. In order to study whether dexamethasone might alter cPLA2 activity in part by increasing p11 expression in human cells, we performed two studies. First, we constructed a p11 antisense plasmid and then stably transfected HeLa cells to examine the AA release in these cells. Western blot studies of cloned transformed cells showed that p11 protein production was decreased in HeLa cells which were transfected with pSp11-plcdNA3.1(+) plasmid compared with HeLa cells, which were transfected with pcDNA3.1(+) plasmid alone (Fig. 7A). There was no change in cPLA2 expression in these cells (Fig. 7B). [3H]AA release from the HeLa cells that were permanently transfected with p11 antisense plasmid was increased both at base line and
after exposure to the calcium ionophore A23187 compared with control cells (Fig. 8).

Increased p11 Expression Inhibits AA Release—In order to determine whether dexamethasone inhibition of cellular PLA₂ activity might be related in part to increasing p11 expression in human epithelial cells, we constructed a p11 expression plasmid and stably transfected HeLa cells to examine the effect of increased p11 expression on AA release in these cells. The effect of the p11 expression plasmid on cellular p11 protein is demonstrated in Fig. 9A. Western blot results showed that p11 protein production was increased in HeLa cells that were transfected with p11-pcDNA3.1(−) plasmid compared with HeLa cells that were transfected with pcDNA3.1(−) plasmid alone. There was no change in cPLA₂ expression (Fig. 9B). AA release from the HeLa cells which were permanently transfected with p11 expression plasmid was decreased both at baseline and after exposure to the calcium ionophore A23187 (Fig. 10). Therefore, dexamethasone treatment increases p11 protein expression and reduces cellular arachidonicate release. Furthermore, increasing cellular p11 protein production independent of dexamethasone treatment reduces cellular AA release as well.

DISCUSSION

p11, or calpactin light chain, is a member of the S-100 family of small calcium binding proteins; however, it has several unique features. S-100 proteins contain two EF hands that function as calcium binding domains (13). p11 does not have the ability to bind Ca²⁺ ions due to amino acid deletions and substitutions in the two EF hand motifs (14, 15). Instead, p11 is present in a variety of cells separately or as a heterotetramer binding to annexin II. The heterotetramer is composed of two copies of the 36-kDa heavy chain, annexin II subunits and two copies of 11-kDa light chain, p11 subunits as (p36)₂(p11)₂ (32, 33).

Glucocorticosteroids are potent anti-inflammatory agents. This anti-inflammatory effect may be produced via a variety of mechanisms. A group of structurally related, calcium-dependent phospholipid-binding proteins, annexins, which were formerly known as lipocortins or calpactins, had been shown to be...
inducible by glucocorticoids. Annexin I has been reported to inhibit sPLA2 activity in vitro (25–30). These observations led to the hypothesis that the inhibition of sPLA2 by annexins is the mechanism of the anti-inflammatory action of glucocorticoids. Subsequent studies failed to show a direct interaction between the 14-kDa PLA2 and annexins. Instead, this inhibition may be dependent on the concentration of substrate (34, 35), the extent of inhibition being more closely related to the inhibitor:substrate rather than the inhibitor:enzyme ratio. In addition, glucocorticoid treatment suppresses the induction of Group II sPLA2 expression in a variety of cells (36–40).

sPLA2 selectively hydrolyzes AA from the sn-2-ester bond of membrane phospholipids. sPLA2 may play an important role in the production of free fatty acids and lysophospholipids, precursors of eicosanoids and PAF, all of which may function as intracellular second messengers or potent inflammatory mediators (1, 3, 5). It has been reported that dexamethasone treatment reduces changes in sPLA2 protein and mRNA levels induced by TNF treatment of HeLa cells (41). Dexamethasone may have other effects on AA metabolism and at earlier time points, including effects perhaps not requiring transcription such as inhibition of phosphorylation of cPLA2 (42). We did not document an effect of dexamethasone on unstimulated expression of cPLA2; however, we did note an effect of dexamethasone on cellular p11 protein and mRNA levels. Because it has been demonstrated that p11 can directly interact with the carboxyl region of cPLA2 and inhibit its activity in vitro (31), we hypothesized that a part of the effect of dexamethasone on cellular AA release might be mediated by a dexamethasone-induced change in p11 protein levels.

Four lines of evidence suggest that dexamethasone may alter cellular arachidonate release in part by induction of p11 protein expression. First, studies in two different cell lines demonstrate that dexamethasone induces human epithelial cell p11 gene expression and protein production. This effect was not associated with a reduction of cPLA2 expression in HeLa cells. RU486, an antagonist that competes with glucocorticoids for binding to the glucocorticoid receptor (43, 44), blocked the stimulatory effect of dexamethasone on p11 protein production, suggesting that dexamethasone-induced p11 gene expression and subsequent protein synthesis occurs via a glucocorticoid receptor-mediated pathway. Second, in dexamethasone-treated cells, there was increased p11 binding to cPLA2 as evidenced by p11 which was precipitated by anti-cPLA2 antibody as a p11-cPLA2 complex. Third, cells stably transfected with a plasmid that expresses p11 antisense mRNA and that subsequently express less p11 protein have enhanced release of prelabeled AA both at base line and after stimulation with the ionophore A23187. Fourth, we studied the effect of p11 on AA release in the setting of overexpression of p11 protein in a human epithelial cell line, Hela cells. The release of prelabeled AA from cells that overexpressed p11 was significantly lower than that from control cells. Therefore, overexpression of p11 inhibits PLA2 activity and reduces the release of AA from [3H]AA-prelabeled cells. Thus, manipulation of p11 levels independent of corticosteroid therapy also alters AA release from permanently transfected cells.

AA release from cell membranes may be a complex process affected by a variety of stimuli and involving multiple enzymes and regulatory proteins. We suggest that one of these effects may be related to modulation of p11 protein production and binding to cPLA2.

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