Glucocorticoid Inhibits Oxidized LDL-Induced Macrophage Growth by Suppressing the Expression of Granulocyte/Macrophage Colony-Stimulating Factor

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Abstract—Glucocorticoid, an anti-inflammatory agent, inhibits the development of atherosclerosis in various experimental animal models. This is partially explained by its ability to inhibit smooth muscle cell migration and proliferation in the intima and to reduce chemotaxis of circulating monocytes and leukocytes into the subendothelial spaces. We have recently demonstrated that oxidized LDL (Ox-LDL) has a mitogenic activity for macrophages in vitro in which Ox-LDL–induced granulocyte/macrophage colony-stimulating factor (GM-CSF) production plays an important role. Proliferation of cellular components is one of the characteristic events in the development and progression of atherosclerotic lesions. In the present study, we investigated the effects of glucocorticoids on Ox-LDL–induced macrophage growth. Dexamethasone, prednisolone, and cortisol inhibited Ox-LDL–induced thymidine incorporation into macrophages by 85%, 70%, and 50%, respectively. Ox-LDL induced a significant production of GM-CSF by macrophages, which was effectively inhibited by dexamethasone, prednisolone, and cortisol by 80%, 65%, and 50%, respectively. Dexamethasone-mediated inhibition of Ox-LDL–induced GM-CSF mRNA expression and macrophage growth was significantly abrogated by RU-486, a glucocorticoid receptor antagonist. Our results suggest that the inhibitory effects of glucocorticoids on macrophage growth may be due to the inhibition of Ox-LDL–induced GM-CSF production through transactivation of the glucocorticoid receptor. (Arterioscler Thromb Vasc Biol. 1999;19:1726-1733.)

Key Words: glucocorticoids ■ dexamethasone ■ oxidized LDL ■ macrophage growth ■ atherosclerosis

Macrophage-derived foam cells are the key cellular elements in the early stages of atherosclerosis and play an important role in the development and progression of atherosclerosis through production of various active molecules, such as cytokines and growth factors. Macrophages take up oxidized LDL (Ox-LDL) through the scavenger receptor pathways and become foam cells. Macrophages and macrophage-derived foam cells proliferate in the atherosclerotic lesions, particularly in the early lesions. Because the growth of cellular components is one of the characteristic features in atherosclerotic lesions, it seems reasonable to expect that macrophage growth might be linked to atherosclerotic processes, probably by enhancing its progression. Yui et al reported that Ox-LDL could induce the growth of starch-induced mouse peritoneal macrophages in vitro. Recent studies have shown that Ox-LDL exhibited a growth-stimulating capacity for other macrophages, such as mouse resident peritoneal macrophages and rat resident peritoneal macrophages, and human monocyte-derived macrophages. Moreover, our biochemical studies showed that scavenger receptor-mediated endocytic internalization of lysophosphatidylcholine (lyso-PC), a major modified lipid moiety of Ox-LDL, is important for Ox-LDL–induced macrophage growth and that Ox-LDL–induced granulocyte/macrophage colony-stimulating factor (GM-CSF) production plays an important role in macrophage growth.

Atherosclerosis is viewed as a chronic inflammatory process because one of its features is accumulation of inflammatory cells and cytokines. Moreover, administration of an anti-inflammatory agent, dexamethasone, suppresses the development of atherosclerosis in various experimental animal models, including Watanabe heritable hyperlipidemic rabbits, cholesterol-fed rabbits, cuff-induced intimal thickening of the rabbit carotid artery, and rat balloon angioplasty model. The inhibitory mechanisms of dexamethasone for the development of atherosclerosis are partially explained by inhibition of smooth muscle cell migration and proliferation and by a reduction in chemotaxis of circulating monocytes and leukocytes into the subendothelial spaces. In addition, Asai et al reported that dexamethasone inhibited the growth of U937 cells, a monocyte/macrophage-like cell line. However, the exact inhibitory mechanism of dexameth-
asosterone for the development of atherosclerosis remains to be elucidated.

Because macrophage-derived foam cells play an essential role in the development of the early stages of atherosclerosis, we investigated the effect of glucocorticoids on Ox-LDL–induced macrophage growth in the present study. Our results demonstrated that glucocorticoids suppressed Ox-LDL–induced macrophage growth through inhibition of Ox-LDL–induced production of GM-CSF, which might be one of the underlying mechanisms of the inhibitory effect of dexamethasone on the development of experimental atherosclerosis in animal models.

**Methods**

**Chemicals**

[methyl-3H]Thymidine and [14C]palmitoyl lyso-PC were purchased from DuPont-NEN. Dexamethasone, prednisolone, cortisol, aldosterone, progesterone, estrone, estradiol, estril, dehydroepiandrosterone (DHEA), testosterone, and mifepristone (RU-486) were purchased from Sigma Chemical Co. All other chemicals were the highest grade available from commercial sources.

**Lipoproteins**

Human LDL (d=1.019 to 1.063 g/mL) was isolated by sequential ultracentrifugation from the plasma of normolipidemic subjects after overnight fasting. LDL was dialyzed against 0.15 mol/L NaCl and 1 mmol/L ethylenediamine-tetraacetic acid (EDTA), pH 7.4. Ox-LDL was prepared by incubation of LDL with 5 μmol/L CuSO4 for 20 hours at 37°C followed by the addition of 1 mmol/L EDTA and cooling.23 The concentrations of proteins were determined by bicinchoninic acid protein assay reagent (Pierce) using bovine serum albumin as a standard.24 Ox-LDL was labeled with [14C]lyso-PC as described previously.13 Specific radioactivity of [14C]lyso-PC–labeled Ox-LDL was 16 000 cpm/μg protein. The level of endotoxin associated with these lipoproteins was <1 pg/μg protein, as measured by a commercially available kit (Toxicolor system; Seikagaku Corp). Moreover, macrophage growth was not influenced by endotoxin at a concentration of <1 ng/mL in our experimental system.

**Cell Culture**

Peritoneal macrophages were collected from nonstimulated male C3H/He mice (25 to 30 g) (Japan SLC, Inc, Hamamatsu, Japan) and suspended in RPMI 1640 medium (Nissui Seiyaku Co) supplemented with 10% heat-inactivated FBS (Life Technologies, Inc), streptomycin, and 100 U/mL of penicillin (medium A). Human peripheral blood monocytes were isolated by the method of Fogelman et al27 using Ficoll/Hypaque gradient centrifugation. The mononuclear cells thus obtained were resuspended in RPMI 1640 supplemented with 20% autologous serum, 0.1 mg/mL of streptomycin, and 100 U/mL of penicillin, plated on serum-treated 10 cm dishes (Falcon), and incubated for 2 hours. Nonadherent cells were removed by washing 3× with PBS, then the adherent cells were detached by incubation in PBS/5% autologous serum containing 0.02% EDTA at 4°C for 30 minutes. The cells were then washed extensively and resuspended in RPMI 1640 supplemented with 5% autologous serum, 0.1 mg/mL of streptomycin, and 100 U/mL of penicillin (medium B). The cells were plated on 10 cm dishes and incubated for 9 days to differentiate into macrophages. The medium was aspirated and replaced every 3 days with fresh medium B. After 9-day incubation, differentiation of monocytes into macrophages was identified by 4 criteria, including (1) adherence to culture plates, (2) morphologic features resembling mononuclear cells after Giemsa staining, (3) the capacity to take up carbon particles, and (4) positive immunohistochemistry with antibody for CD 68. The cells contained >95% macrophages and were >95% viable as determined by trypan blue staining and lactic dehydrogenase release.

** Tritiated Thymidine Incorporation Assay**

The peritoneal cells were adjusted to 4×10⁶ cells/mL for the [3H]thymidine incorporation assay.10 Cell suspensions (100 μL) were dispersed in each well of 96-well tissue culture plates (6.4 mm in diameter, Falcon) and incubated for 90 minutes at 37°C. Nonadherent cells were removed by washing 3× with 100 μL of prewarmed medium A. More than 98% of adherent cells were confirmed to be macrophages by both Giemsa staining and carbon particle uptake.10 These macrophages were cultured at 37°C in 0.1 mL of medium A in the presence of the test lipoproteins without a medium change. Eighteen hours before the termination of the experiments, 10 μL of 10 μCi/mL [3H]thymidine was added to each well and incubated for 18 hours at 37°C. The medium was discarded, and the cells were dissolved in 0.1 mL of 0.5% sodium dodecyl sulfate and subsequently precipitated with 0.1 mL of ice-cold 10% trichloroacetic acid (TCA). The resulting TCA–insoluble material was collected on filters with Labomash LM-101 (Labo Science). The filters were dried, and their radioactivity was counted in a liquid scintillation spectrophotometer.

**Endocytic Degradation and Cell-Association of [125I]Ox-LDL**

Mice were sacrificed by CO2 asphyxiation. Peritoneal macrophages (2×10⁶ cells) in 1 mL of medium A were seeded onto each plastic culture dish (22 mm in diameter, Falcon) and incubated for 90 minutes at 37°C. The monolayers thus formed were washed 3× with 1.0 mL of medium A. Each well was incubated with [125I]Ox-LDL for 6 hours at 37°C in the absence or presence of the indicated concentrations of dexamethasone. Endocytic degradation was determined by TCA-soluble radioactivity in the medium after precipitating free iodine with AgNO3, as described previously.24 Cells were solubilized with 1.0 mL of 0.1 mol/L NaOH and the cell-associated radioactivity was determined as described previously.29

**ELISA for GM-CSF**

Mouse peritoneal macrophages were adjusted to 5×10⁶ cells/mL, and 10 mL of the cell suspension was dispersed in 10 cm plates (10 cm in diameter, Falcon) then incubated for 90 minutes at 37°C. Nonadherent cells were removed by washing 3× with 5 mL of PBS, and adherent cells were cultured at 37°C in 15 mL of medium A with or without the test lipoproteins. During incubation for 24 hours, 300 μL of the medium were collected at the indicated time intervals (the actual incubation times were 0, 3, 6, 9, 12, and 24 hours) and immediately centrifuged at 10 000g for 1 minute to remove any particulate material. The supernatant was stored at −80°C immediately. Then, the frozen culture supernatants were quickly thawed to determine GM-CSF levels in the medium. The concentration of GM-CSF was determined by a commercially available GM-CSF–specific ELISA kit (sensitivity, 5 pg/mL, Amersham) using recombinant murine GM-CSF as a standard.15
Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) Analysis for GM-CSF

Standard molecular biological techniques were used. After incubation of murine peritoneal macrophage monolayers (2 × 10⁶ cells/well) in 6-well plate, 3.5 cm in diameter, Nunc) with 20 μg/mL Ox-LDL for 1 hour, total RNA was extracted with TRIzol (Life Technologies, Inc). The first strand cDNA synthesis containing 1 μg of total RNA was primed with oligo dT. Primers used for PCR amplification of GM-CSF and β-actin were designed on the basis of murine GM-CSF cDNA and murine β-actin cDNA sequences as follows: for GM-CSF: forward primer, TGT GGT CTA CAG CCT CTC AGC (nucleotide 541 to 564 of murine GM-CSF coding sequence); reverse primer, CAA AGG GGA TAT CAG TCA GAA AGG TAC (nucleotide 64 to 87 of murine GM-CSF coding sequence); for β-actin: forward primer, GTG GGC CGC TCT AGG CAC (nucleotide 25 to 45 of murine β-actin coding sequence); reverse primer, CTC TTT GAT GTC ACG CAC GAT TTC (nucleotide 343 to 368 of murine GM-CSF coding sequence,31 the size of RT-PCR products of GM-CSF was expected to be 305 base pairs); for β-actin: forward primer, GTG GGC CGC TCT AGG CAC CAA (nucleotide 25 to 45 of murine β-actin coding sequence); reverse primer, CTC TTT GAT GTC ACG CAC GAT TTC (nucleotide 541 to 564 of murine β-actin coding sequence31 the size of RT-PCR products of β-actin was expected to be 540 base pairs). The cycling conditions in the GeneAmp 9600 System consisted of a first step of 94°C denaturation for 10 minutes, followed by 30 cycles of annealing at 54°C for 60 seconds, extension at 75°C for 90 seconds, and denaturation at 94°C for 30 seconds, with a final elongation step at 75°C for 10 minutes. Amplification products were analyzed by 1.5% agarose gel electrophoresis. To verify that the amplification products were consistent with the reported sequences of murine GM-CSF and β-actin, they were ligated into pGEM-T (Promega), transfected into Escherichia coli XL1-Blue and sequenced by using 373A DNA sequencer (Applied Biosystems).

Miscellaneous

Data were expressed as mean ± SD. Differences between groups were examined for statistical significance using the Student’s t test. A probability value <0.05 was considered significant. The experimental protocol was approved by the Human Ethics Review Committee and the Ethics Review Committee for Animal Experimentation of the Kumamoto University School of Medicine.

Results

Glucocorticoids Inhibit Ox-LDL–Induced Macrophage Growth

As shown in Figure 1, Ox-LDL–induced [³H]thymidine incorporation into macrophages was significantly inhibited by dexamethasone in a dose-dependent manner, whereas dexamethasone alone did not affect [³H]thymidine incorporation into macrophages. The cell counting assay also showed that the Ox-LDL–induced increase in cell number from 1.7 × 10⁴ cells/well to 3.2 × 10⁴ cells/well was inhibited by 75% when 10 nmol/L of dexamethasone was added (the Table). Under these conditions, dexamethasone had no cytotoxic effects on these cells; more than 95% of the cells were viable as confirmed by microscopic examination after trypan blue staining and lactic dehydrogenase release (data not shown). These results demonstrated that dexamethasone inhibits Ox-LDL–induced macrophage growth.

We next examined the effect of several steroids on Ox-LDL–induced thymidine incorporation into macrophages. As shown in Figure 2, dexamethasone, prednisolone, and cortisol significantly inhibited Ox-LDL–induced [³H]thymidine incorporation by 85%, 70%, and 50%, respectively. In contrast, aldosterone did not inhibit [³H]thymidine incorporation by Ox-LDL (Figure 2). Moreover, other steroids, including...
RU-486, a glucocorticoid receptor antagonist, on this phenomenon. As shown in Figure 3, [3H]thymidine incorporation into macrophages was not affected by RU-486 in the presence or absence of Ox-LDL. However, RU-486 significantly abrogated dexamethasone-mediated inhibition of Ox-LDL–induced [3H]thymidine incorporation (Figure 3). These results suggested that the inhibitory effect of dexamethasone on Ox-LDL–induced macrophage growth might be mediated by transactivation of glucocorticoid receptor.

Effect of Dexamethasone on the Uptake of Ox-LDL and Lyso-PC

Dexamethasone increases acetyl-LDL degradation by human monocye-derived macrophages or suppresses the expression of acetyl-LDL receptor on a human macrophage cell line, THP-1 cell. Moreover, we previously demonstrated that the internalization of lyso-PC concomitant with Ox-LDL into macrophages through the scavenger receptor A-I/A-II played an important role in macrophage growth. Thus, to elucidate whether dexamethasone modulates the uptake of Ox-LDL or lyso-PC by macrophages, we examined the effects of dexamethasone on cell-association and degradation of Ox-LDL and on the uptake of lyso-PC by macrophages. Figure 4A shows that cell-association of [125I]Ox-LDL to macrophages was inhibited by dexamethasone in a dose-dependent fashion with maximal inhibition by 20%. Moreover, degradation of [125I]Ox-LDL by cells was also inhibited by dexamethasone by 30% (Figure 4B). Under these conditions, the transfer of lyso-PC from Ox-LDL to macrophages was examined using [14C]lyso-PC–labeled Ox-LDL. Dexamethasone inhibited the amount of [14C]lyso-PC transferred from Ox-LDL to cells by 20% (Figure 4C). Thus, the inhibition of macrophage growth by dexamethasone could be explained at least in part by the inhibition of lyso-PC uptake, although several other inhibitory mechanisms remain unknown.

Glucocorticoids Inhibit Ox-LDL–Induced GM-CSF Production

We have recently demonstrated that Ox-LDL–induced production of GM-CSF plays an important role in Ox-LDL–induced macrophage growth.
induced macrophage growth as a growth priming factor.14 Thus, we next examined the effect of glucocorticoids on Ox-LDL–induced GM-CSF production into the medium using ELISA method. As shown in Figure 5, addition of 20 μg/mL of Ox-LDL significantly induced GM-CSF release into the medium, and the maximal release was observed at 6 hours, although it decreased to the basal level at 24 hours. When macrophages were incubated with Ox-LDL together with different concentrations of dexamethasone, Ox-LDL–induced GM-CSF release was inhibited in a dose-dependent manner (Figure 5). Figure 6 shows that prednisolone and cortisol also significantly inhibited GM-CSF release, whereas estradiol and testosterone had no effect. Among the glucocorticoids tested in the present study, dexamethasone was the most potent inhibitor of GM-CSF release, a finding consistent with its inhibitory effect on Ox-LDL–induced [3H]thymidine incorporation into macrophages (Figure 2). Figure 6 also shows that RU-486 abrogated dexamethasone-mediated inhibition of Ox-LDL–induced GM-CSF release.

To elucidate whether dexamethasone inhibits GM-CSF release from macrophages at the mRNA level, we determined the level of GM-CSF mRNA in macrophages using RT-PCR analysis with parallel determination of β-actin mRNA as a control. As shown in Figure 7, the levels of β-actin mRNA were not affected by Ox-LDL, dexamethasone, and/or RU-486. In contrast, Ox-LDL caused a significant induction of GM-CSF mRNA, which was significantly inhibited by dexamethasone. Consistent with the effect of RU-486 on thymidine incorporation (Figure 3), dexamethasone-mediated inhibition of Ox-LDL–induced GM-CSF mRNA expression was significantly abrogated by RU-486 (Figure 7).

**Discussion**

Previous studies have demonstrated that dexamethasone inhibits atherosclerosis in various experimental models.16–19 Because macrophage-derived foam cells play an important role in the development and progression of atherosclerosis1 and were reported to proliferate in the atherosclerotic lesions,5–7 we investigated in the present study the effect of dexamethasone on the Ox-LDL–induced macrophage growth. Our results showed that glucocorticoids, including dexamethasone, prednisolone, and cortisol, significantly inhibited Ox-LDL–induced macrophage growth (Figures 1 and 2, and the Table). Furthermore, these glucocorticoids significantly inhibited Ox-LDL–induced GM-CSF production (Figures 5 to 7), an effect prevented by a glucocorticoid receptor antagonist, RU-486 (Figures 3 and 7). These results suggested that the inhibitory effect of glucocorticoids on Ox-LDL–induced macrophage growth might be also mediated by activation of the glucocorticoid receptor.

In cholesterol-fed rabbits, administration of glucocorticoid suppresses the development of atherosclerotic lesions17 and reduces macrophage cell counts in atherosclerotic lesions.24 These effects were partially explained by a reduction in chemotaxis of circulating monocytes.22 In the present study, we demonstrated a clear inhibitory effect of dexamethasone on Ox-LDL–induced macrophage growth (Figure 1 and the Table). Moreover, Hamilton16 demonstrated that dexamethasone inhibited M-CSF–induced growth of mouse peritoneal macrophages. Because Ox-LDL and M-CSF are present in atherosclerotic lesions,1–4 in which macrophage growth is
also reported,5-7 inhibition of macrophage growth by dexamethasone might be a possible mechanism that reduces macrophage cell counts in atherosclerotic lesions. It is possible that such an effect may lead to the prevention of development and/or progression of atherosclerosis in cholesterol-fed rabbits.

Based on our recent study that internalization of lyso-PC into macrophages plays an important role in Ox-LDL–induced macrophage growth,13,14 we believe that the inhibitory mechanism of dexamethasone on Ox-LDL–induced macrophage growth is partially explained by the inhibition of uptake of Ox-LDL and lyso-PC (Figure 4). However, when macrophages were incubated with 20 μg/mL of Ox-LDL together with 10 nM of dexamethasone, inhibition of macrophage growth and uptake of lyso-PC were 80% and 20%, respectively (Figures 2 and 4). Based on these results, we postulate the presence of other major inhibitory mechanism(s) of Ox-LDL–induced macrophage growth.

Glucocorticoids, such as dexamethasone, prednisolone, and cortisol, significantly inhibited Ox-LDL–induced GM-CSF production (Figures 5 and 6), which was consistent with their inhibitory effect on macrophage growth (Figure 2 and the Table). These results suggested that inhibition of GM-CSF production by glucocorticoids might cause inhibition of Ox-LDL–induced macrophage growth. Our previous report15 and the present study demonstrated that Ox-LDL could induce an increase in GM-CSF mRNA level and protein release. Moreover, our subsequent preliminary experiments using luciferase assay in which we examined the promoter activity of GM-CSF gene showed that Ox-LDL activated reporter gene expression, suggesting that Ox-LDL could enhance GM-CSF mRNA expression at transcription level. However, post-transcriptional regulation of GM-CSF in macrophages is still unknown at present; the mechanisms of the inhibitory effect of dexamethasone are also poorly understood. Several mechanisms might explain the inhibitory effect of glucocorticoids on GM-CSF expression. Dexamethasone inhibits phorbol 12-myristate 13-acetate–induced phospholipase A2 expression in mouse macrophages via suppression of several kinase activities in the signal chain,37 suggesting that dexamethasone might suppress Ox-LDL–induced signal transduction for GM-CSF expression. Moreover, glucocorticoid receptor itself is a transcriptional factor and the binding of glucocorticoid receptor to glucocorticoid regulating element in promoter lesion of various genes regulates their expression positively or negatively.38,39 Therefore, it is possible that glucocorticoids may inhibit Ox-LDL–induced macrophage growth through inhibition of certain gene expression required for Ox-LDL–induced macrophage growth, including GM-CSF. Furthermore, glucocorticoid receptor is known to bind to activator protein-1 (AP-1) and then inhibit AP-1 action as a transcription factor.40 In T-lymphocytes, AP-1 plays an important role in GM-CSF expression induced by activation of protein kinase C (PKC).41-46 In this regard, we recently demonstrated that Ox-LDL initiated an increase in intracellular Ca2+ with subsequent activation of PKC.47 In a series of preliminary experiments, we also showed that AP-1 and AP-2 are important transcription factors in GM-CSF expression in mouse macrophages using gel retardation and luciferase assays (Matsumura et al, unpublished data, 1998). Moreover, Ares et al48 demonstrated that Ox-LDL induced AP-1 activation in human vascular smooth muscle cells. Thus, we speculate that activation of the glucocorticoid receptor by dexamethasone may inhibit AP-1 activation, thereby inhibiting the expression of GM-CSF in macrophages.

Dexamethasone inhibits the growth of several cell types, such as the growth of interleukin-6–induced myeloma cells,49 thrombin-induced growth of human smooth muscle cells,50 serum-induced growth of mouse fibroblasts,51 and mouse uterine epithelial cells.52 Recently, dexamethasone has also been shown to arrest G1 cell cycle in rat hepatoma cells53 through the expression of CCAAT/enhancer-binding protein alpha.54 Moreover, dexamethasone enhanced an expression of p21 waf1/cip1, a cyclin-dependent kinase inhibitor, which induced G1 arrest in rat hepatoma cell, lung alveolar cells, and mouse fibroblasts.55-57 Thus, it is possible that the cell cycle of macrophages might also be arrested in G1 phase by dexamethasone in Ox-LDL–induced macrophage growth.

In the present study, we demonstrated that glucocorticoids inhibited macrophage growth. Moreover, several other antiatherogenic properties of glucocorticoids have been reported in vitro20-24 and in vivo studies.16-19 However, it is still not clear whether glucocorticoid is a useful agent against atherosclerosis in humans. Because glucocorticoids have various side effects that might worsen atherosclerosis, such as increase in blood pressure, induction of hypercholesterolemia and hypertriglyceridemia, impairment of glucose tolerance, and imbalance of thrombosis and fibrinolysis, long-term clinical trials have not been performed to elucidate the effect of glucocorticoid in normal human subjects. Interestingly, treatment with glucocorticoid in certain patients with rheumatoid arthritis60 and systemic lupus erythematosus61 is associated with increased mortality due to cardiovascular diseases. The exact reasons for the discrepancy between the effect of glucocorticoids on such patients and animal models remains to be resolved. Further epidemiological and pathological studies might solve this issue if a safe local delivery system of glucocorticoid into the atherosclerotic lesions or a glucocorticoid-derivative without these side effects is developed in the future.

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