Mild hyperuricemia induces glomerular hypertension in normal rats

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Departments of 1Nephrology and 2Pathology, Instituto Nacional de Cardiología I Chavez, 14080 Mexico City, Mexico; 3Division of Nephrology, Baylor College of Medicine, Houston, Texas 77030; and 4Hospital Universitario and Universidad del Zulia, Maracaibo, Venezuela

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Sánchez-Lozada, Laura G., Edilia Tapia, Carmen Avila-Casado, Virgilia Soto, Martha Franco, José Santamaria, Takahiko Nakagawa, Bernardo Rodríguez-Iturbe, Richard J. Johnson, and Jaime Herrera-Acosta. Mild hyperuricemia induces glomerular hypertension in normal rats. Am J Physiol Renal Physiol 283: F1105–F1110, 2002.—Mildly hyperuricemic rats develop renin-dependent hypertension and interstitial renal disease. Hyperuricemia might also induce changes in glomerular hemodynamics. Micropuncture experiments under deep anesthesia were performed in Sprague-Dawley rats fed a low-salt diet (LS group), fed a low-salt diet and treated with oxonic acid (OA/LS group), and fed a low-salt diet and treated with oxonic acid and allopurinol (OA/LS/AP group) for 5 wk. The OA/LS group developed hyperuricemia and hypertension compared with the LS group: 3.1 ± 0.2 vs. 1.1 ± 0.2 mg/dl (P < 0.01) and 143 ± 4 vs. 126 ± 2 mmHg (P < 0.01). Hyperuricemic rats developed increased glomerular capillary pressure compared with the LS rats: 56.7 ± 1.2 vs. 51.9 ± 1.4 mmHg (P < 0.05). Pre- and postglomerular resistances were not increased. Histology showed afferent arteriolar thickening with increased α-smooth muscle actin staining of the media. Allopurinol prevented hyperuricemia (1.14 ± 0.2 mg/dl), systemic (121.8 ± 2.8 mmHg) and glomerular hypertension (50.1 ± 0.8 mmHg), and arteriolopathy in oxonic acid-treated rats. Linear regression analysis showed that glomerular capillary pressure and arteriolar thickening correlated positively with serum uric acid and systolic blood pressure. Glomerular hypertension may be partially mediated by an abnormal vascular response to systemic hypertension due to arteriolopathy of the afferent arteriole.

Mildly hyperuricemic rats developed increased glomerular capillary pressure compared with the LS rats: 56.7 ± 1.2 vs. 51.9 ± 1.4 mmHg (P < 0.05). Hyperuricemic rats developed increased glomerular capillary pressure compared with the LS rats: 56.7 ± 1.2 vs. 51.9 ± 1.4 mmHg (P < 0.05). Pre- and postglomerular resistances were not increased. Histology showed afferent arteriolar thickening with increased α-smooth muscle actin staining of the media. Allopurinol prevented hyperuricemia (1.14 ± 0.2 mg/dl), systemic (121.8 ± 2.8 mmHg) and glomerular hypertension (50.1 ± 0.8 mmHg), and arteriolopathy in oxonic acid-treated rats. Linear regression analysis showed that glomerular capillary pressure and arteriolar thickening correlated positively with serum uric acid and systolic blood pressure. Glomerular hypertension may be partially mediated by an abnormal vascular response to systemic hypertension due to arteriolopathy of the afferent arteriole.

uric acid; arteriolopathy; renal hemodynamics; micropuncture; hypertension

CONTROVERSY EXISTS over the role of hyperuricemia in renal disease (16). For example, gout can be associated with a renal lesion (“gouty nephropathy”) characterized by glomerulosclerosis, interstitial fibrosis, and arteriolosclerosis, often with focal urate deposits in the interstitium (30). However, many patients with longstanding gout have hypertension and/or are older, and the renal injury is also compatible with hypertensive or aging-related renal injury (2, 23). A syndrome of familiar juvenile hyperuricemia has also been described with similar histological features, except urate deposition appears to be rare; debate over the role of uric acid in the renal injury in this condition has also raged (6). Hyperuricemia has also been reported to be a risk factor for progression, although the mechanism by which uric acid may accelerate renal disease is unknown. For example, in a recent study of 6,403 subjects, serum uric acid was found to be an independent risk factor for development of renal insufficiency and carried a greater risk than proteinuria (14). Recently, a model of mild hyperuricemia was reported in rats by inhibiting uricase with oxonic acid (19, 20). Rats fed low doses of oxonic acid develop an up to threefold increase in serum uric acid without intra-renal crystal deposition. Rats developed hypertension, afferent arteriolar thickening, and mild renal interstitial fibrosis, with interstitial collagen deposition and macrophage infiltration (19, 20). These effects were most pronounced if the rats were fed a low-sodium diet (19, 20). Because a mild increment of serum uric acid was associated with hypertension and arteriolopathy of preglomerular vessels, the present study was performed to determine the glomerular hemodynamics in this model.

METHODS

Experimental design. All animal procedures were approved by the Animal Care Committee. Male Sprague-Dawley rats (150–250 g) were used in all experiments, and blood pressure and serum uric acid were measured at 2 and 5 wk. To produce hyperuricemia, 2% oxonic acid (Sigma, St. Louis, MO) mixed in a low-sodium diet (0.125% NaCl; Ziegler, Gardner, PA) was administered to the rats (OA/LS group). To distinguish the effects of hyperuricemia from those of oxonic acid; arteriolopathy; renal hemodynamics; micropuncture; hypertension

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Table 1. Glomerular hemodynamics in LS, LS/OA, and LS/OA/AP groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Body Wt, g</th>
<th>Kidney Wt, g</th>
<th>RA, mmHg</th>
<th>RE, mmHg</th>
<th>MAP, mmHg</th>
<th>GFR, ml/min</th>
<th>SNGFR, ml/min</th>
<th>PGC, mmHg</th>
<th>SNGP, mmHg</th>
<th>Kf, mmol/min/l</th>
<th>Kf, ml/min/l</th>
<th>Re, mmHg</th>
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<tbody>
<tr>
<td>LS</td>
<td>274 ± 19</td>
<td>0.9 ± 0.1</td>
<td>19 ± 1</td>
<td>0.9 ± 0.1</td>
<td>111 ± 3</td>
<td>0.7 ± 0.2</td>
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<tr>
<td>LS/OA</td>
<td>251 ± 9.9</td>
<td>0.9 ± 0.1</td>
<td>9 ± 0.9</td>
<td>0.9 ± 0.1</td>
<td>111 ± 3</td>
<td>0.7 ± 0.2</td>
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<td>LS/OA/AP</td>
<td>331 ± 17</td>
<td>1.0 ± 0.5</td>
<td>10 ± 0.5</td>
<td>0.9 ± 0.1</td>
<td>111 ± 3</td>
<td>0.7 ± 0.2</td>
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<td>LS vs. OA</td>
<td>&lt; 0.001</td>
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<td>LS vs. AP</td>
<td>&lt; 0.001</td>
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<td>LS vs. OA/ AP</td>
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Values are means ± SE. SBP, systolic blood pressure; MAP, mean arterial pressure; GFR, glomerular filtration rate; SNGFR, single-nephron filtration rate; PGC, glomerular capillary pressure; Re, afferent resistance; RA, afferent arteriolar radius; RL, renal vascular resistance; Kf, filtration coefficient. *P < 0.05 vs. LS; †P < 0.01 vs. LS; ‡P < 0.001 vs. LS/OA.

Table 2. Hyperuricemia is associated with afferent arteriolar hypertrophy

<table>
<thead>
<tr>
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<th>LS</th>
<th>LS/OA</th>
<th>LS/OA/AP</th>
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<tbody>
<tr>
<td>SBP, mmHg</td>
<td>126.4 ± 1.8</td>
<td>134.3 ± 3.7†</td>
<td>121.8 ± 2.8‡</td>
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<tr>
<td>Serum uric acid, mg/dl</td>
<td>1.11 ± 0.22</td>
<td>3.1 ± 0.2</td>
<td>1.14 ± 0.20†</td>
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<td>Poc, mmHg</td>
<td>51.8 ± 1.4</td>
<td>56.7 ± 1.4*</td>
<td>50.1 ± 0.8§</td>
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<tr>
<td>Arteriolar area, μm²</td>
<td>147.1 ± 5.4</td>
<td>168.3 ± 9.9</td>
<td>122.6 ± 1.8*</td>
</tr>
<tr>
<td>Media-to-lumen ratio</td>
<td>2.33 ± 0.14</td>
<td>3.84 ± 0.48†</td>
<td>1.63 ± 0.04‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. SBP, systolic blood pressure. *P < 0.05 vs. LS; †P < 0.01 vs. LS; ‡P < 0.001 vs. LS/OA.

acid, a group of rats received allopurinol (Sigma; 150 mg/l drinking water), an inhibitor of xanthine oxidase, which is the enzyme responsible for uric acid synthesis, to prevent the rise in uric acid induced by oxonic acid (OA/LS/AP group). We studied the following groups: low-sodium diet alone (LS group, n = 8), OA/LS group (n = 9), and OA/LS/AP group (n = 8). Micropuncture studies were performed at 5 wk. Animals were anesthetized with pentobarbital sodium (30 mg/kg ip) and placed on a thermoregulated table to maintain body temperature at 37°C. Trachea, jugular veins, femoral arteries, and the left ureter were catheterized with polyethylene tubing (PE-240, PE-50, and PE-10). The left kidney was exposed, placed in a Lucite holder, sealed with agar, and covered with Ringer solution. Mean arterial pressure (MAP) was monitored with a pressure transducer (model p23db, Gould, San Juan, PR) and recorded on a polygraph (Grass Instruments, Quincy, MA). Blood was sampled periodically and replaced with blood from a donor rat. Rats were maintained under euvoletic conditions by infusion of isotonic rat plasma (10 ml/kg body wt) during surgery, followed by an infusion of 25% polyfructosan at 2.2 ml/h (Inunest, Laevosan-Gesellschaft, Linz, Austria). After 60 min, five to six 3-min collection samples of proximal tubular fluid were obtained to determine flow rate and polyfructosan concentration. Intra-tubular pressure under free-flow and stop-flow conditions and peritubular capillary pressure were measured in other proximal tubules with a servo-null device (Servo Nulling Pressure System, Instrumentation for Physiology and Medicine, San Diego, CA). Polyfructosan was measured in plasma samples. Glomerular colloid osmotic pressure was estimated in protein from blood of the femoral artery and surface efferent arterioles. Polyfructosan concentrations were determined by the technique of Davidson and Sackner (7). Tubular fluid volume was estimated as previously described (11). Concentration of tubular polyfructosan was measured by the method of Vurek and Pegram (33). Protein concentration in afferent and efferent samples was determined according to the method of Viets et al. (32). MAP, glomerular filtration rate (GFR), single-nephron GFR (SNGFR), proximal tubular pressure, glomerular capillary hydrostatic pressure (Poc), transcapillary hydrostatic pressure gradient (ΔP), single-nephron plasma flow (Qp), afferent (Ra) and efferent (Re) resistances, and filtration coefficient (Kf) were calculated according to equations given elsewhere (11).

Evaluation. In all studies, systolic blood pressure (SBP) was measured by tail-cuff sphygmomanometer using an automated system (Narco Biosystems, Houston, TX). All animals were preconditioned for blood pressure measurements 1 wk before each experiment. Serum uric acid was measured by the colorimetric uricase method using a commercial kit (King Diagnostics).

Renal histology. Renal biopsies were fixed in methyl-Carnoy’s solution and embedded in paraffin. Sections (4 μm) of tissue fixed in methyl-Carnoy’s solution were stained with
periodic acid-Schiff reagent. Arteriolar morphology was assessed in five rats of each group by indirect peroxidase immunostaining for α-smooth muscle actin (DAKO, Carpinteria, CA) (20).

Quantification of morphology. Quantifications were performed blinded. Only vessels adjacent to glomeruli in the outer cortex were selected. Afferent arterioles were distinguished from efferent arterioles by the presence of an internal elastic lamina and by thin, flattened endothelial cells (19). With the use of immersion-fixed tissue, afferent arteriolar wall thickness was measured by computer image analysis. For each arteriole, the outline of the vessel and its internal lumen (excluding the endothelium) was generated using computer analysis to calculate the total medial area (outline – lumen) in 10 arterioles per biopsy. Vessels that were cross sectioned or not sectioned transversally, providing an asymmetrical wall, were excluded from the present study. The media-to-lumen ratio was calculated by the outline-lumen relationship (19).

Statistical analysis. Values are means ± SE. Differences between groups were evaluated by ANOVA with appropriate correction for multiple comparisons (Bonferroni’s correction). The relationship between variables was assessed by linear regression analysis.

RESULTS

General features of the model. Consistent with previous reports (20), mild hyperuricemia was observed in OA/LS rats compared with the LS group (P < 0.05; Table 1) in association with development of modest hypertension noted by intra-arterial and tail-cuff measurements [MAP (P < 0.05; Table 1) and SBP (P < 0.01; Table 2)]. The hyperuricemia and elevation in blood pressure were prevented in the OA/LS/AP group. A significant positive linear regression between serum uric acid levels and SBP was found (r² = 0.49, P < 0.0001). Although body weight at 5 wk was significantly higher in the OA/LS/AP group than in the other groups, the overall weight gain was not different among the groups, indicating similar nutritional conditions (data not shown).

Glomerular hemodynamics. Using micropuncture techniques, we examined the effect of hyperuricemia on glomerular hemodynamics. Table 1 depicts values obtained during micropuncture studies. The mean value for PGC was increased in OA/LS rats to 56.7 ± 1.2 mmHg, a value significantly greater than that observed in the LS group (51.9 ± 1.4 mmHg, P < 0.05) and decreased in the OA/LS/AP group to values similar to those in LS rats (50.1 ± 0.8 mmHg, P < 0.01). A significant positive linear regression was observed between serum uric acid and PGC (r² = 0.34, P = 0.003; Fig. 1). PGC also correlated with SBP (r² = 0.33, P = 0.003; Fig. 2) and MAP (r² = 0.3, P = 0.005).

There were no differences in SNGFR, Kf, or QA among the groups. The similar values of SNGFR between the LS and the OA/LS group, despite higher PGC in the OA/LS group, can be explained by the higher proximal tubular pressure, which offsets PGC by decreasing ΔP. Proximal tubular pressure was higher (+2 mmHg) in OA/LS rats than in the OA/LS/AP group. Because of a higher proximal tubular pressure in the OA/LS group, ΔP was only 2.4 mmHg higher than in the LS group, and the difference was not significant. However, ΔP was significantly lower in the OA/LS/AP rats than in the LS group.

R_A and R_E were not different among groups; however, there was a significant positive correlation between MAP and R_A (r² = 0.3, P = 0.005). Importantly, the normal vasoconstrictive response of preglomerular vessels to increased MAP in the OA/LS group was insufficient to prevent increased transmission of systemic pressure to the glomerular capillaries, as indicated by the rise in P_GC.

Histological studies. Histological findings are shown in Table 2 and Figs. 3 and 4. As we reported previously, there were no significant changes in glomerular or tubulointerstitial structures by routine light microscopy; however, immunostaining for α-smooth muscle actin demonstrated hypertrophy of preglomerular vessels in the OA/LS group. Arteriolar thickening was totally prevented in the OA/LS/AP rats (P < 0.01; Table 2). A significant positive correlation was found
between arteriolar area and SBP ($r^2 = 0.53, P = 0.002$), serum uric acid ($r^2 = 0.44, P = 0.008$), and $P_{GC}$ ($r^2 = 0.32, P = 0.028$; Fig. 4). Arteriolar media-to-lumen ratio was also increased in OA/LS animals compared with the LS group ($P < 0.01$; Table 2). An increase in the arteriolar media-to-lumen ratio was prevented in OA/LS/AP animals ($P < 0.01$; Table 2).

**DISCUSSION**

In this study, we have examined the effect of mild hyperuricemia on glomerular hemodynamics in the rat. The primary new finding is that hyperuricemia in the OA/LS model is associated with glomerular hypertension. Within individual rats, there was a striking correlation between serum uric acid and glomerular hydrostatic pressure. Evidence that this effect was due to uric acid and not oxonic acid was provided by including the group that received allopurinol. This group maintained normal uric acid levels, despite receiving oxonic acid, and showed no increase in $P_{GC}$. It is possible that part of the beneficial effect exerted by allopurinol may be attributed to its antioxidant properties. Allopurinol, by blocking xanthine oxidase, will reduce superoxide anion and uric acid production by this enzymatic pathway. However, in the kidney, expression of xanthine oxidase is limited (26, 35), and it has a minimum participation during oxidative stress induced by ischemia-reperfusion (8, 15). Moreover, the oxidative stress induced by angiotensin II is mediated by NADP/NADPH oxidase (10), which should not be affected by allopurinol. Finally, in previous reports, our laboratory showed that the prevention of hyperuricemia using a uricosuric agent (benzodiarone) avoided the rise in arterial pressure and afferent arteriolopathy in this model (19). The observation that lowering uric acid by two different ways controlled blood pressure and arteriolopathy in oxonic acid-treated rats provides strong evidence that these effects are mediated by uric acid independent of oxidative stress.

The normal response to an increase in MAP is afferent arteriolar vasoconstriction, which is an autoregulatory mechanism that acts to prevent the transmission of the increased pressure to the glomerular circulation. Afferent arteriolar vasoconstriction tended to be higher in the OA/LS group, but it was not significantly different from the LS or OA/LS/AP groups.

The reason for a rise of $R_A$ in hyperuricemic rats that is insufficient to prevent transmission of increased pressure to the glomeruli may relate to the afferent arteriolopathy that occurs in this model (19). The arteriolopathy was characterized in this study by increased arteriolar thickness and media-to-lumen ratio with increased a-smooth muscle actin staining. It has been previously reported to develop independently of blood pressure, although it is dependent on the renin-angiotensin system (19). It may also be mediated by direct effects of uric acid on vascular smooth muscle cells (19, 27). Interestingly, there was a significant correlation between arteriolar thickening and glomerular pressure. One may speculate that arteriolar disease may have contributed to the transmission of SBP, because proliferation of vascular smooth muscle cells and increased collagen deposition in the vascular wall might be expected to increase rigidity of the vascular wall and thus limit its capacity to contract in response to higher perfusion pressure.

An intriguing finding was that the increased glomerular pressure in hyperuricemic rats was not associated with a simultaneous rise in single-nephron filtration rate, since the other determinants of GFR, $Q_a$ and $K_t$, were not changed. This finding could be explained by a concomitant rise in proximal tubular pressure, which offset the elevation of $P_{GC}$ and maintained the $\Delta P$. There is no apparent explanation for the rise in intratubular pressure; one possibility, however, is that higher plasma levels of uric acid may induce the formation of intratubular urate crystals, which could produce a mild tubular obstruction. In this regard, histological analysis did not demonstrate urate deposition or tubular dilatation. Independently of the mechanism responsible for the rise in intratubular pressure, we do not believe that tubular obstruction could explain the
rise in glomerular pressure. In previous studies evaluating the effect of ureteral obstruction on glomerular hemodynamics, glomerular pressure was elevated transiently after complete ureteral obstruction but returned to normal values after 24 h (34); in studies with partial ureteral obstruction, glomerular pressure was unchanged (4). Moreover, in the only study in which glomerular hemodynamics and tubuloglomerular feedback (TGF) were determined in rats with chronic partial ureteral obstruction, P_G was unchanged, and the activity of the TGF mechanism was increased. Such an increase in TGF activity would result in vasoconstriction of preglomerular vessels, which would reduce SNGFR (22).

Increased glomerular pressure is known to precede and is thought to be partially responsible for late development of hypertrophy and sclerosis in other experimental models, such as subtotal renal ablation. P_G was slightly lower in our hyperuricemic rats than in rats 4–6 wk after five-sixths nephrectomy: 56.7 vs. 60 mmHg (1, 5, 13, 17, 18). However, the rise of P_G in hyperuricemic rats probably reflects a more significant dysfunction of preglomerular vessels, because after renal ablation, blood pressure is higher (170–190 mmHg), renal mass is reduced, and there is a significant degree of afferent dysfunction; in contrast, in hyperuricemic rats, hypertension is less severe and the nephron population remains intact.

These studies were performed under low-salt dietary conditions. In this dietary condition, hyperuricemia had the most prominent effects on blood pressure and renal injury (19); therefore, we were most interested in the glomerular hemodynamic changes in this condition. However, it is known that a low-salt diet alone results in some alterations in glomerular hemodynamics compared with a normal-salt diet (11, 31). Salt depletion alone induced a slight elevation of MAP, a lower total GFR, and a lower SNGFR (11, 31). The effect of salt depletion on SNGFR is due to decrements in K_f and Q_A, despite higher P_G and AP. In the present study, these changes were particularly accentuated in the LS group compared with other studies (3, 28) and likely relate to the more prolonged period of salt depletion in the present study (5 vs. 2 wk) and, potentially, greater activation of the renin-angiotensin system. Calculated R_A and R_E in the LS group also showed a vasoconstrictor effect and were higher than reported for rats fed a normal-salt diet (11, 31) or fed a low-salt diet for a shorter period of time (3, 28). Although the low-salt diet does alter glomerular hemodynamics, the comparison between groups remains valid.

Whether hyperuricemia also increases glomerular pressure under normal- or high-salt dietary conditions was not addressed in this study. However, previous studies in hyperuricemic rats fed a normal-salt diet have documented increased systemic pressures, increased renin expression, and development of an afferent arteriolopathy (19, 20), so it is likely that similar changes in glomerular hemodynamic changes may occur.

The importance of these findings in relation to human disease is uncertain. One must be careful in extrapolating from animal models to human disease. Nevertheless, chronic hyperuricemia has been associated with renal disease in patients with gout (9, 25, 30) and has been used to predict progression in IgA nephropathy (24, 29) and development of renal insufficiency in the normal population (14). Hyperuricemia has also been reported to accelerate experimental cyclosporin nephropathy (21).

In summary, hyperuricemic rats fed a low-salt diet develop glomerular hypertension, which appears to be due to insufficient vasoconstriction of the afferent arteriole. We postulate that this may be due to development of an arteriolopathy that may alter the response of preglomerular vessels, thus allowing the transmission of systemic pressure to the glomerular capillary tuft. Because hyperuricemia is a common and easily treatable condition, it is important to clarify whether there is a pathogenic role for uric acid in renal disease.

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REFERENCES


