Nitro-oleic acid protects the mouse kidney from ischemia and reperfusion injury

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Liu H, Jia Z, Soodvilai S, Guan G, Wang M-H, Dong Z, Symons JD, Yang T. Nitro-oleic acid protects the mouse kidney from ischemia and reperfusion injury. Am J Physiol Renal Physiol 295: F942–F949, 2008. First published August 27, 2008; doi:10.1152/ajprenal.90236.2008.—Nitroalkene derivatives of linoleic acid (nitrooleic acid; LNO2) and nitro-oleic acid (OA-NO2) are endogenous lipid products with potent anti-inflammatory properties (4, 38). The present study was undertaken to evaluate the therapeutic potential of OA-NO2 in a mouse model of renal ischemia-reperfusion (I/R) injury. B6129SF2/J mice were subjected to bilateral renal ischemia for 30 min, followed by 24 h of reperfusion. Fifty minutes after ischemia, mice received intraperitoneal (ip) injections of OA-NO2 (500 µg/kg; I/R OA-NO2), vehicle for OA-NO2 (i.e., 0.8 ml/kg ethanol; I/R veh), or oleic acid (500 µg/kg; I/R OA) every 6 h during the 24-h recovery period. A sham-operated group was not subjected to ischemia and received 0.8 ml/kg ethanol ip every 6 h during the 24-h recovery period (sham veh). While plasma urea and creatinine were elevated (P < 0.05) in I/R veh vs. sham veh mice, the severity was less (P < 0.05) in I/R OA-NO2 animals. Indices of histological damage, polymorphonucleocyte infiltration, together with expression of intracellular adhesion molecule-1, interleukin-1β, and tumor necrosis factor-α, p47phox, and gp91phox were greater in I/R veh vs. sham veh mice, but were attenuated (P < 0.05) in I/R OA-NO2 animals. Because indices of renal dysfunction were similar between I/R veh and I/R OA mice (P > 0.05), but less (P < 0.05) in I/R OA-NO2 animals compared with both groups, protection from bilateral renal ischemia is afforded by the nitrated but not free form of oleic acid. Together, delayed administration of nitroalkene fatty acid OA-NO2 attenuates renal I/R injury in the mouse likely via inhibition of the inflammatory response.

METHODS

Materials. 9-Nitro-oleic acid and 10-nitro-oleic acid are two regiosomers of nitro-oleic acid (OA-NO2), which are formed by nitration of oleic acid (OA) in approximately equal proportions in vivo (4). The two compounds (9-nitro-oleic acid: catalog no. 10008042; 10-nitro-oleic acid: catalog no. 10008043) were purchased from Cayman Chemical (Ann Arbor, MI), dissolved in ethanol, and used as a 1:1 mixture.

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mixture of the isomers. OA was purchased from the same company (catalog no. 90260) and dissolved in the same solvent. All other reagents were purchased from Sigma-Aldrich unless otherwise specified.

Animals and treatment groups. All protocols were approved by the Institutional Animal Care and Use Committee of the University of Utah. Three-month-old male B6129SF2/J mice were maintained in a temperature-controlled barrier facility with a 12:12-h light-dark cycle and were given free access to standard laboratory chow and tap water. Animals were anesthetized initially with 2–5% isoflurane, placed on a heated surgery table, and maintained on 2% isoflurane while breathing spontaneously. After a 1-cm incision in the abdomen was made, the left and right renal arteries were located, isolated, and occluded for 30 min using microaneurysm clips to produce ischemia. After removal of the clips, verification of reperfusion, and closing of the incision in two layers, anesthesia was terminated and 1 ml of 37°C saline was injected into the abdomen to supplement fluid loss. One hour after the commencement of ischemia, the animals were randomly divided to receive intraperitoneal (ip) injections of OA-NO2 (500 μg/kg), vehicle for OA-NO2 (i.e., 0.8 ml/kg ethanol), or oleic acid (500 μg/kg) every 6 h. A sham-operated group underwent identical surgical procedures except that microaneurysm clamps were not applied; these mice received 0.8 ml/kg ethanol ip every 6 h. In a separate experiment, the I/R animals received a single injection of OA-NO2 (2.0 mg/kg) or ethanol (0.8 ml/kg). After 24 h, mice were anesthetized using 2% isoflurane, 500–600 μl of blood was obtained from the inferior vena cava, and both kidneys were excised.

Measurement of MPO. MPO was measured in one kidney as an indicator of PMN infiltration. Immediately upon excision, the kidney was weighed, homogenized in 10 mmol/l potassium phosphate buffer containing 0.5% hexadecyltrimethylammonium bromide, centrifuged for 15 min at 1,500 g at 4°C, and the supernatant was used to assess MPO activity (ng/100 mg wet wt) using spectrophotometric techniques according to the manufacturer’s guidelines (Hycult Biotechnology, Uden, The Netherlands).

Measurement of circulating TNF-α. Circulating TNF-α was measured by using a commercially available enzyme immunoassay kit (BD Biosciences, San Jose, CA) according to the manufacturer’s instructions.

Measurement of biochemical parameters. Blood samples from anesthetized mice were obtained after renal ischemia-reperfusion for 24 h. Plasma levels of urea and creatinine were measured using standard urease assay/conductivity and picric acid reactions, respectively.

Morphological studies. Kidneys were hemisectioned and fixed by direct immersion in 3% paraformaldehyde for 16 h. Following embedding in paraffin, 4-μm sections were prepared and stained with hematoxylin and eosin and analyzed with light microscope. Renal pathology scores were generated by an observer who was blind as to the identity of the specimen. The following parameters were scored on a 1–3 scale as described elsewhere (40): 0, normal histology; 1, tubular cell swelling, brush-border loss, with up to 1/3 of tubular profile showing nuclear loss; 2, as for score 1, but greater than 1/3 but less than 3/5 of tubular profile shows nuclear loss; and 3, greater than 3/5 of tubular profile shows nuclear loss. The histological score for each kidney was calculated by addition of all 100 scores with a maximum score of 300.

Real-time RT-PCR. Under isoflurane anesthesia, kidneys were harvested and preserved in RNAlater solution (Ambion, Austin, TX). The tissue samples in the RNAlater solution were kept on ice after sampling, stored overnight at 4°C, and kept frozen at –20°C until RNA extraction. Total RNA was isolated using TRIzol (Invitrogen, Carlsbad, CA), and cDNA was synthesized using SuperScript (Invitrogen). The sequence of oligonucleotides used for real-time PCR (RT-PCR) is listed as follows: ICAM-1 sense: 5’GGTGCAGAGTGTTCTTCTCG-3’ and ICAM1 antisense: 5’CCAAGGCTCCGCTCCTGTTCT-3’; p47phox sense: 5’GTCGTGGAGAGAAGGCGAG-3’ and p47phox antisense: 5’-CGCTTTGATGGGTTATGACCG-3’; gp91phox sense: 5’-CGGTATTGGAGACTGGA-3’ and gp91phox antisense: 5’-CTTGGAAATGGGGCAAGG-3’; and GAPDH sense: 5’-GTCCTACTACATTGGGAGA-3’ and GAPDH antisense: 5’-TCATGGTGACCTTGCCGAG-3’. Real-time RT-PCR was performed using Sybergreen and the ABI Prism 7900 Sequence Detection System. The amplification was carried out for 40 cycles with conditions of 15-s denaturation at 95°C.

Immunoblotting. The lysates of the kidney were stored at −80°C until assayed. Protein concentrations were determined using Coomassie reagent. An equal amount of the whole tissue protein (60 μg) was denatured at 100°C for 10 min, separated by SDS-PAGE, and transferred onto nitrocellulose membranes. The blots were blocked overnight with 5% nonfat dry milk in Tris-buffered saline (TBS), followed by incubation for 1 h with rabbit polyclonal antibody against IL-1β (catalog no. sc-7884, Santa Cruz Biotechnology, Santa Cruz, CA), mouse monoclonal antibody against TNF-α (catalog no. sc57469, Santa Cruz Biotechnology), or mouse monoclonal antibody against α-tubulin (catalog no. T5168, Sigma, St. Louis, MO). The blots were washed with TBS followed by incubation with goat anti-rabbit or anti-mouse horseradish peroxidase-conjugated secondary antibody. Immune complexes were detected using ECL methods. The immunoreactive bands were quantified using the Gel and Graph Digitizing System (Silk Scientific, Tustin, CA).

Measurement of thiobarbituric acid-reactive substances. The measurement of thiobarbituric acid-reactive substances (TBARS) in the mouse kidney was based on the formation of malondialdehyde. The kidney was weighed, homogenized in 10 mmol/l potassium phosphate buffer containing 0.5% hexadecyltrimethylammonium bromide, centrifuged for 15 min at 1,500 g at 4°C, and the supernatant was used to measure thiobarbituric acid-reactive substances (TBARS) in the kidney as an index of lipid peroxidation.

Fig. 1. Effect of nitro-oleic acid (OA-NO2) on acute renal failure induced by ischemia-reperfusion (I/R). Male 3-mo-old B6129SF2/J mice were subjected to bilateral renal ischemia for 30 min by clamping of the renal artery, followed by reperfusion. One hour after the ischemia, vehicle (I/R veh) or OA-NO2 (I/R OA-NO2) was administered at 500 μg/kg every 6 h via intraperitoneal injection. Twenty-four hours after I/R, the animals were killed for evaluation of renal injury. Sham-operated mice served as a control (Sham veh). Values are means ± SE. A: plasma blood urea nitrogen (BUN). B: plasma creatinine (Cr). Sham veh: n = 5; I/R veh: n = 6; I/R OA-NO2: n = 6.
by using a commercially available TBARS Assay kit (catalog no. 10009055, Cayman Chemical) according to the manufacturer’s instructions.

Statistical analysis. Values shown represent means ± SE. Data were analyzed using one-way ANOVA followed by a Bonferroni posttest. A P value < 0.05 was considered significant.

RESULTS

Renal injury. After 24 h of reperfusion, plasma urea and creatinine were 5.6- and 9.3-fold greater, respectively, in I/R vehicle-treated vs. sham vehicle-treated mice [plasma blood urea nitrogen (BUN): 198.7 ± 22.8 vs. 35.6 ± 2.7 mg/dl, P < 0.01; plasma creatinine: 2.6 ± 0.47 vs. 0.26 ± 0.05 mg/dl, P < 0.01] (Fig. 1). While the increases in plasma urea and creatinine were 3.9- and 5.7-fold were greater, respectively in I/R OA-NO2 vs. sham vehicle-treated mice, it was less severe compared with I/R vehicle-treated animals (plasma BUN: 139.2 ± 5.9 mg/dl; plasma creatinine: 1.62 ± 0.31 mg/dl in the I/R OA-NO2 group) (Fig. 1). Compared with sham vehicle-treated group, I/R vehicle-treated mice exhibited marked renal pathologies such as tubular necrosis, dilation of renal tubules, and luminal casts. Remarkably, these histological changes were attenuated in I/R OA-NO2 mice (Fig. 2A). These mice had a significantly reduced semiquantitative histological damage score in the renal cortex compared with I/R vehicle-treated mice (Fig. 2B). These data indicate that functional and histological indices of renal I/R injury were attenuated by OA-NO2 treatment during the 24-h reperfusion period.

Renal MPO levels. MPO is a predominant enzyme in monocytes and in the azurophilic granules of PMN and is released upon neutrophil activation. This enzyme has been shown to play a detrimental role in the induction of renal I/R injury (30). Therefore, we determined tissue MPO levels using ELISA. Renal MPO levels were 4.6-fold greater in I/R vehicle-treated vs. sham vehicle-treated mice (Fig. 3). Strikingly, the increase in renal MPO was almost completely abolished in I/R OA-NO2 mice.

![Fig. 2. A: representative photomicrographs (hematoxylin and eosin staining, magnification ×200 and ×400) of renal cortex of the kidneys of sham veh, I/R veh, and I/R OA-NO2 mice. B: semiquantitative analysis of histological appearance. Values are means ± SE. Sham veh: n = 5; I/R veh: n = 6; I/R OA-NO2: n = 6.

![Fig. 3. ELISA analysis of kidney MPO in sham veh, I/R veh, and I/R OA-NO2 mice. The values were normalized by wet kidney weight. Values are means ± SE. Sham veh: n = 5; I/R veh: n = 6; I/R OA-NO2: n = 6.](http://ajprenal.physiology.org/)

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mice, demonstrating the ability of OA-NO2 treatment during reperfusion to attenuate I/R-induced PMN infiltration (Fig. 3).

Expression of proinflammatory cytokines and adhesion molecules. By real-time RT-PCR, renal expression of both IL-1β and ICAM1 exhibited a >10-fold increase in I/R vehicle-treated vs. sham vehicle-treated mice. Compared with I/R vehicle-treated mice, this increase was significantly attenuated in I/R OA-NO2 mice (Fig. 4). Similar results were obtained concerning circulating TNF-α as assessed by enzyme immunoassay (Fig. 4), and kidney protein abundance of TNF-α and IL-1β by immunoblotting (Fig. 5). Taken together, OA-NO2 ameliorates the release of proinflammatory cytokines and adhesion molecules in response to renal I/R.

Renal oxidative stress. Renal p47phox and gp91phox were 24.5- and 2.0-fold greater, respectively, in I/R vehicle-treated vs. sham vehicle-treated mice (Fig. 6). While the increase in p47phox (15.5-fold) and gp91phox (1.2-fold) was greater in I/R OA-NO2 vs. sham vehicle-treated mice, it was less severe compared with I/R vehicle-treated animals (Fig. 6). The levels of kidney TBARS, an index of lipid peroxidation, were significantly elevated in I/R vehicle-treated vs. sham vehicle-treated mice and were almost completely normalized in I/R OA-NO2 mice (Fig. 6). These data suggest that OA-NO2 lessened NADPH oxidase subunit activation and ROS generation in response to I/R.

Effect of a single injection of OA-NO2. Of note, the above-discussed data were all obtained with multiple ip injections of OA-NO2 (500 µg/kg every 6 h). We also examined the effect of a single ip injection of OA-NO2 (2 mg/kg) on I/R-induced renal dysfunction. Compared with I/R vehicle-treated mice, the I/R OA-NO2 (single injection) mice had a modest attenuation of the increase in plasma BUN and creatinine, but this did not reach statistical significance (plasma BUN: 202.8 ± 3.9 vs. 163.8 ± 15.8 mg/dl, P > 0.05; plasma creatinine: 2.8 ± 0.1 vs. 2.0 ± 0.5 mg/dl, n = 4, P > 0.05). These findings suggest that multiple injections are likely required to produce the full beneficial effect of OA-NO2 at least in the mouse model of renal I/R injury.

Effect of OA on I/R-induced renal injury. These experiments determined whether the protective effect of OA in response to renal I/R is specific to the nitrated (i.e., OA-NO2) or native form (i.e., OA). Functional (Fig. 7) and histological (Fig. 8) indices of renal dysfunction were similar in kidneys from I/R vehicle-treated and I/R OA-treated mice, documenting the lack of renoprotection with OA.

DISCUSSION

NO2-FA, notably nitroalkene derivatives of LNO2 and OA-NO2, are recently identified as endogenous signaling molecules; they are detected at micromolar concentrations in healthy human plasma (4). In vitro evidence suggests that these nitrated lipids possess potent anti-inflammatory properties and also function as endogenous PPARγ ligands (4, 38), suggesting their therapeutic potential for an array of human diseases, such as inflammatory diseases. In the present study, we tested the hypothesis that OA-NO2 attenuates injury in a mouse model with 30 min of bilateral renal ischemia and 24 h of reperfusion. Functional and histological indices of glomerular dysfunction, renal PMN infiltration, proinflammatory cytokines, and indices of oxidative stress were less severe in mice treated with OA-NO2 compared with those wherein vehicle or OA was administered during reperfusion. Of note, this observation was made with delayed administration of OA-NO2, which is of clinical importance since, in a clinical setting, ARF is usually diagnosed after the insult has already occurred. To our knowledge, these data provide the first evidence that OA-NO2 protects from renal I/R injury in the mouse.

Bilateral renal ischemia for 30 min followed by 24-h reperfusion produced significant renal injury in the present study. First, I/R-induced glomerular dysfunction, as reflected by elevated plasma urea and creatinine concentrations, was present in vehicle-treated vs. sham-operated mice. Furthermore, histological indices of tubular injury in kidneys from mice that completed I/R support the aforementioned functional evidence. Second, renal I/R produced marked increases in MPO activity in vehicle-treated animals, indicating that PMN infiltration into kidney tissue was more pronounced compared with sham-operated animals. Third, proinflammatory mediators measured...
in renal tissue (i.e., ICAM-1, IL-1β) and plasma (i.e., TNF-α, IL-1β) were activated to a greater degree in I/R vs. sham-operated mice. Finally, indices of oxidative stress, including the expression of p47phox and gp91phox, the key subunits of NADPH oxidase, and the levels of TBARS, were elevated in response to I/R. Collectively, these data indicate that our I/R protocol evoked significant renal injury. To test whether OA-NO2 ameliorates indices of renal I/R injury, we administered this compound at 1 h of ischemia, and every 6 h for 24 h thereafter. Plasma urea and creatinine, renal tubular damage, MPO activity, proinflammatory cytokines, and p47phox and gp91phox gene expression were less in I/R OA-NO2 vs. I/R vehicle-treated mice. As such, functional and histological damage, PMN infiltration, inflammation, and indices of oxidant stress, respectively, were attenuated by the nitrated fatty acid OA-NO2.

Inflammation has been recognized as a critical factor in the development and progression of I/R injury. Specifically, inflammation is an important mechanism to initiate and maintain renal cell injury as it potentiates both necrosis (26, 27) and apoptosis (11–13). Early in the 1980s, Romson and coworkers (34) observed that neutrophil depletion reduced myocardial injury resulting from temporary artery occlusion. Similarly, prevention of PMN adherence using a monoclonal antibody against the β-chain of the CD18 complex significantly attenuated I/R-induced microvascular permeability in the intestine (19). Neutrophil invasion of damaged tissues constitutes the local inflammatory response in part by releasing their lysosomal constituents including MPO. MPO, a 140-kDa protein present in the cytoplasm of neutrophils, represents one of the most abundant enzymes released on neutrophil activation (21). Renal I/R injury is associated with neutrophil infiltration (18) and increased tissue MPO activity (29, 32). A definitive role of MPO in renal I/R injury is recently demonstrated using MPO knockout mice (MPO−/−) (30). These mice exhibited improved renal function after I/R compared with their wild-type controls. Interestingly, MPO release by activated neutrophils is important for the activation and adherence of other neutrophils (20, 22). In line with this notion, neutrophil accumulation was significantly reduced in Mpo−/− mice (30). As expected, we found that I/R vehicle-treated mice had a marked increase in renal MPO levels compared with sham controls. Strikingly, the rise of MPO after I/R was almost completely blocked by delayed administration of OA-NO2, suggesting that inhibition of neutrophil activation may represent a primary mechanism for the renoprotective action of the nitrated lipid. Indeed, there is in vitro evidence that LNO2 inhibited phorbol 12-myristate 13-acetate- or N-formyl-Met-Leu-Phe-evoked neutrophil activation, as assessed by measurements of superoxide generation, Ca2+ influx, elastase release, and CD11b expression (8).

A major superoxide-generating system in activated neutrophils is NADPH oxidase, which is composed of membrane-associated subunits, p22phox, gp91phox, and cytosolic subunits, p47phox, p67phox, and p40phox. Among these subunits, gp91phox and p47phox are of particular importance as the former contains the catalytic domain and the latter is necessary for cytosolic subunit translocation and for initiation of NADPH oxidase assembly (3, 14, 15). We found that OA-NO2 was effective in reducing I/R-induced expression of both gp91phox and p47phox. Considering that the activated neutrophils may constitute a major source of ROS production during I/R, it seems reasonable to speculate that the reduction of NADPH oxidase expression by OA-NO2 might be the result of reduced neutrophil infiltration. It is also possible that OA-NO2 may exert a direct inhibitory effect on gene expression of NADPH oxidase. Of
OA-NO2 treatment produced a nearly complete blockade of I/R-induced increases in renal TBARS, which cannot be fully explained by the partial effect on NADPH oxidase expression. Therefore, it seems reasonable to speculate that other sources than NADPH oxidase may also contribute to I/R-induced ROS generation and may serve as an additional target of OA-NO2.

In the present study, the anti-inflammatory properties of OA-NO2 in the mouse model of renal I/R injury was also evidenced by amelioration of the production of proinflammatory cytokines (i.e., TNF-α and IL-1β) and adhesion molecules (i.e., ICAM1), which may involve not only neutrophils but also other inflammatory cells such as macrophages and lymphocytes. We found that OA-NO2 significantly reduced I/R-induced increases in renal IL-1β, and ICAM1 expression and circulating TNF-α. In general, these findings agree with the observation that LNO2 and OA-NO2 exerted a direct inhibitory effect on secretion of various proinflammatory cytokines as well as the NF-κB activation in RAW264.7 macrophages exposed to lipopolysaccharide (10).

A significant body of evidence demonstrates renoprotective actions of all three PPAR subtypes, α, δ, and γ, in renal I/R injury. Pharmacological activation of each one of the PPAR subtypes was able to ameliorate I/R-induced renal dysfunction and histological damage (17, 33, 35). Conversely, genetic deficiency of either PPARα or PPARδ in mice accelerated renal I/R injury (23, 33). Although all three PPAR subtypes shared anti-inflammatory and antioxidant properties, they may protect against renal I/R injury via different mechanisms. PPARα provided protection likely via activation of fatty acid β-oxidation (33), a mechanism that also appeared to protect against cisplatin-induced nephrotoxicity (24, 25), while PPARδ may act via activation of the PKB/Akt pathway, leading to the increased spread of renal tubular epithelial cells (23). Through a poorly characterized mechanism, PPARγ agonists exerted protective effects against not only I/R but also various kidney injuries including diabetic nephropathy, cisplatin-induced nephro-

Fig. 6. Real-time RT-PCR analysis of the expression of p47phox (A) and gp91phox (B) and measurements of thiobarbituric acid-reactive substances (TBARS) in the kidneys of sham veh, I/R veh, and I/R OA-NO2 mice. Values are means ± SE. Sham veh: n = 5; I/R veh: n = 6; I/R OA-NO2: n = 6.

Fig. 7. Effects of oleic acid (OA) on renal dysfunction in mice subjected to I/R. Shown are plasma BUN (A) and Cr (B) in sham veh, I/R veh, and I/R OA mice. Male 3-mo-old B6129SF2/J mice were subjected to bilateral renal ischemia for 30 min by clamping of the renal artery, followed by reperfusion. One hour after the ischemia, vehicle (I/R veh) or OA (I/R OA) was administered at 500 μg/kg every 6 h via intraperitoneal injection. Of note, the sham veh and I/R veh mice in these experiments were separate from those described in Fig. 1. Twenty-four hours after I/R, the animals were killed for evaluation of renal injury. Values are means ± SE; n = 5/group.
toxicity, experimental glomerulonephritis, cyclosporine-induced renal injury, and hypertensive nephropathy. OA-NO2 is reported to activate all three PPAR subtypes, with significant activation of PPARγ at 100 nM and PPARα and PPARδ at ∼300 nM (4), suggesting possible involvement of PPARs in mediating the renoprotective action of OA-NO2. Our study is limited in the lack of measurement of tissue concentrations of OA-NO2. Therefore, it is unclear whether the tissue concentrations of OA-NO2 achieved with our experimental protocol will be in a range for selective activation of PPARγ or activation of all PPAR subtypes. It is also possible that OA-NO2 may act independently of PPARγ or other PPAR subtypes. In line with the latter possibility, the anti-inflammatory properties of OA-NO2 in cultured macrophages were shown to be independent of PPARγ (10).

Renal I/R is the most common cause of ARF. An urgent need exists to define mechanisms responsible for the onset and severity of ARF and to identify new therapeutic targets and intervention strategies. Herein, we show that the endogenous nitrated lipid OA-NO2 ameliorates injury in response to bilateral renal I/R in the mouse. The attenuation of functional and histological indices of injury likely resulted from the ability of OA-NO2 to reduce inflammation, PMN infiltration, and ROS generation. Existing treatments of renal injury in response to I/R generally have not been efficacious. The present findings provide important insights into the use of endogenous nitrated fatty acids in this regard. Future studies are warranted to understand their mechanism (s) of action more precisely.

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