Prostaglandin E<sub>1</sub> Reduces the Glomerular mRNA Expression of Monocyte-Chemoattractant Protein 1 in Anti-Thymocyte Antibody-Induced Glomerular Injury<sup>1</sup>


ABSTRACT

To study whether prostaglandins (PG) can regulate the mRNA expression of monocyte-chemoattractant protein 1 (MCP-1) in glomerular immune injury, MCP-1 mRNA levels were evaluated in anti-thymocyte antibody (ATS)-induced glomerular injury by Northern blotting and reverse transcription-polymerase chain reaction. Immune injury was induced in vivo by the intravenous application of ATS to male Wistar rats and in vitro by the perfusion of isolated rat kidneys with ATS and rat serum. In vivo 3 h and 5 days after antibody application, glomerular mRNA expression of MCP-1 was markedly enhanced compared with controls. In the isolated perfused kidney, antibody and complement also induced an increase in MCP-1 expression at 10 min and 60 min after antibody perfusion. When the rats were treated with PGE (250 µg, twice daily), the increase in MCP-1 expression was reduced. This was associated with a reduction of intraglomerular recruitment of monocytes/macrophages. In the isolated perfused kidneys, PGE<sub>1</sub> (1 mg/L) prevented the antibody- and rat serum-stimulated increase in glomerular MCP-1 mRNA expression. These data demonstrate that PGE<sub>1</sub> reduces glomerular MCP-1 mRNA expression in glomerulonephritis and in the isolated perfused rat kidney after induction of immune injury with antibody and complement. The data suggest that prostaglandins might mediate MCP-1 effects in glomerular immune injuries.

Key Words: Monocyte-chemoattractant protein-1, prostaglandin E<sub>1</sub>, anti-thymocyte antibody-induced glomerulonephritis, monocytes, isolated perfused rat kidney

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Prostaglandins of the E series have beneficial effects on several entities of glomerulonephritis. Prostaglandins reduce the formation of immune complexes, inhibit antibody formation, and improve glomerular pathology (1-4). The latter effect is partially a result of the inhibition of leukocyte infiltration into the glomerulus (5). The mechanisms by which prostaglandins reduce inflammatory cell recruitment into the glomerulus are unclear. Recently, a group of cytokines have been described that exhibit strong chemoattractant activities and are involved in the inflammatory cell migration into injured tissues (6). These cytokines, which are also called chemokines, are divided in two groups according to the position of the first two of the four cysteine residues in their amino acid sequence. In the -C-C-group, the first two cysteine residues are directly adjacent, and in the -C-X-C-group they are separated by another amino acid. Monocyte-chemoattractant protein-1 (MCP-1) belongs to the -C-C- group and exerts strong chemoattractant activities on monocytes and lymphocytes (7-9). MCP-1 is expressed and released by a series of immune and nonimmune cells (7). In mesangial cells, its formation is stimulated by several mediators of inflammation (10-13). MCP-1 mRNA expression is also present in the glomeruli of animals and humans with glomerulonephritis and has been reported to be in temporal association with the infiltration of monocytes/macrophages (M/M) (14,15). MCP-1 is thus a candidate that might be responsible for recruiting inflammatory cells into the glomerular environment after tissue injury. Because prostaglandins can ameliorate the infiltration of monocytes in glomerulonephritis (5), we hypothesized that one possible mechanism of the prostaglandin action could be the reduction of MCP-1 expression in glomerular resident cells. Therefore, the effect of prostaglandin E<sub>1</sub> on the expression of MCP-1 in the model of anti-thymocyte antibody-induced glomerular injury was studied. Using Northern blot analysis and reverse transcription-polymerase chain reaction (RT-PCR), we found that PGE<sub>1</sub> inhibits the anti-thymocyte antibody-induced glomerular mRNA expression of MCP-1, which supports the view that prostaglandins could ameliorate the infiltration of monocytes into the glomerulus by the inhibition of MCP-1 production.

METHODS

In Vivo Studies

Induction of Glomerulonephritis. Immune-mediated mesangial cell injury was induced in white male Wistar rats (180 to 200 g body weight) by the intravenous injection of 0.5
30 mL/100 g body weight of an immunoglobulin G (IgG) preparation of a rabbit anti-rat thymocyte serum (ATS). ATS was induced in New Zealand rabbits by repeated immunization with thymocytes from Lewis rats as described (16). The specificity of the antibodies was tested in vitro and in vivo for their reactivity with mesangial cells. Details of the characterization of the antisera were described earlier (16). The glomerulonephritis that develops after the antibody is characterized by an immune complex formation on mesangial cells, complement activation, and mesangiolysis, which is followed by mesangial cell proliferation and an increase in extracellular matrix. The morphologic and functional characteristics of this glomerular lesion have been described earlier (16,17).

**Animal Groups.** To evaluate the effect of prostaglandin E1 on the expression of MCP-1 in nephritic rats, animals were treated with PGE1. Three groups of rats were studied. Control rats (N = 5, each time point) received 0.5 mL/100 g body weight of non-antibody IgG intravenously. Nephritic rats (N = 5, each time point) received 0.5 mL of an antithymocyte serum. Control and nephritic rats received 0.5 mL of the PGE1 carrier (1% ethanol in 0.9% NaCl) subcutaneously and twice daily after non-antibody IgG or ATS injection. Nephritic rats + PGE1 (N = 5, each time point) animals were treated with PGE1 (250 μg/rat twice daily sc in 0.5 mL of 1% ethanol in 0.9% NaCl). PGE1 injection was started 20 min after ATS. Three hours and 5 days after the application of the antibody, animals were nephrectomized for collection of renal tissue. Glomeruli were isolated from each kidney for extraction of total RNA. Glomerular isolation was performed by a sieving technique, which was described earlier (18). The purity of the preparation was >95%. Tissue sections were collected from one kidney of each animal for immunohistology. Three complete sets of experiments were performed.

**In Vitro Studies.** To evaluate the effect of prostaglandins on the mRNA expression of MCP-1 by resident glomerular cells independent of infiltrating leukocytes, immune injury was induced in isolated perfused rat kidneys. In anesthetized animals, the right kidneys were removed. A perfusion catheter (PP50 tubing; Portex, Hythe, UK) was inserted into the aorta and advanced to the origin of the left renal artery. After ligation of the aorta above the renal artery, the perfusion was started, and the renal vein was opened to allow free perfusate flow. The kidney was removed and placed into a heated organ bath (37°C). Perfusion experiments were performed at constant pressure (100 mm Hg) and temperature (38°C). After equilibration for 10 min, the experiments were started. A single-pass perfusion system was applied, which consisted of a heated perfusate reservoir containing 2 L of perfusion fluid that was preheated for 30 min with oxygen. During the experiments, the perfusate was permanently oxygenated by a capillary module (Enka Labormodul, Wuppertal, Germany). Perfusion pressure was generated by a peristaltic pump (Gilson, Langenfeld, Germany).

**Perfusate.** The perfusate was a modified Krebs-Henseleit solution that contained (all data as mM if not stated otherwise): sodium 145, potassium 5.0, chloride 110, magnesium 1.0, calcium 1.0, hydrogen carbonate 27.4, hydrogenophosphate 0.66, dihydrogenophosphate 0.3, glucose 7.6, urea 6.0, insulin 200 mg/L (Merck, Darmstadt, Germany), glutamine 0.4 (Sigma Chemicals, Munich, Germany), amino acids (Aminoplasmazped. 5%, 22 mL/L; Braun, Melsungen, Germany). A gelose preparation was used as a colloidsomatic agent (Faemacce#, Behringwerke, Marburg, Germany) at a concentration of 35 g/L. The solution was filtered through a 0.45-μm cellulose acetate filter before the experiment (Sartorius, Göttingen, Germany). Details of the methods and the characterization of the model are described elsewhere (19).

**Induction of Immune Injury.** Ten min after the start of the perfusion, immune injury was induced in the isolated kidneys. The following groups were studied:

**Group 1:** Controls (N = 5): perfusate only.
**Group 2:** Antibody alone (N = 5): rabbit anti-thymocyte serum (ATS). The antibody (300 μL antiserum in 5 mL perfusate) was applied in 60 s.
**Group 3:** Antibody + rat serum (N = 5): ATS was immediately followed by 2 mL of 1:5 diluted rat serum which was applied in 60 s.
**Group 4:** Antibody + heat-inactivated rat serum (N = 5): same as Group 3, however, rat serum was heat-inactivated (4 h at 56°C) before perfusion.
**Group 5:** Non-antibody IgG (N = 3).
**Group 6:** Non-antibody IgG + rat serum (N = 3).
**Group 7:** Rat serum alone (N = 3).
**Group 8:** Antibody + rat serum + PGE1 (N = 5). PGE1 perfusion (1 mg/L in the perfusate) was started immediately after the application of the rat serum and was continued throughout the experiment.

**Isolation of Total RNA and Northern Blot Hybridization.** Cellular RNA from whole glomeruli was isolated by the guanidinium isothiocyanate method (20). RNA was isolated from each perfused kidney or from five pooled kidneys of the in vivo experiments. Total RNA (20 μg) was electrophoresed through a 1.2% agarose gel containing 2.2 M formaldehyde. Equal loading of lanes was evaluated by ethidium bromide staining of the 18S and 28S rRNA. The RNA was transferred to nylon membranes (Zetabind; Cuno, Meriden, CT) by vacuum blotting and ultraviolet cross-linking. The blots were hybridized with a cDNA probe for JE/MCP-1 (21) after [59P32]CTP-labeling by random oligonucleotide priming of the cDNA insert (577-base pair [bp] Eco-R 1 fragment). The membranes were washed to a final high stringency in 0.1 × saline sodium phosphate EDTA (SSPE)/1.0% sodium dodecyl sulfate (1 × SSPE = 0.18 M NaCl/10 mM sodium phosphate, pH 7.4/1 mM EDTA) for 30 to 60 min at 65°C. Autoradiography was performed with the intensifying screen at ~70°C for appropriate time periods. The size of the respective RNA was identified by comparison of its mobility with the ethidium bromide-stained RNA standards. The membranes were rehybridized with a cDNA probe encoding for the genes GAPDH or 18S rRNA, respectively, to account for small loading and transfer variations. Exposed films were scanned with a laser densitometer (Hoefer Scientific Instruments, San Francisco, CA) and relative RNA levels were calculated.

**RT-PCR for MCP-1.** For RT-PCR, 5 μg of RNA in 7.5 μL H2O were incubated at 65°C for 3 min to unite secondary RNA structure. To minimize differences between the tubes, a master mix containing 5.5 μL first-strand buffer (250 mM Tris-HCl, 375 mM KCl, 15 mM MgCl2, 3.4 μL deoxynucleotide triphosphates (dNTP) (10 mM each), 2.7 μL dithiothreitol (0.1 M), 0.5 μL Poly dT Primer (Pharmacia, Freiburg, Germany), 14 U RNAse (Promega, Madison, WI) and 200 U M-MLV Reverse Transcriptase (Gibco BRL, Eggensstein, Germany) per sample were prepared and added to each sample in equal quantity. The RT reaction was carried out for 90 min at 37°C. To perform PCR, the following sequence was used based on the following rat cDNA: sense primer: 5' ACA GTT GCT GCC TGT AT 3'; antisense primer: 5' CAC ACT TOT CTG GCT GCT GCC TGT AT 3'; and antisense primer: 5' CAC ACT TOT CTG GCT GCC TGT AT 3'.
TCA TAC 3' (produced with Oligo 1000 DNA Synthesizer, Beckman, Munich, Germany). To 5 μL of each sample 18.2 μL H2O, 2.5 μL 10 x PCR-Buffer (500 mM KCl, 100 mM Tris HCl, 1% Triton X100, Sigma), 1.5 μL MgCl2 (25 mM), 0.8 μL sense and antisense primer (50 ng/μL each), 1.0 μL of an internal standard or H2O, respectively (PCR MIMIC; Clon- tech, Palo Alto, CA), and 0.5 U Taq DNA Polymerase (Promega) were added. The standard concentrations used ranged between 0.01 and 0.1 pg/μL. Rat MCP-1 standard was prepared using the sense primer 5’ ACA GTT GCC TGT AT CCG AAG TGA AAT CTC CTC CG 3’ and the antisense primer 5’ CAC ACT AGT CTC CTG TCA TAC TTG AGT CCA TGG GGA GCT TT 3’ (MCP-1 specific parts of the primers underlined). The primers were annealed to a BamHI/EcoRI v-erbB fragment according to the Mimic Kit protocol. The v-erbB fragment was used to avoid interference with the rat MCP-1 cDNA. The resulting 580-bp fragment had annealing sites for the same rat MCP-1 primers used for the amplification of the native MCP-1 fragment derived from glomerular RNA. To correct for transfer variations and quality differences of RNA and RT, an additional PCR for rat GAPDH was run using the following cDNA: sense primer, 5’ AAT GGA TGO AOO ACO An 3’; antisense primer, 5’ GTA GOC ATA TFO OAT OAT OAT A 3’ encoding for a 520-bp fragment. PCR was run for 28 cycles using the following temperature profile: denaturation at 95°C for 10 s, annealing for 20 s at 57°C, and extension for 40 s at 72°C. Finally, an extension step for 5 min at 72°C was performed. Each sample was evaluated with different standard concentrations. 10 μL of each reaction cup were run on a 1.5% agarose gel that contained 1 mg/mL ethidium bromide and photographed in ultraviolet light using a Polaroid 655 film (Polaroid, Cambridge, MA). Photographs were analyzed by densitometry with a HSI densitometer and absorption was calculated with Quick Integration Algorithm of the program GS 365W (both from Hoefer Scientific, San Francisco, CA). With this approach, a standard curve between the PCR product and the number of cycles is obtained, which shows linearity (Figure 1). PCR was performed with two standard concentrations.

**Histology**

Renal tissue from animals or isolated perfused kidneys was obtained from all kidneys and was assessed for ATS and complement C3, as well as for glomerular M/M infiltration. The tissues were either frozen in liquid nitrogen or fixed in 4% buffered formaldehyde.

To study ATS and rat C3 binding in kidneys, paraffin-embedded tissue sections were stained with a goat antibody directed against rabbit IgG (DAKOPATTS, Hamburg, Germany) and a mouse monoclonal antibody against rat C3. PAS stains were also performed. The antibodies were developed using the alkaline phosphatase anti-alkaline phosphatase (APAAP) technique. To analyze the infiltration of M/M into nephritic glomeruli, kidney tissue was cut and stained with an antibody directed against the monocyte specific marker ED-1. Appearance of ED-1 positive cells was assessed by light microscopy in a blinded fashion. A total number of at least 180 glomeruli per time point was evaluated and the cell numbers of ED-1 positive cells are given per glomerular cross section.
Figure 3. When nephritic kidneys (Day 5) were stained with an antibody to ED-1, positive cells were detected in glomeruli (3a), whereas in PGE1-treated animals, ED-1-positive cells were only sparcely detectable.

section as means ± SE. Statistical analysis was performed with analysis of variance.

CH50 Levels

To study whether PGE1 treatment affects complement activation, normal rats were either treated with PGE1 (250 μg/twice daily; N = 3) or received the PGE1 carrier solution (1% ethanol; N = 3). At 3 h and 5 days after PGE1, serum was collected from the tail vein for CH50 levels, which were determined according to the method of Mayer (22).

RESULTS

Histology

Intravenous application of ATS-induced proliferative glomerulonephritis (Figure 2) which is also characterized by the infiltration of ED-1 positive cells (Figure 3). Staining of the isolated kidneys, perfused with ATS and rat serum with antibodies against rabbit IgG and C3, revealed a selective antibody binding in the glomerular mesangium (Figures 4 and 5). This demonstrates ATS binding to mesangial cells with consecutive complement activation. Perfusion of rat kidneys with PGE1 did not alter antibody binding or C3 staining when assessed by immunohistology (data not shown). Similarly, in rats that received antibody, PGE1 treatment did not affect antibody binding or C3 staining (data not shown).

In Vivo Experiments

Northern Blot Analysis and RT-PCR. The Northern blot analysis from normal, nephritic, and PGE1-treated nephritic glomeruli demonstrated marked differences in the steady state mRNA levels for MCP-1. In glomeruli from rats that received non-antibody IgG, mRNA for MCP-1 was barely detectable at 3 h and 5 days. Three h after the induction of the nephritis, mRNA levels for MCP-1 increased. Densitometric analysis revealed a twofold increase when compared with controls (Figure 6 and Table 1). By densitometry, the increase in MCP-1 mRNA levels at Day 5 was
Figure 4. Perfusion of the isolated kidney with ATS resulted in a selective binding of antibody to the glomerular mesangium, which was demonstrated by staining with a goat-anti-rabbit IgG.

sevenfold compared with glomeruli from controls (Table 1). When the rats were treated with PGE1, the increase in mRNA levels for MCP-1 after ATS at 3 h and 5 days was reduced (Figure 6 and Table 1). These data were observed with similar differences in two additional sets of experiments.

When analyzed by RT-PCR, similar data were obtained (Figure 7, Table 1). There was an increase in the 420-bp MCP-1 fragment at 3 h and 5 days after the induction of the lesion, which was reduced when the animals were treated with PGE1. This was not an effect of the RT, because there were no significant differences between the mRNA levels of MCP-1 (420 bp) and GAPDH (520 bp).

Isolated Perfused Rat Kidney. Perfusion of isolated rat kidneys with ATS and rat serum induced increased glomerular mRNA levels compared with the corresponding controls at 10 min and 60 min (Figure 8, Table 1). When the isolated kidneys were perfused with PGE1, the glomerular mRNA levels of MCP-1 were reduced. These alterations were found to a similar degree in four additional experiments. When kidneys were perfused with antibody alone, non-antibody IgG, non-antibody IgG + rat serum, rat serum alone, or ATS + heat-inactivated rat serum, no differences were detected in glomerular mRNA levels of MCP-1 between controls and experimental kidneys (no data shown).

CH50 Levels. CH50 levels between control and PGE1-treated rats were not significantly different before treatment (data are given as dilution of the serum, which induces 50% lysis) (control, 144 ± 17; PGE1, 135 ± 20). At 3 h and 5 days, CH50 levels remained unchanged between control animals (3 h, 141 ± 19; 5 days, 147 ± 7) and PGE1-treated rats (3 h, 146 ± 18; 5 days, 144 ± 14).

Infiltration of Monocytes/Macrophages (M/M). The number of M/M in glomeruli of nephritic rats significantly increased at 3 h and 5 days after the injection of the antibody (Table 2). PGE1 treatment reduced the infiltration of M/M.

DISCUSSION

Leukocyte infiltration into injured tissues from the blood begins with the binding to the vascular endo-
PGE₁ and MCP-1 Expression

MCP-1 expression is also increased in glomerulonephritis of rats and humans (14,15). Because MCP-1 is a chemoattractant for monocytes (26), CD4+ cells, and CD8+ cells, as well as for natural killer cells (9), it might play an important role in the recruitment of leukocytes into injured glomeruli, similar to that demonstrated for other chemokines (32–34).

In contrast to the chemoattractants that mediate the influx of leukocytes into tissues, prostaglandins inhibit the recruitment of inflammatory cells by mechanisms that are so far unclear (1,5). Recent in vitro studies in a macrophage cell line (35) and mesangial cells in culture (11) demonstrated that PGE₁ and PGE₂ decreased the mRNA expression of MCP-1 after induction by LPS and inflammatory mediators. Because an increase of MCP-1 mRNA expression was recently found in the anti-thymocyte antibody-induced glomerulonephritis, we studied the effect of PGE₁ on glomerular MCP-1 expression in this animal model. Similarly, as demonstrated in earlier studies (14), the induction of the nephritis increased mRNA expression of MCP-1 (Figures 6 and 7). When the rats were treated with PGE₁, this increased mRNA expression at 3 h and 5 days was blocked (Figures 6 and 7). The reduction of MCP-1 mRNA levels was associated with a decrease in infiltrating ED-1+ cells into the glomerulus. The PGE₁ effect on MCP-1 mRNA expression was not the result of an interference with glomerular antibody binding or complement activation, because immunohistochemistry demonstrated that ATS and O3 staining were not different from that of untreated rats and the assessment of OH50 levels over 5 days did not reveal differences between PGE₁-treated and control rats. These in vivo studies, however, cannot define whether in fact antibody and complement induced MCP-1 expression by glomerular resident cells,

**Table 1. Densitometric analysis of the RT-PCR and the Northern Blot**

<table>
<thead>
<tr>
<th>RT-PCR—In Vivo Experiments (see Figure 4)</th>
<th>Cont. 3 h</th>
<th>ATS 3 h</th>
<th>ATS + PGE₁ 3 h</th>
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<tr>
<td>MCP-1/Standard 0.05 % of control</td>
<td>0.272</td>
<td>1.078</td>
<td>0.507</td>
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<th>ATS + PGE₁ 10'</th>
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<tr>
<td>MCP-1/Standard 0.02 % of control</td>
<td>0.139</td>
<td>0.624</td>
<td>0.106</td>
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<td></td>
<td>100</td>
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<th>Northern Blot—In Vivo Experiments (see Figure 3)</th>
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<th>ATS 10'</th>
<th>ATS + PGE₁ 5 days</th>
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<tbody>
<tr>
<td>MCP-1/18S % of control</td>
<td>0.256</td>
<td>0.654</td>
<td>0.155</td>
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<td></td>
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<th>ATS + PGE₁ 5 days</th>
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<tr>
<td>0.393</td>
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<td>100</td>
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<table>
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<tr>
<th>Cont. 60'</th>
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<th>ATS + PGE₁ 60'</th>
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<tr>
<td>0.282</td>
<td>1.472</td>
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<table>
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<tr>
<th>Cont. 60'</th>
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<th>ATS + PGE₁ 5 days</th>
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</thead>
<tbody>
<tr>
<td>0.152</td>
<td>1.153</td>
<td>0.485</td>
</tr>
<tr>
<td>100</td>
<td>758</td>
<td>319</td>
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*MCP-1, monocyte-chemoattractant protein-1; Cont., control; ATS, anti-thymocyte antibody; PGE₁, prostaglandin E1.
Figure 7. Competitive RT-PCR demonstrates that MCP-1 mRNA expression (420 bp) increases at 3 h (ATS 3h) and 5 days (ATS 5d) when the nephritis was induced, compared with controls (control 3 h; control 5 d). This increase is completely blocked by PGE₁ at 3 h (ATS + PGE₁ 3 h) and markedly reduced at 5 days (ATS + PGE₁). Similar changes were observed in two additional complete sets of experiments. To validate the use of the assay at different standards, two different standard concentrations were applied (0.05 pg/μL and 0.1 pg/μL). The increased concentrations of the standard lead to a reduction of MCP-1 in all experiments, however, the differences between the experimental groups persist, which demonstrates that the data are reproducible at different standard concentrations.

because PGE₁ might inhibit the infiltration of ED1+ cells, and because monocytes produce MCP-1 (26), the glomerular MCP-1 mRNA levels could partially derive from monocytes. To further characterize whether antibody and complement can induce MCP-1 expression in glomerular resident cells and whether it is regulated by prostaglandins, studies in the isolated perfused rat kidney were performed.

As shown in Figures 4 and 5, perfusion of rat kidneys with ATS and rat serum leads to a selective binding of the antibody to mesangial cells with activation of complement, which stimulates glomerular MCP-1 mRNA levels at 10 min and 60 min. When rat kidneys were perfused with PGE₁, MCP-1 mRNA levels were reduced. When the rat kidneys were perfused with antibody alone, antibody plus heat-inactivated rat serum, non-antibody IgG plus rat serum or rat serum alone, MCP-1 mRNA levels were not different from controls. Thus, the increase in glomerular MCP-1 mRNA expression depends on antibody binding and complement activation and demonstrates that resident glomerular cells can release chemokines, which might exert biologic effects on leukocytes.

Table 2. ED1 positive cells/glomerular cross-section

<table>
<thead>
<tr>
<th>Time</th>
<th>Control Nephritis Nephritis + PGE₁</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>3 h</td>
<td>1.47 ± 0.7</td>
</tr>
<tr>
<td>5 days</td>
<td>1.63 ± 0.4</td>
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<sup>a</sup> Significance of F = 0.001 throughout.

The mechanism for how PGE₁ reduces MCP-1 mRNA expression in glomeruli cannot be assessed in our in vivo or in vitro system; however, it might include the stimulation of cAMP. Studies in monocytes (35) and mesangial cells (11) reveal that increased intracellular levels of cAMP suppress MCP-1 expression. Other mechanisms might also be possible, since MCP-1 gene expression is mediated through multiple signaling pathways (36), including oxygen radicals (37). It has recently been demonstrated that cytokine-
induced MCP-1 gene expression in mesangial cells is dependent on binding of nuclear factor (NF) transcription factors (38). This confirms data in other cell types (36) and supports the concept that cytokines are genes that are expressed upon the activation of NF κB (39). Because PGE₂ attenuates the increase in NF κB, probably by an increase in cAMP in cultured mesangial cells (40), it might be possible that the PGE₁ effect is the result of a reduction of NF κB binding.

In summary, these data present evidence that antibody and complement can induce MCP-1 expression in primary glomerular cells independent of blood-derived inflammatory cells. The experiments further demonstrate that PGE₁ inhibits antibody and complement-mediated increase in glomerular MCP-1 expression and reduces MCP-1 mRNA levels in glomeruli of nephritic animals. The reduction of MCP-1 mRNA in nephritic glomeruli is associated with an impaired recruitment of monocytes into the glomerulus, which includes the possibility that the PGE₁-mediated reduction in glomerular inflammatory cell recruitment is mediated by the inhibition of chemokines.

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REFERENCES


