Uremia induces abnormal oxygen consumption in tubules and aggravates chronic hypoxia of the kidney via oxidative stress

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Am J Physiol Renal Physiol 299: F380–F386, 2010. First published June 2, 2010; doi:10.1152/ajprenal.00175.2010.—In addition to causing uremic symptoms, uremic toxins accelerate the progression of renal failure. To elucidate the pathophysiology of uremic states, we investigated the effect of indoxyl sulfate (IS), a representative uremic toxin, on oxygen metabolism in tubular cells. We demonstrated an increase in oxygen consumption by IS in freshly isolated rat and human proximal tubules. Studies utilizing ouabain, the Na-K-ATPase inhibitor, and apocynin, the NADPH oxidase inhibitor, as well as the in vivo gene-silencing approach to knock down p22phox showed that the increase in tubular oxygen consumption by IS is dependent on Na-K-ATPase and oxidative stress. We investigated whether the enhanced oxygen consumption led to subsequent hypoxia of the kidney. An increase in serum IS concentrations in rats administered indole was associated with a decrease in renal oxygenation (8 h). The remnant kidney in rats developed hypoxia at 16 wk. Treatment of the rats with AST-120, an oral sorbent (AST-120), suggesting involvement of IS as a mediator of progression of kidney dysfunction (18, 19). Studies utilizing subtotally nephrectomized rats treated with indoleacetic acid showed that deterioration of renal functions was associated with an increase in serum IS levels and aggravation of tubulointerstitial damage (25).

As a final common pathway in end-stage kidney injury, chronic hypoxia in the tubulointerstitium has been the focus of recent studies and has been intensively validated by many studies (5, 7, 10). While mechanisms of chronic hypoxia in the kidney are multifactorial (17), a role of uremic toxins in oxygen metabolism in the kidney remains unknown. Here, we investigated the effect of IS on oxygen metabolism in freshly isolated kidney proximal tubular cells ex vivo, and the implications for kidney oxygenation in vivo.

MATERIALS AND METHODS

Isolation of proximal tubular cells. Primary proximal tubular cells were isolated from 12- to 14-wk-old male Sprague-Dawley rats (Scanbur, Sollentuna, Sweden) for oxygen consumption measurements as previously described (12, 23).

Human proximal tubular cells were isolated according to a modified procedure originally described by Hawksworth (9). In brief, an otherwise healthy part of the nephrectomized kidney, as determined by the surgeon, was placed in ice-cold balanced salt solution (BBS; in mmol/l: 5.37 KCl, 0.44 KH2PO4, 137 NaCl, 0.34 Na2HPO4, 1.35 NaHCO3, 5.56 d-glucose, 25 HEPES, and 0.5 EGTA, as well as 0.5% BSA and 50 mg/l streptomycin, pH adjusted to 7.2). The kidney cortex tissue was dissected, and the tissue was chopped coarsely with a scalpel. The tissue was transferred to new ice-cold BBS and centrifuged at 100 g for 2 min. The resulting pellet was resuspended in DMEM/Ham’s F12 nutrient mixture (1:1, containing 15 mmol/l HEPES, 14.28 mmol/l NaHCO3, and 50 mg/l streptomycin), and the centrifugation was repeated three times. The final pellet was resuspended in preheated (37°C) DMEM/DMEM/Ham’s F12 nutrient mixture containing 0.4% (wt/vol) collagenase A (Clostridium histolyticum, 0.5 U/mg) and incubated for 70 min at 37°C. Thereafter, the cell suspension was cooled on ice and filtered through graded filters with pore sizes of 180, 75, 53, and 38 μm, respectively. After filtration, the cells were pelleted using a low centrifugal force (400 g, 4 min) and resuspended in a collagenase-free DMEM/Ham’s F12 nutrient mixture. The rinsing procedure was repeated three times to ensure a final collagenase-free cell suspension.

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Approval by ethical committees. All animal experiments were performed in accordance with the National Institutes of Health guidelines for use and care of laboratory animals and approved by the local ethical committees. The local human ethics committee at Uppsala University approved all protocols involving patients, and informed written consent was obtained from every patient before being enrolled in the study.

Patient characteristics. Weight, height, blood pressure, and standard blood samples were taken the day before the nephrectomy and subsequently analyzed according to established procedures at the Clinical Chemistry Laboratory at the University Hospital, Uppsala, Sweden.

Measurements of oxygen consumption by isolated proximal tubular cells. Oxygen consumption was determined using the 384-well BD oxygen biosensor system (BD Biosciences) at 37°C as previously described (9). Cells were incubated with 1.0 μM-5.0 mM IS (Sigma-Aldrich, St. Louis, MO) for 30 min before oxygen consumption measurements. Additional groups were coincubated with either ouabain (1.0 mM, Sigma-Aldrich) or apocynin (1.0 mM, Sigma-Aldrich). Plates were read from the bottom using a microplate reader (Safire II, Tecan Austria, Grödig, Austria) with 485 ± 10-nm excitation and 630 ± 10-nm emission. Data were normalized to background fluorescence and expressed as relative fluorescent units according to manufacturer’s instructions and presented as relative changes compared with untreated control cells.

In vivo gene silencing using small interfering RNA. Small interfering (si) RNA against p22phox was constructed and delivered as previously described (15). In brief, a total of 50 μg of two siRNA constructs targeting p22phox (GenBank accession no. U18729; sequences 299–320 (AAATTACTACGTCCGGGCTGT) and 590–611 bp (AACCACAATTCCAGTGACAGAT); Qiagen, Valencia, CA) was delivered via the jugular vein to isoflurane-anesthetized rats using 6 ml of a delivery solution (TransIT, Mirrus, Madison, WI). Forty-eight hours thereafter, proximal tubular cells were isolated and oxygen consumption was measured as described above.

Protein isolation and Western blotting. Infusion of 20 ml cold PBS was started once the right renal vein was cut open to remove blood. The renal cortex was homogenized in lysis buffer (1.0% NP-40, 0.5% sodium deoxycholate, 0.1% SDS, 10 mM NaF, 80 mM Tris, pH 7.5) containing enzyme inhibitors (Complete Mini, Roche Diagnostics, Mannheim, Germany) and phosphatase inhibitor cocktail (Sigma-Aldrich). Samples (100 μg/well) were run on 12.5% Tris-HCl gels with Tris/glycine/SDS buffer (Bio-Rad, Hercules, CA). The proteins were detected, after transfer to nitrocellulose membranes, with rabbit anti-p22phox (1.5 μg/ml, ab75941; Abcam, Cambridge, UK) and horseradish peroxidase-conjugated secondary antibody (goat anti-rabbit 1:10,000; Sigma-Aldrich) by an ECL camera (Kodak Image Station 2000, New Haven, CT). This antibody detects two distinct bands (19 and 21 kDa), but only the 21-kDa band was quantified for the p22phox analysis. β-Actin was detected with mouse anti-rat α-actin antibody (1:10,000; Sigma-Aldrich) and secondary horseradish peroxidase-conjugated anti-mouse antibody (1:20,000; Sigma-Aldrich).

Animal model of high IS concentrations in the blood. We obtained male Sprague-Dawley rats at the age of 8 wk from Japan Charles River (Yokohama, Japan). After 20 h of starvation, indole (purchased from Merck, Whitehouse Station, NJ) was given in 0.5% methyl cellulose (Wako Pure Chemical Industries, Osaka, Japan) at indicated doses via gavage. Six hours after administration of indole, 60 mg/kg of pimonidazole was given intraperitoneally, followed by death and harvest of the kidneys 2 h later. The kidneys were fixed with neutral buffered formalin. Serum creatinine levels were measured with the Jaffé method utilizing a commercial kit (Wako). Control and indole groups were composed of 6 animals each.

Remnant kidney model. The remnant kidney (RK) model was constructed in two steps. One week before disease induction, rats received a right heminephrectomy. At day 0 they were again anesthetized, and infarction of approximately two-thirds of the left kidney was accomplished by ligation of the posterior and one or two anterior branches of the main renal artery. Twelve weeks after induction of the disease, animals were randomly divided into two groups; RK + vehicle: vehicle treatment, and RK + AST-120: AST-120 administration. Blood pressure was measured by the tail-cuff method 3 wk after the start of the treatment (15 wk after induction of the model). After 4 wk of treatment (16 wk after induction of the model), urine was collected using a metabolic cage, followed by death under ether anesthesia. Two hours before death, 60 mg/kg of pimonidazole was given intraperitoneally. The kidneys were fixed with neutral buffered formalin. Urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) was measured using a commercial ELISA kit (Japan Institute for the Control of Aging, Shizouka, Japan).

Measurement of serum IS levels. Serum IS levels were measured by a mobile phase, 5% tetrahydrofuran/0.1 M KH2PO4 (pH 6.5) at a flow rate of 1 ml/min, and fluorescence detection (excitation 295 nm, emission 390 nm) utilizing HPLC (Shimadzu, Kyoto, Japan) as described previously (21).

Assessment of pimonidazole accumulation. Pimonidazole accumulation in hypoxic cells was assessed by immunodetection utilizing Hypoxyprobe-1 Mb1 (1/200, Chemicon), as described previously (29). Color was developed with H2O2 and DAB to yield brown staining. Morphometric quantification of a positive-staining area was assessed in a blinded manner under ×100 magnification utilizing Scion Image software (Scion, Frederick, MD). At least 20 randomly selected cortical tubulointerstitial areas from each sample were evaluated.

Histological and immunohistochemical studies. Paraffin-embedded sections of 3-μm thickness were stained with periodic acid-Schiff reagents. Tubular injury was scored in a blinded manner by estimation of the percentage of tubules in the outer medulla and corticomedullary junction that showed epithelial necrosis or had necrotic debris or cast as follows: grade 0, no morphological deformities; grade 1, <25%;

Fig. 1. Oxygen consumption by freshly isolated rat proximal tubules. Oxygen consumption by freshly isolated proximal tubular cells from Sprague-Dawley rats was measured by the BD Biosensor System after incubation with different concentrations of indoxyl sulfate (IS; ▲), IS and 1.0 mM apocynin (●), or IS and 1.0 mM ouabain (○). An additional group of rats () was administered small interfering (si) RNA against p22phox 48 h before the isolation of the proximal tubular cells. IS increased oxygen consumption in normal untreated rat proximal tubules at the concentrations of 0.1 mM or more. *P < 0.05 vs. corresponding untreated control baseline. #P < 0.05 vs. corresponding IS-treated group.
Table 1. **Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>72 ± 5</td>
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<tr>
<td>Plasma creatinine, μmol/l</td>
<td>89.3 ± 20.5</td>
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<tr>
<td>Serum C-peptide, nmol/l</td>
<td>2.95 ± 0.44</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.13 ± 0.49</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>134 ± 23</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73 ± 5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.4 ± 4.4</td>
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</table>

Values are means ± SD; n = 4.

Increased oxygen consumption in rat proximal tubules at the concentrations of 0.1 mM or more (Fig. 1).

**Increase in oxygen consumption by isolated human proximal tubular cells by IS.** We freshly isolated proximal tubular cells from Sprague-Dawley rats and measured oxygen consumption in these cells incubated with different concentrations of IS. Neither the cell medium nor 0.1–5.0 mM IS displayed any increase in these cells incubated with different concentrations of IS. IS and 0.1 mM apocynin (▲), or IS and 1.0 mM ouabain (●) n = 4 for each. *P < 0.05 vs. corresponding untreated control group. #P < 0.05 vs. corresponding IS-treated group.

**RESULTS**

Increase in oxygen consumption by isolated rat proximal tubular cells by IS. We freshly isolated proximal tubular cells from Sprague-Dawley rats and measured oxygen consumption in these cells incubated with different concentrations of IS. Neither the cell medium nor 0.1–5.0 mM IS displayed any oxygen consumption when run without cells being present. IS and 1.0 mM apocynin (▲), or IS and 1.0 mM ouabain (●) n = 4 for each. *P < 0.05 vs. corresponding untreated control group. #P < 0.05 vs. corresponding IS-treated group.
the enzyme complex composed of six subunits, including membrane-associated components of the flavoprotein catalytic core, gp91phox (now named Nox-2) and p22phox. We delivered siRNA via the jugular vein and successfully knocked down p22phox protein expression in the kidney cortex (Fig. 3).

Freshly isolated proximal tubular cells from p22phox knockdown rats did not show an increase in oxygen consumption by IS (Fig. 1).

Decreased oxygenation of the kidney and a decline in renal function in animals treated with indole. Next, we examined whether an increase in serum IS concentrations induced hypoxia in the kidney in vivo. We evaluated a temporal profile of serum IS concentrations after oral administration of indole and observed a significant increase in serum IS concentrations (Fig. 4A).

We then evaluated oxygenation in the kidney of rats administered indole at a dose of 100 mg/kg. Oxygenation status was estimated by morphometric analysis of the standard pimonidazole staining method. While 17.2 ± 9.4 × 10^3 pixels were pimonidazole positive in indole-treated animals, 4.2 ± 5.1 × 10^3 pixels were positive in vehicle-treated rats (Fig. 4B). Hypoxia in rats with indole treatment was associated with a small but statistically significant decrease in renal functions (serum creatinine, 59.3 ± 9.7 μmol/l in indole-treated rats vs. 39.8 ± 4.4 μmol/l in vehicle-treated rats, P < 0.005) (Fig. 4C). These changes were not associated with histological damages in the kidney (Supplemental Fig. 1; supplemental material for this article is available online at the journal website).

Decreased oxygenation of the kidney in uremic animals. To investigate a role of uremic toxins in oxygen metabolism in the kidney in vivo, we induced the RK model in rats. RK animals developed a marked elevation of serum IS levels compared with sham-operated rats. Treatment with AST-120, an oral charcoal adsorbent which removes uremic toxins, completely abolished an increase in serum IS levels (Table 2).

We then evaluated oxygenation in the kidney of rats administered indole at a dose of 100 mg/kg. Oxygenation status was estimated by the standard pimonidazole-staining method. We did not observe pimonidazole accumulation in the superficial cortex of sham-operated animals. While

Table 2. Physiological parameters of experimental animals

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>RK + Vehicle</th>
<th>RK + AST-120</th>
</tr>
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<tbody>
<tr>
<td>Body weight, g</td>
<td>624.9 ± 12.8</td>
<td>561.6 ± 12.0</td>
<td>549.7 ± 21.0</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>116.8 ± 3.9</td>
<td>162.8 ± 8.2</td>
<td>143.2 ± 10.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>94.0 ± 4.6</td>
<td>124.4 ± 5.8</td>
<td>110.5 ± 9.6</td>
</tr>
<tr>
<td>Serum creatinine, μmol/l</td>
<td>36.3 ± 0.9</td>
<td>106.2 ± 7.1</td>
<td>85.8 ± 3.5*</td>
</tr>
<tr>
<td>Serum indoxyl sulfate, mg/dl</td>
<td>0.094 ± 0.021</td>
<td>0.450 ± 0.086</td>
<td>0.087 ± 0.015*</td>
</tr>
<tr>
<td>Proteinuria, mg/day</td>
<td>9.9 ± 0.6</td>
<td>187.7 ± 22.8</td>
<td>79.7 ± 13.6*</td>
</tr>
</tbody>
</table>

Values are means ± SE. RK, remnant kidney. The difference determined by ANOVA was significant in all parameters. *Statistically significant difference between RK + vehicle and RK + AST-120.
the remnant kidney showed accumulation of pimonidazole in the cortex, a decrease in serum IS levels was associated with a reduction of pimonidazole, suggesting improvement of PO2 in the RK (Fig. 5A). Morphometric analysis confirmed amelioration of hypoxia in the rats treated with AST-120 (Table 3). Reduction of serum IS levels showed good correlation with amelioration of pimonidazole accumulation (Fig. 5B, correlation coefficient \( r = 0.73 \)).

Amelioration of kidney injury by reduction of IS in uremic animals. Improvement of oxygenation of the kidney by reduction of serum IS levels was associated with improvement of renal functions at the end of the study, as estimated by serum creatinine and proteinuria (Table 2).

Reduction of IS in uremic animals also led to amelioration of histological injury. While RK developed focal segmental glomerulosclerosis and severe tubulointerstitial injury, reduction of IS by AST-120 resulted in milder tubulointerstitial injury (Supplemental Fig. 2). Amelioration of tubulointerstitial injury was confirmed by semiquantitative histological analysis (Table 3).

We also employed histological injury markers to evaluate kidney injury in the experimental animals. We performed immunohistochemical analysis of vimentin, a marker of tubular injury, and observed improvement of tubular damages in animals treated with AST-120 (Table 3 and Supplemental Fig. 3). When we identified activated myofibroblasts in the interstitial area using anti-\(\alpha\)-smooth muscle actin antibody, areas positive for the staining were reduced in animals treated with AST-120 (Table 3 and Supplemental Fig. 4). Furthermore, infiltration of macrophages was decreased in rats treated with AST-120 (68.2 ± 4.9 vs. 51.8 ± 5.1/visual field, \( P < 0.05 \)).

As described above, our in vitro studies utilizing cultured tubular cells showed that the increase in oxygen consumption induced by IS was mediated, at least in part, by oxidative stress. Therefore, we investigated whether restoration of oxygenation and improvement of tubulointerstitial damage in RK was associated with amelioration of oxidative stress. We used nitrotyrosine as a marker of oxidative stress, and found reduction of nitrotyrosine accumulation in tubules of RK in animals treated with AST-120 (Supplemental Fig. 5). We also measured urinary 8-OHdG for 24-h urine collection as a marker of oxidative stress. Urinary 8-OHdG in RK rats was significantly decreased by reduction of uremic toxins (219.3 ± 19.2 vs. 47.4 ± 7.4 ng/24 h, \( P < 0.001 \)). The level of urinary 8-OHdG in RK rats treated with AST-120 was equivalent to that in sham-operated animals (38.0 ± 16.4 ng/24 h).

DISCUSSION

Our studies clearly indicated that IS aggravated hypoxia of the kidney via enhancement of tubular oxygen consumption. The concentrations of IS we used in our ex vivo studies are

Table 3. Histological analysis of experimental animals

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>RK+Vehicle</th>
<th>RK+AST-120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pimonidazole-positive pixel counts</td>
<td>62,374 ± 14,007</td>
<td>239,735 ± 10,221</td>
<td>117,400 ± 14,049*</td>
</tr>
<tr>
<td>PAS injury score</td>
<td>0.0 ± 0.0</td>
<td>2.6 ± 0.3</td>
<td>1.6 ± 0.3*</td>
</tr>
<tr>
<td>Vimentin-positive tubules/visual field</td>
<td>0.1 ± 0.0</td>
<td>12.8 ± 2.0</td>
<td>4.5 ± 1.8*</td>
</tr>
<tr>
<td>(\alpha)-Smooth muscle actin-positive pixel counts</td>
<td>16,208 ± 10,615</td>
<td>85,874 ± 9,787</td>
<td>47,838 ± 8,865*</td>
</tr>
</tbody>
</table>

Values are means ± SE. PAS, periodic acid-Schiff. The difference determined by ANOVA was significant in all parameters. *Statistically significant difference between RK+vehicle and RK+AST-120.
consistent with previous studies (16). Serum levels of IS in nondialysis patients with chronic kidney disease were reported to be ~0.08 mM, while those in hemodialysis patients were 0.36 mM (20). In our in vitro studies, we observed an increase in oxygen consumption with IS at the concentrations of 0.05 mM and 0.1 mM, in human and rat tubules, respectively. The concentrations of IS we achieved in our in vivo studies in rats are ~0.15 mM (3 mg/dl). Thus the effects of IS on abnormal oxygen metabolism in tubules were observed within a physiologically relevant range of uremic states.

The significant electrolyte transport in the proximal tubule relies on ATP, which mainly originates from oxygen-consuming oxidative phosphorylation. The importance of maintaining sufficient oxygen supply for normal tubular function is demonstrated by the fact that already limited exposure to an hypoxic insult will result in loss of tubular function in the S3 segment of the proximal tubule (2). However, the present study shows that chronically decreased oxygen availability throughout the kidney, including the cortical region, results in altered kidney function. Proximal tubules are vulnerable to oxygen depletion because of large energy demands to reabsorb sodium via Na-K-ATPase. Evaluation of Po2 in the kidneys of anesthetized rats showed that acetazolamide, which decreases proximal tubule metabolism, selectively increased cortical Po2 (2). Our studies demonstrated that an increase in oxygen consumption by proximal tubular cells with IS was linked to activity of Na,K-ATPase under both basal conditions and stimulation with IS because the increase in oxygen consumption was sensitive to ouabain.

IS is one of the most powerful inducer of free radicals among various uremic toxins, and tubulointerstitial damage induced by IS can be explained by induction of oxidative stress in proximal tubular cells (16). Induction of intracellular superoxide production via NADPH oxidase was also shown in cultured rat mesangial cells (8). Thus we investigated an effect of oxidative stress on oxygen metabolism in tubular cells. In contrast to ouabain, apocynin had no effect on oxygen consumption by tubular cells under basal conditions. However, apocynin blocked the increase in oxygen consumption by IS, demonstrating that enhancement of oxygen consumption by IS was intricately linked to oxidative stress. Our in vivo gene-silencing approach (15) confirmed that enhanced oxygen consumption by IS was dependent on oxidative stress.

A link between increased formation of reactive oxygen species (ROS) and decreased renal Po2 has been well established in a model of diabetic nephropathy (22, 23). In addition, deleterious effects of the renin-angiotensin system on the kidney include hypoxia induced by oxidative stress. Blantz and colleagues (4) showed inefficient oxygen utilization of tubules induced by activation of the renin-angiotensin system in the RK model of chronic kidney disease. Welch and colleagues (32) reported that administration of angiotensin II in rats reduced Po2 in the proximal tubule in association with decreased efficiency of oxygen usage for sodium transport (32). These effects of angiotensin II on tubular hypoxia were blunted by the antioxidant.

The ROS directly interacts with nitric oxide (NO), forming peroxynitrite and thus reducing NO bioavailability. Reduced NO results in increased oxygen consumption via dysregulation of mitochondrial respiration (26, 33). The potency of NO-mediated inhibition of renal oxygen usage was demonstrated by the pioneering study of Laycock et al. (13), in which they showed that administration of a NO synthase (NOS) inhibitor increased the overall renal oxygen usage, despite a reduction in the glomerular filtration rate and transported sodium. Studies of tissues from Fischer 344 rats showed NO destruction by superoxide as the reason for decreased NO availability with subsequent stimulation of oxygen consumption (1). Apocynin suppressed oxygen consumption, suggesting NADPH oxidase as the enzyme responsible for enhanced superoxide production. Furthermore, Deng and colleagues (3) have reported that neuronal NOS was the isoform accounting for most of the inhibitory effect on mitochondrial respiration in the kidneys.

Results of our ex vivo studies were supported by our in vivo studies. First, we demonstrated that an acute increase in serum IS levels induced hypoxia of the kidney in association with a small but statistically significant increase in serum creatinine levels. Our target of investigation is chronic hypoxia as a mediator of chronic kidney disease, however, and we then employed the RK model to investigate an effect of uremia on oxygen metabolism in the kidney.

We previously showed development of hypoxia in the RK (14, 30). Furthermore, activation of hypoxia-inducible factor to enhance adaptive mechanisms against hypoxia ameliorated histological damages and renal dysfunction in the RK model (27, 29). To investigate a contribution of uremic toxins in the progression of the RK model, we employed AST-120. AST-120 is a charcoal adsorbent which decreases serum levels of uremic toxins including IS, and in addition to ameliorating uremic symptoms, it stunted the progression of renal dysfunction in human patients with diabetic nephropathy (11). We observed that treatment of RK rats with AST-120 improved renal oxygenation and protected the kidney. The kidneys in animals treated with AST-120 also showed a decrease in oxidative stress. These results extended our in vitro observations and suggested that uremic toxins per se play a pathogenic role in abnormal oxygen metabolism, at least in part via oxidative stress in the RK at a late stage.

In conclusion, our studies for the first time demonstrated that IS, a representative uremic toxin, increases oxygen consumption and aggravates local hypoxia in renal tubular cells via enhancement of oxidative stress. Uremic states per se may accelerate progression of renal dysfunction via aggravation of chronic hypoxia as a final common pathway to end-stage renal disease.

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DISCLOSURES

F. Nishijima is an employee of the Kureha Corporation.

REFERENCES


