Effects of acute and chronic L-arginine treatment in experimental hyperuricemia


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Sánchez-Lozada LG, Tapia E, López-Molina R, Nepomuceno T, Soto V, Ávila-Casado C, Nakagawa T, Johnson RJ, Herrera-Acosta J, Franco M. Effects of acute and chronic L-arginine treatment in experimental hyperuricemia. Am J Physiol Renal Physiol 292: F1238–F1244, 2007. First published December 26, 2006; doi:10.1152/ajprenal.00164.2006.—Experimental hyperuricemia (HU) results in preglomerular arteriopathy, cortical vasoconstriction, and glomerular hypertension. Recently, uric acid has been shown to induce endothelial dysfunction. We therefore studied the effect of acute and chronic administration of L-arginine (a substrate for endothelial nitric oxide synthase) on the renal hemodynamic and vascular structural alterations induced by HU. To induce HU, oxonic acid (OA; 750 mg·kg−1·day−1) was administered in male Sprague-Dawley rats. To study the acute effect of arginine, nine rats received L-arginine (L-Arg; 15 mg·kg−1·min−1) during micropuncture. To elucidate the chronic effect of L-Arg, OA + 1% L-Arg (n = 8) and OA + 2.5% L-Arg (n = 6; drinking water) were evaluated throughout the 5-wk period. Eight normal control (N), and eight OA, rats were also studied. Kidneys were fixed by perfusion and afferent arteriole morphology was evaluated. HU rats developed the renal functional and structural alterations described and had suppressed urinary excretion of NO2/NO3. Acute stimulation of nitric oxide (NO) synthesis markedly increased urinary NO2/NO3, lowered systemic blood pressure, and relieved cortical vasoconstriction despite a significant increment of glomerular hypertension and afferent arteriole damage. Increasing doses of chronic L-Arg were associated with increasing excretion of urinary NO2/NO3, reduction of systemic hypertension, and prevention of cortical vasoconstriction (2.5% L-Arg). In addition, both doses prevented glomerular hypertension and preglomerular arteriopathy. Thus an acute relief of renal vasoconstriction in the setting of afferent arteriole damage cannot reverse glomerular hypertension, likely due to impairment in preglomerular autoregulation. On the other hand, chronic L-Arg preserved arteriolar structures probably mediated by the antiproliferative effect of NO on vascular smooth muscle cells.

endothelial dysfunction; renal cortical vasoconstriction; glomerular hypertension; arteriopathy

Recent studies suggest that hyperuricemia may be able to cause both hypertension and kidney disease. Subjects with elevated serum uric acid levels are at high risk for developing hypertension (17) and kidney disease (16). Hyperuricemia is also common in subjects with untreated hypertension (5, 12). Perhaps most importantly has been the observation that experimental hyperuricemia in rodents results in the development of hypertension and kidney disease (28, 29, 33). The kidney disease is characterized by the development of arteriolar sclerosis (preglomerular arteriopathy), glomerular hypertrophy and sclerosis, and progressive interstitial fibrosis in the absence of intrarenal crystal deposition (28, 29, 33). The underlying hemodynamic mechanisms associated with uric acid-mediated hypertension and renal disease have been elucidated in micropuncture studies. Hyperuricemia is associated with the development of cortical vasoconstriction (37, 38) resulting in tubulointerstitial changes consistent with ischemia and which is thought to have a role in the development of salt sensitivity and hypertension (45). Hyperuricemic rats also develop thickened preglomerular arterioles, which along with the efferent arterioles, vasoconstrict and mediate a fall in single-nephron glomerular filtration rate (SNGFR) and renal plasma flow (37). Interestingly, the diseased preglomerular arterioles do not constrict enough to prevent the transmission of the elevated systemic pressures into the glomerulus, and as a consequence glomerular hypertension also develops (37, 38). Hence, one observes an unusual situation in which both glomerular hypertension and reduced renal blood flow develop. We suggested that these hemodynamic changes induced by hyperuricemia may provide a mechanism for renal progression in subjects with hypertension (18).

Understanding the mechanisms driving the cortical vasoconstriction in response to hyperuricemia is thus of great importance. In this regard, experimental studies have shown that uric acid can reduce nitric oxide levels in endothelial cells (21, 23). Uric acid can also impair aortic ring vasodilation in response to acetylcholine, which is known to be mediated in part by endothelial nitric oxide (32). Furthermore, hyperuricemic rats have low plasma nitric oxide (as reflected by low nitrites and nitrates) which can be rescued by lowering uric acid levels (23). In addition, chronic treatment with the substrate of the nitric oxide synthase (NOS) L-arginine (L-Arg) to hyperuricemic rats lowered arterial hypertension, decreased renin, and increased NOS-1 expression in the macula densa despite persistence of hyperuricemia (28). Most impressively, hyperuricemic individuals have endothelial dysfunction (46), and lowering uric acid has been shown to improve endothelial function in numerous studies (4, 6, 9, 11, 15, 30).

The mechanism by which uric acid limits the availability of NO is not known; however, it was recently shown that uric acid

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may increase the activity of NADPH oxidase in cultured adipocytes (39). Increased production of reactive oxygen species and oxidative stress were associated with a significant decrement of NO bioavailability and increase in protein nitrosylation (39). Thus these findings support a direct role for uric acid in mediating endothelial dysfunction.

On the other hand, supplementation of l-Arg as a therapeutic measure against endothelial dysfunction appears to have positive benefits for cardiovascular and renal disease (3, 7, 22, 35, 36). Despite the presence of potentially adequate quantities of l-Arg inside cells, previous studies demonstrated that the administration of l-Arg can increase endothelial NO production (42).

Since a lack of NO is known to cause both renal vasoconstriction as well as preglomerular arteriopathy (34), it seems likely that endothelial dysfunction might be responsible for the effects of hyperuricemia on renal hemodynamics. We therefore tested the hypothesis that endothelial dysfunction may have a role in the renal hemodynamic response to hyperuricemia, by administering l-Arg acutely to rats with hyperuricemia-induced hypertension. In addition, we addressed the participation of endothelial dysfunction on the development of preglomerular vessels arteriopathy by administering l-Arg chronically to hyperuricemic rats.

METHODS

Five groups of male Sprague-Dawley rats were studied (290–350 g, Harlan Mexico). All groups were fed with normal rat chow during the study (l-Arg 1.06%, cat. no. 2018S Harlan Teklad, Indianapolis, IN). Eight rats served as a normal control group (N). Thirty-one rats received oxonic acid once a day by gastric gavage (750 mg/kg body wt). All groups were followed for 5 wk. Experiments were approved by the Ethics Committee of Instituto Nacional de Cardiología Ignacio Chavez.

To evaluate both acute and chronic effects of l-Arg administration, we divided oxonic acid-treated rats in the following groups: OA control group (OA; n = 8); OA + acute l-Arg group (OA + AA; n = 9), in which rats received l-Arg (15 mg·kg⁻¹·min⁻¹) during the micropuncture experiment along with the infusion of polyfructosan; OA + chronic l-Arg 1% group (OA + CA-1; n = 8), in which animals received 1% of l-Arg in drinking water during the 5 wk of the follow-up; and OA + chronic l-Arg 2.5% group (OA + CA-2.5; n = 6), in which rats received 2.5% of l-Arg in drinking water during the 5 wk of the follow-up.

Measurements. At the end of 5 wk, systolic blood pressure (SBP) was measured in conscious rats by tail cuff sphygmomanometer (XBP-1000 Kent Scientific, Torrington, CT). All animals were preconditioned for blood pressure measurements 1 wk before each experiment. Plasma uric acid (Uricostat) was measured at the same time point. In urine samples taken during micropuncture, the excretion of the final products of NO metabolism (NO₂⁻/NO₃⁻) was measured. Samples were first incubated with Escherichia coli nitrate reductase to convert NO₂⁻ to NO₃⁻, as described previously (1, 14). After incubation, total NO₃⁻ was measured using the Griess reagent. Known concentrations of NaN₃ and NaNO₂ were used as standards in each assay. Data were corrected by whole GFR and are expressed as nanomoles per milliliters.

Micropuncture. 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 PT300; Grass Telefactor, Warwick, RI) connected to the catheter in the femoral artery and recorded on a polygraph (Grass Instruments, Quincy, MA). Blood samples were taken periodically and replaced with blood from a donor rat. Rats were maintained under euvolemic conditions by infusion of 10 ml/kg body wt of isotonic rat plasma during surgery, followed by an infusion of 25% polyfructosan, at 2.2 ml/h (Inutest, Fresenius Kabi, Linz, Austria) in normal and six OA rats; the rest of the OA group received l-Arg (15 mg·kg⁻¹·min⁻¹) along with the polyfructosan. After 60 min, five to seven samples of proximal tubular fluid were obtained to determine flow rate and polyfructosan concentrations. Intratubular pressure under free-flow (FF) and stop-flow (SFP) conditions and peritubular capillary pressure (Pc) were measured in other proximal tubules with a servo-null device (Servo Nulling Pressure System; Instrumentation for Physiology and Medicine, San Diego, CA). Glomerular colloid osmotic pressure was estimated from protein concentrations obtained from blood of the femoral artery (Ca) and surface efferent arterioles (Ce). Polyfructosan was measured in plasma and urine samples by the anthrone-based technique of Davidson and Sackner (8).

The volume of fluid collected from individual proximal tubules was estimated from the length of the fluid column in a constant-bore capillary tube of known internal diameter. The concentration of tubular polyfructosan was measured by the microfluorimetric method of Vurek and Pegram (43). Protein concentration in afferent and efferent samples was determined according to the method of Viets et al. (41). GFR, SNGFR, glomerular capillary hydrostatic pressure, single-nephron plasma flow, afferent (AR), efferent (ER) resistances, and Kf were calculated with equations previously reported (2).

Renal histology and quantification of morphology. After the micropuncture study, kidneys were washed by perfusion with PBS and fixed with 4% paraformaldehyde at ~100 mmHg of MAP. Kidneys were then excised and weighed. Renal biopsies were embedded in paraffin. Four-micrometer sections of fixed tissue were stained with periodic acid Schiff (PAS) reagent. Arteriolar morphology was assessed by indirect peroxidase immunostaining for α-smooth muscle actin (DAKO, Carpinteria, CA). Renal sections incubated with normal rabbit serum were used as negative controls for immunostaining against α-smooth muscle actin (37).

Only vessels situated in close proximity to the glomerulus were measured. For each arteriole, the outline of the vessel and its internal lumen (excluding the endothelium) were generated using computer analysis (Image Pro-Plus 5.0, Media Cybernetics, Silver Spring, MD) to calculate the total medial area (outline − inline), in 10 arterioles per biopsy. The media/lumen ratio was calculated by the outline-inline relationship (37). Quantifications were performed blinded.

Statistical analysis. Values are expressed as means ± SE. Groups were analyzed by one-way ANOVA and the following set of comparisons were performed: N, OA, OA + AA, and N, OA, OA + CA-1, and OA + CA-2.5. The relationship between variables was assessed by correlation analysis. Statistical analysis was performed with Prism version 3.03 (GraphPad Software, San Diego, CA). P < 0.05 was considered significant.

RESULTS

General parameters. Body weight was comparable in all groups of rats at the end of the study (N: 342 ± 7 g; OA: 347 ± 15 g; OA + AA: 356 ± 4 g; OA + CA-1: 343 ± 5 g, and OA + CA-2.5: 346 ± 2 g), suggesting a similar food consumption among the groups.

As we previously reported (28, 37, 38), after 5 wk of OA administration rats developed hyperuricemia (N: 1.4 ± 0.14 mg/dl; OA: 3.35 ± 0.17 mg/dl; P < 0.001 vs. N) and systemic hypertension (SBP; N: 122 ± 1.2 mmHg; OA: 148 ± 4.3 mmHg; P < 0.001 vs. N) compared with normal control rats (Fig. 1). The group which received acute l-Arg during mi-
cropuncture had similar values of UA and SBP as the OA control group at the end of week 4 [UA: 3.11 ± 0.22 mg/dl, P < 0.001 vs. N, P = not significant (ns) vs. OA; SBP: 153 ± 3.0 mmHg, P < 0.001 vs. N, P = ns vs. OA].

Neither dose of L-Arg administered chronically modified UA levels compared with OA group (OA+CA-1: 3.81 ± 0.35 mg/dl, P = ns vs. OA; OA+CA-2.5: 3.21 ± 0.37 mg/dl, P = ns vs. OA). Chronic administration of 1% of L-Arg did not have a hypotensive effect in OA-treated animals (147 ± 3.4 mmHg, P = ns vs. OA); however, 2.5% of L-Arg mildly but significantly reduced SBP (135 ± 4.2 mmHg, P < 0.05 vs. OA).

Glomerular hemodynamics. Urinary excretion of NO₂⁻/NO₃⁻ is shown in Fig. 2. In the OA group the excretion of NO stable end products was suppressed compared with normal control rats (N: 6.13 ± 0.6 nmol/ml GFR; OA: 0.80 ± 0.2 nmol/ml GFR). Although by ANOVA this difference did not reach statistical significance, when we compared these two groups with an unpaired t-test the P value was statistically significant (P < 0.0001).

Acute infusion of L-Arg in OA-treated rats was associated with a considerable increment of urinary NO₂⁻/NO₃⁻ excretion of almost 10 times compared with the normal control group and 75 times compared with OA rats (OA+AA: 59.0 ± 13.0 nmol/ml GFR P < 0.001 vs. N and P < 0.001 vs. OA+V).

Increased doses of chronic L-Arg treatment was associated with augmented excretion of urinary NO₂⁻/NO₃⁻. Thus rats which received 1% L-Arg excreted 18.1 ± 4.5 nmol/ml GFR (P < 0.05 vs. OA) and animals which received 2.5% L-Arg excreted 33.5 ± 10.3 nmol/ml GFR (P < 0.001 vs. OA, P < 0.05 vs. N, P < 0.05 vs. OA+CA-1).

In the hyperuricemic (OA) group, MAP was significantly higher (N: 123 ± 3 mmHg; OA: 149 ± 2 mmHg; P < 0.001) while whole GFR was similar compared with normal control animals (N: 0.85 ± 0.1 ml/min; OA+V: 0.68 ± 0.1 ml/min; P = ns). These findings are similar to our earlier studies of hyperuricemic rats (OA treated) at 5 wk (37).

Acute stimulation of NO synthesis with acute L-Arg infusion decreased MAP (127 ± 4 mmHg, P < 0.01 vs. OA) and raised whole GFR (1.2 ± 0.2 ml/min, P < 0.05).

As with systolic blood pressure, lower chronic doses of L-Arg (1%) did not modify MAP measured in anesthetized animals during micropuncture (150 ± 7 mmHg, P = ns vs. OA, P < 0.01 vs. N) neither did the 2.5% dose of L-Arg (141 ± 3 mmHg; P = ns vs. OA, P < 0.01 vs. N). Whole kidney GFR was similar in OA+CA-1 compared with the OA group (0.92 ± 0.1 ml/min, P = ns vs. OA), whereas the increment in GFR observed with OA+CA-2.5 reached statistical significance compared with OA rats (1.2 ± 0.2 ml/min, P < 0.05 vs. OA).

Previously, we reported that OA-induced hyperuricemia was associated with cortical vasoconstriction, a decrease in SNGFR, and a reduction in the glomerular plasma flow and ultrafiltration coefficient; these changes were coupled with a rise in both afferent and efferent arteriolar resistances (37). In the present study, we confirmed these findings: OA rats had lower SNGFR (N: 28 ± 1 nl/min; OA: 18 ± 2 nl/min, P < 0.05; Fig. 3), reduced glomerular plasma flow (N: 91 ± 10 nl/min; OA+V: 67 ± 6 nl/min, P < 0.01), and a decreased ultrafiltration coefficient (N: 0.035 ± 0.003 nl·s⁻¹·mmHg⁻¹; OA: 0.015 ± 0.002 nl·s⁻¹·mmHg⁻¹; P < 0.01). Similarly, hyperuricemia was associated with an increase in afferent (N: 3.45 ± 0.3 dyn·s·cm⁻²; OA: 6.0 ± 0.6 dyn·s·cm⁻², P < 0.01 vs. OA, Fig. 3) and efferent resistances (N: 1.9 ± 0.2 dyn·s·cm⁻²; OA+V: 3.2 ± 0.3 dyn·s·cm⁻², P < 0.01 vs. OA, Fig. 3).

Stimulation of NO synthesis with acute L-Arg infusion completely reversed cortical vasoconstriction. Furthermore, SNGFR (OA+AA: 44 ± 10 nl/min, P < 0.05 vs. OA, Fig. 3),
glomerular plasma flow (OA+AA: 183 ± 38, P < 0.01 vs. OA, P < 0.05 vs. N), and ultrafiltration coefficient significantly rose (OA+AA: 0.031 ± 0.006 nl·s⁻¹·mmHg⁻¹, P < 0.05 vs. OA). Acute l-Arg-induced vasodilation in OA-treated rats was further evidenced by a significant decrement of afferent (OA+AA: 2.0 ± dyne·s·cm⁻², P < 0.001 vs. OA, Fig. 3) and efferent arteriolar resistances (OA+AA: 1.5 ± 0.2 dyne·s·cm⁻², P < 0.001 vs. OA, Fig. 2).

One percent of l-Arg administered chronically to hyperuricemic rats partially alleviated cortical vasoconstriction. We observed slight increments of SNGFR (26 ± 1 nl/min, P = ns vs. OA), glomerular plasma flow (101 ± 5 nl/min, P = ns vs. OA), and ultrafiltration coefficient (0.027 ± 0.001 nl·s⁻¹·mmHg⁻¹, P = ns vs. OA), although they did not reach statistical significance. However, the reduction in afferent (4.1 ± 0.3 dyne·s·cm⁻², P < 0.01 vs. OA) and efferent resistances (1.9 ± 2 dyne·s·cm⁻², P < 0.001 vs. OA) were significant compared with the OA group.

On the other hand, higher chronic dose of l-Arg (2.5%) fully prevented cortical vasoconstriction. SNGFR (57 ± 15 nl/min, P < 0.001 vs. OA; P < 0.01 vs. N), glomerular plasma flow (207 ± 52 nl/min, P < 0.001 vs. OA; P < 0.01 vs. N), and ultrafiltration coefficient (0.069 ± 0.02 nl·s⁻¹·mmHg⁻¹, P < 0.001 vs. OA; P < 0.01 vs. N) reached values even greater than that observed in the normal group. In addition, reductions of afferent (2.4 ± 0.5 dyne·s·cm⁻², P < 0.001 vs. OA, P < 0.05 vs. OA+CA-1) and efferent (1.2 ± 0.2 dyne·s·cm⁻², P < 0.001 vs. OA) resistances were significant.

In contrast, mild hyperuricemia results in glomerular hypertension despite cortical vasoconstriction (37, 38). In the present study, we confirmed this effect (N: 49 ± 1.1 mmHg; OA: 56 ± 1.6 mmHg, P < 0.05, Fig. 2).

Although acute l-Arg infusion fully prevented cortical vasoconstriction, it induced a further increment of glomerular pressure (63 ± 3 mmHg, P < 0.05 vs. OA; P < 0.01 vs. N, Fig. 2). To better understand why glomerular pressure remained elevated in the setting of lower blood pressure and renal vasodilatation in OA acutely administered l-Arg, we calculated the ER/AR ratio. This relationship was similar between normal and OA groups (N: 0.57 ± 0.1; OA: 0.55 ± 0.02), while in OA rats acutely administered l-Arg the ratio of ER/AR was significantly higher (OA+l-Arg: 0.86 ± 0.1, P < 0.01 vs. OA; P < 0.05 vs. N), suggesting that in this group ER was relatively elevated compared with the other two groups. In addition, we found a positive correlation between ER/AR ratio and glomerular pressure (r = 0.8, P < 0.0001; Fig. 4A).

In contrast, both doses of l-Arg administered chronically prevented the rise of glomerular pressure (OA+CA-1: 51 ± 2 mmHg, P < 0.05 vs. OA, OA+CA-2.5: 49 ± 1 mmHg, P < 0.01 vs. OA).

Arteriolar morphology. We also evaluated the effect of acute l-Arg infusion on the arteriolar lesion which is known to be present in hyperuricemic rats (29, 37, 38). Similar to previous reports (29, 37, 38), OA-induced hyperuricemia was associated with arteriolar wall thickening (N: 2.2 ± 0.3; OA: 3.7 ± 0.4, P < 0.01; Fig. 4B). As expected, acute l-Arg infusion did not have any effect on this structural modification of the preglomerular vessels (OA+AA: 3.6 ± 0.3, P < 0.01 vs. N; Fig. 4B).
While acute L-Arg did not modify the preglomerular lesion, the chronic administration of L-Arg totally prevented vascular wall thickening (OA+CA-1: 2 ± 0.1, \( P < 0.001 \) vs. OA, OA+CA-2.5: 2.7 ± 0.2, \( P < 0.05 \) vs. OA).

Furthermore, a positive correlation was demonstrated between media/lumen ratio and glomerular pressure when all groups were analyzed together (\( r = 0.61, P = 0.0001 \); Fig. 4C).

**DISCUSSION**

In this study, we examined the effect of acute and chronic administration of L-Arg on the glomerular hemodynamic changes induced by mild hyperuricemia in rats. We first confirmed that after 5 wk of OA treatment rats developed hyperuricemia, arterial and glomerular hypertension, cortical vasoconstriction, and arteriopathy of the afferent arteriole (37); in addition, as previously reported (23), OA-induced hyperuricemia was associated with a decreased synthesis of NO as indicated by the suppression of urinary excretion of \( \text{NO}_2/\text{NO}_3 \). On the other hand, acute and chronic L-Arg administration in hyperuricemic rats stimulated NO synthesis, as reflected by a marked increment of \( \text{NO}_2/\text{NO}_3 \) urinary excretion.

The primary finding was that the acute administration of L-Arg could reverse the renal cortical vasoconstriction and that this was associated with an increase in SNGFR and a decrease in MAP. However, glomerular hypertension was not improved, likely due to the presence of the preglomerular arteriolar lesion that we previously showed to correlate with impaired autoregulation. In contrast, the chronic administration of L-Arg (mainly the high dose) from the initiation of the model was able to prevent both systemic and glomerular hypertension and the renal vasoconstriction, and this was associated with maintenance of normal afferent arteriolar morphology. Thus these results support the notion that endothelial dysfunction contributes to the systemic hypertension, renal vasoconstriction, glomerular hypertension, and arteriopathy observed in rats with hyperuricemia-induced hypertension.

NO is a labile substance, with a short half-life, which decomposes rapidly to \( \text{NO}_2 \) and \( \text{NO}_3 \) in biological solutions (27); these stable end products have been measured as an index of NO production (31). In the present study, we found that OA-treated animals had an almost suppressed excretion of \( \text{NO}_2/\text{NO}_3 \) coupled to systemic hypertension and renal cortical vasoconstriction. In this respect, a significant decrement of urinary excretion of \( \text{NO}_2/\text{NO}_3 \) has been reported in other models of hypertension, endothelial dysfunction, and renal vasoconstriction such as dTGR rats (30), lead-induced hypertension (39), aging spontaneously hypertensive rats (25), and rats administered ANG II (13) and L-NAME (34).

The acute infusion of L-Arg was associated with a marked increase in urinary nitrates, suggestive of an increase in endothelial NO production. Moreover, increased doses of L-Arg administered chronically also induced increased excretion of urinary nitrates, suggesting a dose-related effect. In concert with the rise in nitrite excretion, we observed a significant reduction in cortical vasoconstriction and in systemic hypertension in acutely infused rats, whereas during chronic treatment only the higher dose of L-Arg (2.5%) partially reduced blood pressure. This apparent paradox might be related to a higher plasma concentration of L-Arg that would have been administered chronically also induced increased excretion of urinary nitrates, suggesting a dose-related effect. In concert with the rise in nitrite excretion, we observed a significant reduction in cortical vasoconstriction and in systemic hypertension in acutely infused rats, whereas during chronic treatment only the higher dose of L-Arg (2.5%) partially reduced blood pressure. This apparent paradox might be related to a higher plasma concentration of L-Arg that would have been predicted to occur during acute infusion.

An important observation in this study was that acute L-Arg administration corrected the renal vasoconstriction but not the glomerular hypertension, while chronic administration also prevented the rise in glomerular pressure. This is likely because the immediate correction of endothelial dysfunction could not reverse the structural changes in the glomerular arterioles, whereas chronic stimulation of NO synthesis with L-Arg was able to prevent the afferent arteriole hypertrophy. In this regard, it is well known that NO has an antiproliferative effect on vascular smooth muscle cells (10, 19).

We previously reported that the induction of preglomerular arteriolar disease disrupts normal renal autoregulation and results in the development of glomerular hypertension (37, 38). In this study, we observed that the renal vasodilatation induced by acute L-Arg acted to enhance glomerular pressures further, likely because the diseased arterioles could not constrict adequately in response to systemic pressure. Consistent with these
findings was the presence of a positive correlation between the individual values of media/lumen ratio and glomerular pressure. In addition, the ER/AR ratio was higher in OA+ AA than in OA (0.64 ± 0.02 vs. 0.86 ± 0.13). Therefore, efferent resistance, despite a significant decrement in L-Arg-infused rats, is still elevated for the rise in glomerular plasma flow (175% higher in OA+AA); this effect could contribute to maintain glomerular hypertension. In support of this contention, we found a positive linear relationship between the ER/AR ratio and glomerular pressure when N, OA, and OA+AA animals were included (r = 0.80, P < 0.0001).

We do not know the reason why ER was proportionally more elevated in OA+AA rats; one possible explanation could be the preferential effect of NO on afferent arterioles (24); another possibility may relate to the proliferative effect of uric acid on vascular smooth muscle cells (29). In renal vascular beds, hyperuricemia may induce vascular changes in a wide variety of arterial vessels (20); thus involvement of the post-glomerular arteriole could impair its ability to vasodilate in response to NO.

On the other hand, chronic L-Arg administration in addition to preventing renal vasoconstriction also preserved arteriolar structure and maintained glomerular pressure within normal levels. The effect of preserving afferent arteriole morphology on the renal autoregulatory response was better demonstrated in rats which received the lower dose of L-Arg. Thus, although 1% of L-Arg did not reduce systemic hypertension, the increment of blood pressure was not transmitted to glomerular capillaries due to an adequate increment in afferent resistance in these animals.

The mechanism by which uric acid inhibits endothelial NO levels is an area of intense study. Cell culture studies have demonstrated that uric acid must enter the endothelial cell in order for an inhibition of endothelial NO levels to occur (21). The effect to reduce endothelial NO levels is also not immediate, and consistent with this observation is the finding that acute infusion of urate into humans does not cause endothelial dysfunction (44). There is some evidence that the effect of uric acid to stimulate oxidant production, either NADPH oxidase (39) or via stimulation of C-reactive protein (21). In this regard, while uric acid may function as an antioxidant, it can also assume prooxidative effects under a variety of conditions (26).

In conclusion, both endothelial dysfunction and arteriolar damage participate in the glomerular hemodynamic alterations induced by mild hyperuricemia. Endothelial dysfunction appears to drive the renal vasoconstriction, whereas arteriolar damage predisposes to glomerular hypertension. The combination of these major mechanisms likely accounts for both the risk for hypertension and renal progression observed with experimental hyperuricemia.

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DISCLOSURES

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