Uric Acid Stimulates Monocyte Chemoattractant Protein-1 Production in Vascular Smooth Muscle Cells Via Mitogen-Activated Protein Kinase and Cyclooxygenase-2

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Abstract—Previous studies have reported that uric acid stimulates vascular smooth muscle cell (VSMC) proliferation in vitro. We hypothesized that uric acid may also have direct proinflammatory effects on VSMCs. Crystal- and endotoxin-free uric acid was found to increase VSMC monocyte chemoattractant protein-1 (MCP-1) expression in a time- and dose-dependent manner, peaking at 24 hours. Increased mRNA and protein expression occurred as early as 3 hours after uric acid incubation and was partially dependent on posttranscriptional modification of MCP-1 mRNA. In addition, uric acid activated the transcription factors nuclear factor-κB and activator protein-1, as well as the MAPK signaling molecules ERK p44/42 and p38, and increased cyclooxygenase-2 (COX-2) mRNA expression. Inhibition of p38 (with SB 203580), ERK 44/42 (with UO126 or PD 98059), or COX-2 (with NS398) each significantly suppressed uric acid–induced MCP-1 expression at 24 hours, implicating these pathways in the response to uric acid. The ability of both N-acetyl-cysteine and diphenyleneionium (antioxidants) to inhibit uric acid–induced MCP-1 production suggested involvement of intracellular redox pathways. Uric acid regulates critical proinflammatory pathways in VSMCs, suggesting it may have a role in the vascular changes associated with hypertension and vascular disease. **(*Hypertension*. 2003;41:1287-1293.)**

Key Words: atherosclerosis ■ chemokines ■ hyperuricemia ■ arteriolosclerosis

Both systemic and vascular inflammation appear to have a key role in atherogenesis.[1] Of the various inflammatory mediators, the chemokine monocyte chemoattractant protein-1 (MCP-1) has been shown to have a major role in the initiation of atherosclerotic lesions.[2,3] Early human atheromatous plaques have been found to express MCP-1 in both vascular smooth muscle cells (VSMCs) and infiltrating macrophages,[4] whereas animal models of atherosclerosis show increased VSMC MCP-1 expression[5] in some cases preceding leukocyte infiltration.[6] Further supporting a pathogenetic role for MCP-1 are several studies showing decreased development of vascular lesions in experimental models in which MCP-1 was inhibited[7] or in which either MCP-1 or its receptor, CCR2, were knocked out.[3,8]

Recent studies have demonstrated that an elevated serum uric acid level is also associated with circulating levels of systemic inflammatory mediators in a variety of conditions, including congestive heart failure.[9] Although uric acid has been generally considered inert, there is evidence that soluble uric acid can induce VSMC proliferation in vitro.[10] Recent studies have shown that uric acid–induced VSMC proliferation is mediated by the activation or induction of extracellular signal–regulated kinase (ERK) mitogen-activated protein kinases (MAPK), cyclooxygenase-2 (COX-2), and platelet-derived growth factor (PDGF).[11,12] In experimental animal models (generated by feeding rats the uricase inhibitor oxonic acid), elevated serum uric acid levels are associated with vascular disease in vivo.[11–13] In addition, hyperuricemic rats developed hypertension and renal disease in the absence of uric acid crystal deposition.[11–13]

These various observations led us to examine the hypothesis that uric acid has direct proinflammatory effects on VSMCs. In the present study, we report that soluble crystal- and endotoxin-free uric acid can increase MCP-1 production in rat VSMCs in vitro. The mechanism involves not only the previously reported activation of ERK44/42 MAPK and COX-2 in VSMC but also the activation of p38 MAPK and the nuclear transcription factors nuclear factor-κB (NF-κB) and activator protein-1 (AP-1). Redox pathways in VSMCs also appear to be implicated. These findings may provide a mechanism through which uric acid could mediate vascular disease.

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Methods

Cell Culture

Primary rat aortic VSMCs were obtained from Dr Andrew Kahn (University of Texas, Houston), maintained as described[14], and strictly used between passages 5 to 12. Before incubation with uric acid or other compounds, VSMCs were serum-deprived in 0.4% FBS for 48 to 72 hours.

Tests for Uric Acid Crystals, Endotoxin, Mycoplasma, and Cell Toxicity

In experiments requiring uric acid-incubation, media was prewarmed (37°C), and uric acid (Ultrapure, Sigma; 2.5 to 10 mg/dL) was added. The mixture was again warmed (37°C, 30 minutes) and passed through sterile 0.20-μm filters. Control media was treated the same way. Crystals were not detectable under these conditions (polarizing microscopy), nor did they develop during cell incubation. Assessment of conditions required to generate crystals revealed that refrigeration, time, and urate concentration were important factors. Media containing 20 to 30 mg/dL uric acid showed the sudden appearance of multiple, negatively birefringent crystals after 3-day refrigeration. Warming (37°C) resulted in their complete disappearance, usually within 15 to 30 minutes.

Endotoxin was not detectable in all batches of uric acid (limulus amebocyte assays; BioWhittaker Inc) on 10 mg/dL uric acid media (indicating $<$0.015 endotoxin U/mL). Mycoplasma contamination was also excluded (Immu-Mark Myco-Test; ICN Biomedicals). Uric acid, dimethyl sulfoxide, inhibitor, and antioxidant doses reported were not associated with increased toxicity (TOX-7 lactate dehydrogenase assay; Sigma) compared with media without these compounds.

RNase Protection Assay

RNase protection assays (RPAs) were performed on 2- to 4-μg RNA by using the RPAs I kit (Torrey Pines Biolabs). The rat riboprobes used have all been described previously.[15,16]

Real-Time Reverse Transcriptase–Polymerase Chain Reaction

Real-time, 1-step reverse transcriptase–polymerase chain reaction (RT-PCR) was performed with SYBR green PCR reagents (Sigma), the Thermoscript RT-PCR system (Invitrogen), and the Opticon DNA engine (MJ Research Inc); 100 ng total RNA was reverse transcribed before PCR. Primers were as follows: MCP-1, fwd 5′-CACTGGCAAGATGATCCCAATG-3′, rev 5′-CTTCTACAG-AAGTGCTTGAGGTGG-3′; and GAPDH, fwd 5′-ACCCCCAA-TGTATCCGTTGT-3′, rev 5′-TACTCC TT GG AG GC CATGTA-3′. Amplicon sizes were 311 bp (MCP-1) and 299 bp (GAPDH). Reaction specificity was confirmed by electrophoretic analysis of products before real-time RT-PCR, and bands of expected size were detected. Ratios for MCP-1/GAPDH mRNA were calculated for each sample and expressed as mean±SD.

ELISA for MCP-1 Protein

Cells in 24-well plates (5×10^4/well) were serum deprived at 70% confluence; then media with or without uric acid (2.5 to 10 mg/dL) was added. Inhibitor concentrations used were PD 98059 12.5 μmol/L, SB 203580 5 μmol/L (Calbiochem), UO126 5 μmol/L (Cell Signaling), and NS398 (Cayman) 10 μmol/L (30-minute preincubation). Antioxidant concentrations were N-acetyl-cysteine (NAC) 1.25 mmol/L and diphenyleneionium (DPI) 2.5 μmol/L. Media supernatants were collected and spun to remove dead or nonadherent cells, and adherent cells were lysed. Supernatant MCP-1 was measured by enzyme-linked immunosorbent assay (ELISA; OptEIA MCP-1 set, BD Pharmingen). Experiments were performed in triplicate or quadruplicate and verified on at least 2 occasions. Results were expressed as total supernatant MCP-1 per milligram cell protein (mean±SD).

Electrophoretic Mobility Shift and Supershift Assays

Nuclear proteins were isolated as previously described.[17] Protein concentrations were equalized and then assayed for NF-κB and AP-1 binding activity by using radiolabeled double-stranded consensus oligonucleotides (Promega). Supershift assays used rabbit polyclonal antibodies to NF-κB subunits, p65 and p50, and AP-1 subunits, *c*-fos, *c*-jun, and JunB (Santa Cruz).

Western Blotting

Cells were incubated with or without uric acid as described. Lysate protein concentrations were equalized, resolved on sodium dodecyl sulfate–polyacrylamide gel electrophoresis gels (40 μg protein/well), and transferred to nitrocellulose membranes. Phospho-specific (monoclonal) and total (polyclonal) MAPK primary antibodies and HRP-linked secondary antibodies (Cell Signaling) were used.

Statistical Analysis

All values are expressed as mean±SD. ANOVA followed by Bonferroni correction was used in all instances, except in the uric acid dose-response ELISA, which was assessed with the Pearson correlate. Significance was defined as $P<0.05$.

Results

MCP-1 mRNA Expression in Rat VSMCs Is Increased by Uric Acid

To determine whether uric acid has a role in regulating inflammatory mediators in VSMCs, uric acid–induced expression of MCP-1, tumor necrosis factor-α (TNF-α), and interleukin 1-β (IL-1β) mRNA was assessed by using RPA. Uric acid–containing media consistently increased MCP-1 mRNA expression compared with control media, after 24 hours of incubation (Figure 1A). MCP-1 mRNA was not usually detectable in VSMCs at baseline or after incubation with control media. In multiple time-course experiments with uric acid incubations ranging between 1 and 48 hours (5 separate experiments), MCP-1 mRNA expression was generally first detectable at 6 hours and peaked at 24 hours (Figure 1A). On occasion, MCP-1 mRNA was detectable 3 hours after uric acid incubation (data not shown), but usually, the RPA sensitivity did not allow this to be demonstrated. To further delineate the early time-course of the MCP-1 mRNA upregulation, real-time RT-PCR was used as an alternative more-sensitive technique. This showed uric acid–incubated cells to have 1.8-fold higher MCP-1 mRNA expression than that of controls at 3 hours (data not shown, $P<0.05$). Both IL-1β and TNF-α mRNA were not detectable in VSMCs by RPA but were easily demonstrated in rat macrophages (NR8383) after lipopolysaccharide stimulation (Figure 1A).

To assess whether uric acid was responsible for altering MCP-1 mRNA stability, cells were incubated with actinomycin D (5 μg/mL) in the presence or absence of uric acid (5 mg/dL), and MCP-1 mRNA decay was assessed by real-time RT-PCR (Figure 1B). This method was chosen instead of RPA because of its greater sensitivity and its ability to assess MCP-1 mRNA decay without prior upregulation of MCP-1 mRNA. MCP-1 mRNA half-life approximately doubled from 2 hours in controls to 4 hours in uric acid–incubated cells. MCP-1/GAPDH mRNA ratios were significantly different between the 2 groups of samples at 2 and 4 hours, with control-incubated cells showing more rapid MCP-1 mRNA

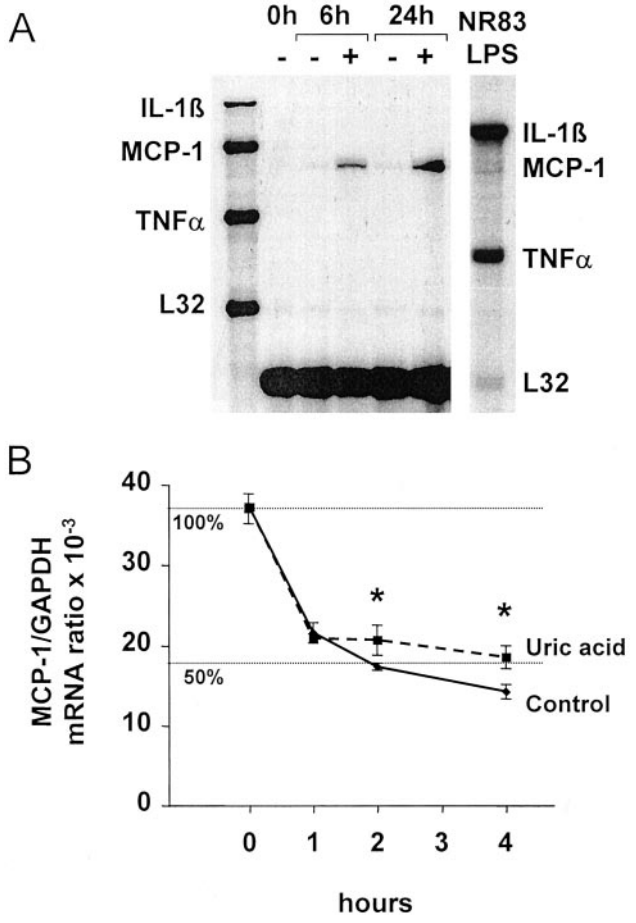

Figure 1. Uric acid upregulates MCP-1 mRNA (A) and increases MCP-1 mRNA stability (B). A, RNase protection assay examining MCP-1, TNF-α, and IL1-β mRNA expression in rat VSMCs with (+) and without (−) uric acid incubation (5 mg/dL) relative to L32. Probes (lane 1) contain polylinker regions and are longer than protected bands. MCP-1 mRNA was not detectable before incubation with uric acid (0h) or in negative controls at 6 and 24 hours (−). In contrast, MCP-1 mRNA was detectable in uric acid-incubated VSMCs at 6 and 24 hours (+). IL1-β and TNF-α mRNA expression was not detectable in any of the VSMC samples but was prominent in positive controls that were performed simultaneously (lipopolysaccharide-stimulated rat macrophages; NR8383 LPS). B, Decay curves showing the MCP-1/GAPDH mRNA ratio in control cells (solid line) compared with uric acid–incubated cells (dashed line). Real-time RT-PCR was performed after incubation with actinomycin D (5 μg/mL) with or without uric acid (5 mg/dL). The 2 horizontal dotted lines represent the ratios before actinomycin D incubation (100%), and after decay of half the MCP-1 mRNA (50%). Uric acid decreased the rate of MCP-1 mRNA decay, significantly prolonging the half-life to 4 hours, compared with 2 hours in controls. MCP-1/GAPDH mRNA ratios at 2 and 4 hours were significantly different between the 2 groups (*$P<0.05$, n=4).

decay than did uric acid–incubated cells (Figure 1B, $P<0.05$, n=4).

Uric Acid Increases Production of MCP-1 Protein by Rat VSMC

The associated uric acid–induced increase in MCP-1 expression was assessed by ELISA on media supernatants collected at various time points (Figure 2A). Uric acid (5 mg/dL) significantly increased MCP-1 production at 3, 6, and 24

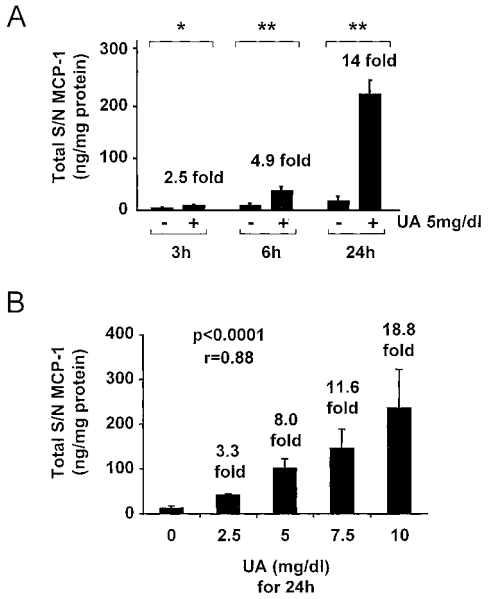

Figure 2. Uric acid increases production of MCP-1 by rat VSMCs. Time-course (A) and dose-response (B) of the uric acid–induced effect on MCP-1 expression by rat VSMCs using ELISA. A, Incubation of cells with uric acid (5 mg/dL; +) led to increased supernatant MCP-1 relative to controls (−) at 3, 6, and 24 hours (*$P<0.05$, **$P<0.01$, n=4 per group). B, Supernatant MCP-1 correlated significantly with media concentration of uric acid. The effect of uric acid (0 to 10 mg/dL) was assessed at 24 hours (4 samples per concentration). The fold-increase in supernatant MCP-1 for each uric acid concentration relative to 0 mg/dL is indicated at the top of each bar (Pearson correlate, $r=0.88$, $P<0.0001$; n=total of 20). For all experiments, total supernatant MCP-1 was corrected for cell protein concentration and expressed as mean±SD.

hours when compared with that of control media (Figure 2A). The effect of uric acid was also found to be dose-dependent (Figure 2B), with a progressive increase in supernatant MCP-1 being observed at 24 hours, as uric acid concentration in the media was increased (Figure 2B; Pearson correlate $r=0.88$, $P<0.0001$). Although the effect of uric acid on MCP-1 production was consistently demonstrated in early-passage cells, considerable variation in the MCP-1 fold-induction was noted between experiments. As an example, the uric acid–induced MCP-1 increase at 24 hours in response to 5 mg/dL (from 6 separate experiments) ranged from 3- to 14-fold. The batch of cells used, as well as their confluence and passage number, appeared to be an important factor in the variation observed, with younger-passage subconfluent cells showing the greatest response.

NFκB and AP-1 Are Activated in Rat VSMCs by Uric Acid

The transcription factors NF-κB and AP-1 have been reported to be involved in the regulation of MCP-1 expression.[18] The effect of uric acid on these molecules was therefore examined in VSMCs by electrophoretic mobility shift assay. Nuclear lysates from uric acid–incubated cells (5 mg/dL) showed greater activation of both NF-κB and AP-1 than did control lysates (Figures 3A and 3C). In both instances, increased activation was early, evident after 15 minutes of incubation with uric acid and peaked at 30 minutes. By using supershift

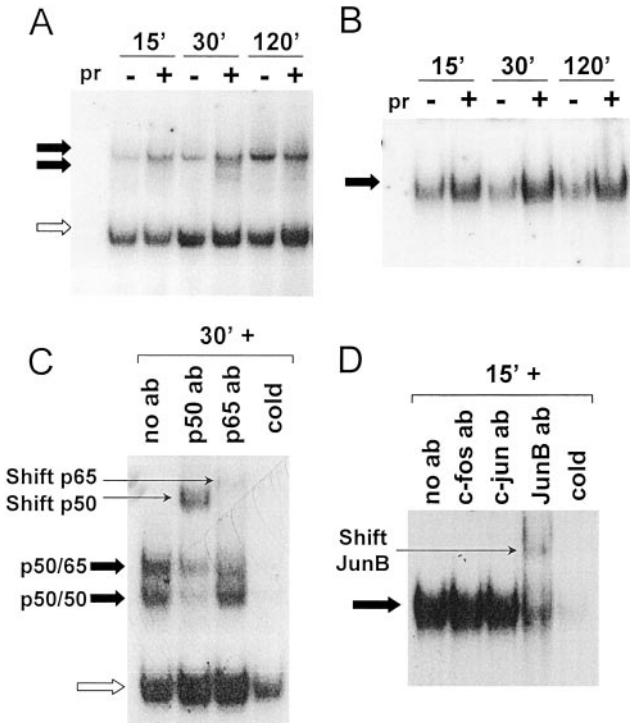

Figure 3. Uric acid activates the transcription factors NFκB and AP-1 in rat VSMCs. Electrophoretic mobility shift assays on nuclear lysates from rat VSMCs incubated with and without uric acid (A, for NF-κB; B, for AP-1); and supershift assays using specific antibodies to monomeric p50 and p65 NFκB subunits (C) or *c*-fos, *c*-jun, and JunB AP-1 subunits (D). Uric acid–incubated cells (+) showed greater activation of NF-κB and AP-1 at 15, 30, and 120 minutes compared with controls (−). A and C, Solid arrows indicate NF-κB dimers identified as p50/65 and p50/50 in the supershift assays (C). Open arrows show a nonspecific band that was not competed out by excess unlabeled probe (C; cold). Supershifted bands are indicated (C; shift p65, shift p50). B and D, Arrows indicate AP-1 dimers consisting at least partially of JunB as assessed by supershift assays (D). The shifted AP-1 band was completely eliminated by incubation with excess unlabeled competitor oligonucleotide (D; cold). Supershifted complexes bound to the JunB ab are indicated (D; shift JunB). Probe incubated in binding buffer without nuclear lysate showed no shifted band (A and B; pr, lane 1). Blots shown are representative of 3 experiments.

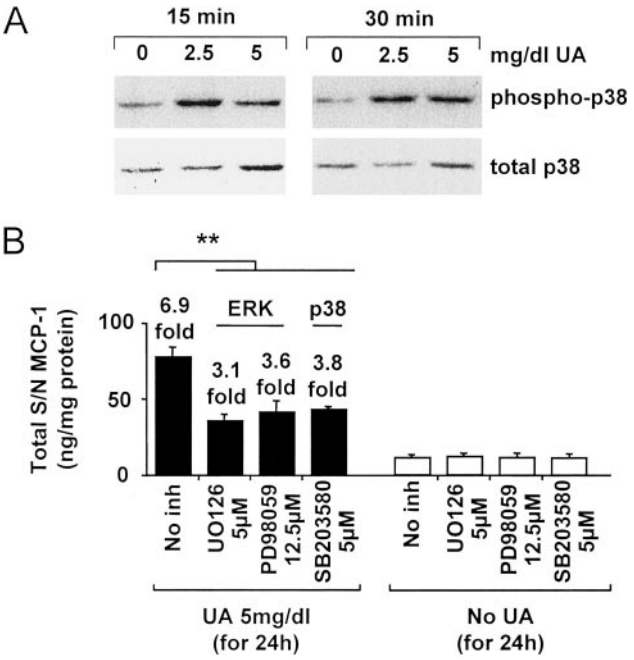

Figure 4. Uric acid–induced MCP-1 upregulation is mediated by p38 and ERK 44/42 MAPK. A, Western blot showing activation of p38 MAPK (phospho-p38) by 2.5 and 5 mg/dL uric acid at 15 and 30 minutes. After identifying active p38 (phospho-p38), membranes were stripped of antibodies and reexamined for total p38 (lower panels). We recently demonstrated similar activation of ERK 44/42 in another report[12] and this was confirmed (data not shown). B, Supernatant MCP-1 measurements by ELISA, showing a decrease in the uric acid–induced MCP-1 secretion at 24 hours by MAPK inhibitors. Two ERK pathway inhibitors (UO126 and PD 98059) and a p38 pathway inhibitor (SB 203580) were used. Each agent inhibited the increase in supernatant MCP-1 by ≈50% (B; solid bars, $^{**}P<0.01$, n=3). MCP-1 measurements from control samples (no uric acid) with or without inhibitors are also shown (B; open bars). The fold-increase in supernatant MCP-1 relative to controls is indicated at the top of each solid bar.

assays, NF-κB activation was shown to involve the p50 and p65 monomers (Figure 3B), whereas AP-1 activation involved predominantly the JunB monomer and not *c*-jun or *c*-fos (Figure 3D).

Uric Acid–Induced MCP-1 Upregulation in Rat VSMCs Is Dependent on p38 and ERK44/42 MAPK

To identify potential signaling pathways involved in the uric acid–induced MCP-1 upregulation, p38 and ERK44/42 MAPK activation was examined. We have recently reported that uric acid (3 mg/dL) can activate ERK44/42 MAPK in rat aortic VSMCs at 30 and 120 minutes,[12] and these findings were confirmed in this group of studies with activation seen as early as 15 minutes with 5 mg/dL uric acid (data not shown). Activation of p38 MAPK was also seen after incubation of VSMCs with uric acid (2.5 and 5 mg/dL) for 15 and 30 minutes (Figure 4A).

To assess the role of these 2 pathways, the effect of p38 and ERK44/42 MAPK inhibitors on uric acid–induced upregulation of MCP-1 was examined at the time of peak MCP-1 expression (24h). Supernatant MCP-1 was measured by ELISA (Figure 4B). SB 203580 (p38 pathway inhibitor), UO126, and PD 98059 (ERK pathway inhibitors) all had a similar effect, decreasing the total MCP-1–secreted protein by ≈50% without evidence of toxicity (Figure 4B, $P<0.01$). These findings implicate both the p38 and ERK44/42 MAPK signaling pathways in the uric acid–induced MCP-1 upregulation.

Uric Acid–Induced MCP-1 Upregulation Is Dependent on Increased COX-2 Expression

As COX-2 is known to be increased in association with both p38 MAPK and NFκB activation, the role of COX-2 in the uric acid–induced MCP-1 upregulation was examined. VSMC COX-2 mRNA expression increased after incubation with uric acid for 3 and 6 hours (Figure 5A). COX-2 inhibition with NS398 significantly decreased the uric acid–induced total secreted MCP-1 at 24 hours compared with that of controls, without evidence of toxicity (Figure 5B; $P<0.01$, n=3).

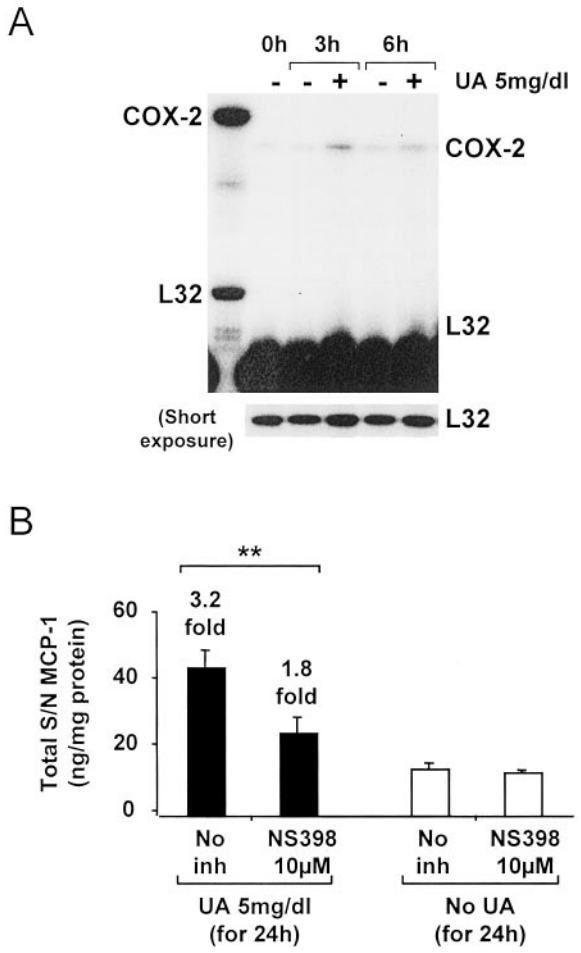

Figure 5. Uric acid–induced MCP-1 upregulation is mediated by COX-2. A, RNase protection assay examining COX-2 mRNA expression in rat VSMCs with (+) and without (−) uric acid incubation (5 mg/dL) relative to L32. The same membrane exposed to film for only a short time is also shown at the bottom of panel A to better demonstrate relative L32 mRNA expression between samples. COX-2 mRNA was not detectable before incubation with uric acid (0h) and only weakly evident at 6 hours in controls (6h −). COX-2 mRNA expression in uric acid–incubated VSMCs at 3 and 6 hours (+) was more prominent than in corresponding controls at the same time-point. B, Supernatant MCP-1 by ELISA showing a decrease in the uric acid–induced MCP-1 secretion at 24 hours by NS398 (COX-2 inhibitor). Uric acid induced a 3.2-fold increase in supernatant MCP-1 (first solid bar) compared with controls (first open bar). COX-2 inhibition decreased this to 1.8-fold (second solid bar, $^{**}P<0.01$, n=3).

Redox-Sensitive Pathways Are Implicated in Uric Acid–Induced MCP-1 Upregulation

As p38 MAPK, AP-1, NF-κB, and MCP-1 are all known to be regulated through redox-sensitive pathways, the effect of antioxidants on the uric acid–induced MCP-1 upregulation was examined. NAC and DPI were both found to inhibit uric acid–induced MCP-1 production by ≈50% at 24 hours (Figure 6, $P<0.01$, n=4). This occurred without evidence of cell toxicity by lactate dehydrogenase assay.

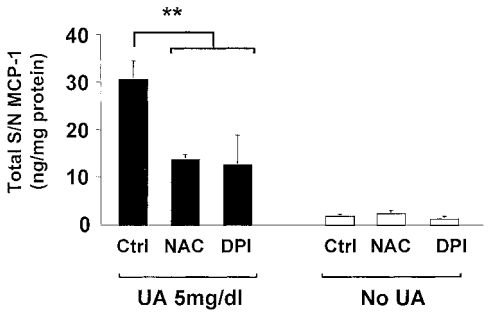

Figure 6. Uric acid–induced MCP-1 upregulation involves redox-sensitive pathways. Supernatant MCP-1 by ELISA, showing a decrease in the uric acid–induced MCP-1 secretion at 24 hours in the presence of the antioxidants NAC (2.5 mmol/L) and DPI (5 μmol/L). NAC (second bar) and DPI (third bar) decreased the uric acid–induced MCP-1 production (ctrl + UA; first bar) by ≈50% ($^{**}P<0.01$; n=4). NAC and DPI in the absence of uric acid had no effect on MCP-1 production (open bars, no UA).

Discussion

In the present study, we report that soluble uric acid stimulates increased production of the chemokine MCP-1, by rat VSMCs in vitro. The increase in MCP-1 production occurred in a time- and dose-dependent manner, with both mRNA and protein being upregulated within a few hours of incubation of the VSMCs with uric acid. The rapidity of the increase led us to examine possible posttranscriptional effects of uric acid, as well as various signaling pathways and transcription factors known to be important in MCP-1 regulation.

Our initial findings were that the uric acid–induced increase in MCP-1 synthesis was partially dependent on increased MCP-1 mRNA half-life. We subsequently found that transcription factors known to be involved in MCP-1 regulation (NF-κB and AP-1) were also activated very early (at 15 minutes), suggesting that both transcriptional and posttranscriptional factors were involved in the increased MCP-1 synthesis. The possibility that specific MAPK was involved in this process was also examined. We have previously shown that uric acid activates ERK44/42 MAPK in rat VSMCs in vitro, and that this mediates uric acid–induced VSMC proliferation.[12] In these studies, we confirmed the activation of ERK44/42 MAPK and showed that this partially mediated the uric acid–induced increase in MCP-1 synthesis. We also examined p38 MAPK, which is strongly linked to inflammation and has been shown to regulate MCP-1 expression in several cell types in response to various mediators.[19] P38 MAPK was also rapidly activated in rat VSMCs by uric acid, and its inhibition partially blocked the increase in MCP-1 production. We additionally found that COX-2 partially mediated the uric acid–induced increase in MCP-1 synthesis. This is of interest as we have previously shown that COX-2 mediates uric acid–induced VSMC proliferation, in part, through thromboxane generation.[11]

It is important to note that uric acid levels in most mammals differ from that seen in humans. This difference arises because in most mammals, the uricase (urate oxidase) enzyme metabolizes uric acid to allantoin. By comparison, in higher hominoids (great apes and humans) this enzyme has been mutated,[20] resulting in higher serum uric acid levels. In humans, hyperuricemia is defined as a uric acid level >7 mg/dL (with a normal range of ≈2 to 7 mg/dL). In rats, the normal uric acid level is much lower (≈0.8 to 1.5 mg/dL).

Uric acid concentrations used in the in vitro studies presented here are ≈2- to 3-fold that observed in the normal rat and, therefore, are in the range of what may be observed in disease in these animals. The possibility that this may be clinically relevant is supported by a recent study in our laboratory in which the effect of hyperuricemia was examined in a model of progressive renal disease (the remnant kidney or RK model).[11] In these studies, RK rats that received the uricase inhibitor oxonic acid developed modest hyperuricemia (4.0±0.6 mg/dL) compared with that of RK controls (2.7±0.6 mg/dL; $P<0.05$ at 2 weeks). Interestingly, these rats showed much more severe vascular disease and intrarenal macrophage accumulation.[11] We have retrospectively tested sera and found that hyperuricemic RK rats also had higher serum MCP-1 levels at 2 weeks (136.8±39.7 ng/mL) compared with that of control RK rats (82.8±8.3 ng/mL; $P<0.05$). This was associated with substantial macrophage accumulation in the intrarenal blood vessels (data not shown). This emphasizes the need to address the role of uric acid in the systemic inflammatory response in patients with cardiovascular and renal disease.

Further assessing the mechanism through which uric acid mediated its effects, we found that redox pathways were implicated. The ability of both NAC and DPI to inhibit the uric acid–induced increase in MCP-1 suggested that uric acid was acting in a prooxidative manner. This is of interest because uric acid is often thought of as an antioxidant.[21] Despite this, several studies have demonstrated that uric acid can be prooxidative and may generate free radicals.[22–25] The ability to activate p38 MAPK, NF-kB, and AP-1, as well as to increase MCP-1 expression, is consistent with an oxidant-driven pathway.[26,27]

In conclusion, we have found that uric acid can induce inflammatory pathways in rat VSMCs in vitro, with activation of p38 MAPK, NF-κB, and AP-1 and increased expression of COX-2 and MCP-1. Although the inflammatory potential of crystalline uric acid has been well known, this study provides the first evidence that soluble uric acid can also engage these pathways. These findings add further intrigue to the controversy surrounding the possible pathogenetic role of uric acid in hypertension, vascular disease, and atherosclerosis in man.[28–31]

Perspectives

The association between hyperuricemia, hypertension, and vascular disease has been appreciated for many decades.[32] More than a century ago, Mahomed[33] alluded to this association by noting that hypertensive subjects often had a family history of gout. Since then, several epidemiological studies have shown elevated serum uric acid levels to be independently associated with the incidence of hypertension, coronary artery disease, cardiovascular disease, and death.[28–30] Recent studies also show elevated serum uric acid levels to be associated with greater renal disease progression in patients with immunoglobulin A nephropathy.[34,35] Despite these associations, the possible pathogenetic role of uric acid in these disorders has long been debated. Much of the controversy has centered around the fact that hyperuricemia is seen to "cluster" with various known and accepted cardiovascular risk factors. In addition, several other epidemiological studies have not clearly shown the "independence" of hyperuricemia as a risk factor in multivariate analyses, particularly in the male population.[36,37] Although speculative, this data suggests that the induction of inflammatory pathways in VSMCs by uric acid may have a role in the initiation of vascular disease and hypertension. Future studies will be necessary to determine the relevance of these findings to cardiovascular disease in man.

Acknowledgments

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