Testosterone exacerbates obstructive renal injury by stimulating TNF-α production and increasing proapoptotic and profibrotic signaling

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Metcalfe PD, Leslie JA, Campbell MT, Meldrum DR, Hile KL, Meldrum KK. Testosterone exacerbates obstructive renal injury by stimulating TNF-α production and increasing proapoptotic and profibrotic signaling. Am J Physiol Endocrinol Metab 294: E435–E443, 2008. First published December 11, 2007; doi:10.1152/ajpendo.00704.2006.—Upper urinary tract obstruction is a common cause of renal dysfunction in children and adults. While there is clinical evidence of an increased male incidence and mortality rate with acute renal failure, the effect of gender and testosterone on obstructive renal injury has not previously been evaluated. We hypothesized that testosterone exacerbates proinflammatory TNF-α production and proapoptotic and profibrotic signaling during renal obstruction, resulting in increased apoptotic cell death and tubulointerstitial fibrosis. To study this, male, female, castrated male, and testosterone-treated oophorectomized female rats were subjected to sham operation or 3 days of unilateral ureteral obstruction (UUO). Renal cortical tissue was then analyzed for TNF-α production; proapoptotic caspase-8,-9, and -3 activity; apoptotic cell death; profibrotic transforming growth factor-β1 production; and α-smooth muscle actin expression. In a separate arm, glomerular filtration rate (inulin clearance) was measured in rats pre- and post-UUO. Male and testosterone-treated oophorectomized female rats demonstrated a significant increase in TNF-α production, caspase activity, apoptotic cell death, tubulointerstitial fibrosis, and renal dysfunction during UUO compared with castrated males and normal female rats subjected to the same time course of obstruction. These results demonstrate that endogenous testosterone production in normal male rats and testosterone exogenously administered to oophorectomized females significantly increases TNF production and proapoptotic and profibrotic signaling during renal obstruction, resulting in increased apoptotic cell death, tubulointerstitial fibrosis, and renal dysfunction.

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gender and sex steroids on obstructive renal injury has not previously been evaluated. We hypothesize that testosterone exacerbates proinflammatory TNF-α production and proapoptotic and profibrotic signaling during renal obstruction, resulting in increased apoptotic cell death and tubulointerstitial fibrosis. To test this hypothesis, the effect of male gender and testosterone administration to oophorectomized females on obstruction-induced renal injury was studied.

Materials and Methods

Animals, experimental groups, and operative techniques. The animal protocol was reviewed and approved by the Indiana University School of Medicine Animal Care and Use Committee. Adult Sprague-Dawley rats (2 mo old, 250–350 g [weights varied with gender]) were acclimated and maintained on a standard pellet diet for 1 wk before intervention. After induction of isoflurane anesthesia, the left ureter in each rat was isolated and completely ligated via a midline laparotomy. Sham-operated animals underwent an identical surgical procedure without ureteral ligation. At the completion of the experiment, the animals were reanesthetized, the left kidneys were removed and snap frozen in liquid nitrogen, and the animals were subsequently euthanized. The animals were divided into four experimental groups: males (M), females (F), castrated males (CM), and oophorectomized females injected with testosterone (OFT). All animals underwent either sham surgery or unilateral ureteral obstruction (6 animals/group). Vaginal smears were obtained daily in the normal females to document the phase of their estrous cycle, and obstruction was induced when the females were proestrous. Castrated males and oophorectomized females underwent a gonadectomy in their first week of life. Oophorectomized females were injected with testosterone propionate intramuscularly daily (500 μg/kg) for 2 wk before surgical intervention as described by Park et al. (38).

Serum testosterone levels. Blood samples were obtained from all animals just before induction of ureteral obstruction. Serum levels of testosterone were measured using an enzyme immunoassay system (Beckman Coulter, Fullerton, CA) according to the manufacturer’s instructions. All samples were tested in duplicate, and testosterone levels were determined from a semilogarithmic straight line standard curve. The testosterone enzyme immunoassay has a sensitivity of 10 ng/dl and a detection range up to 1,600 ng/dl, with an intra-assay imprecision of 3.9% and an interassay imprecision of 7%.

Tissue homogenization. A portion of the renal cortex from each kidney was homogenized for testing in an ELISA. Homogenization was performed after the tissue samples had been diluted in 5 vol of homogenate buffer (10 mM HEPES pH 7.9, 10 mM KCl, 0.1 mM EGTA, 1 mM DTT, and 0.5 mM PMSF) using a vertishear tissue homogenizer. Renal homogenates were centrifuged at 3,000 g for 15 min at 4°C, and the supernatants were subsequently stored at −80°C.

TNF-α and TGF-β1 protein expression. Renal cortical homogenate supernatant TNF-α and TGF-β1 protein contents were determined using an ELISA. All samples were run in a single assay with homogenate buffer used as a zero control. The TNF-α ELISA was performed by adding 100 μl of each sample to wells in a 96-well plate of a commercially available rat TNF-α ELISA kit (BD Biosciences, San Diego, CA) according to the manufacturer’s instructions. The TGF-β1 ELISA was performed by activating latent TGF-β1 in each homogenized sample by adding 1 N HCl to each sample at a 1:25 dilution for 60 min at 4°C. The samples were then neutralized with 1 N NaOH and immediately tested. One-hundred microliters of each sample were added to wells in a 96-well plate of a commercially available rat TGF-β1 ELISA kit (R&D Systems, Minneapolis, MN), and the assay was performed according to the manufacturer’s instructions. All samples were tested in duplicate, and cytokine levels were determined from a log-log straight line standard curve. The ELISA results were expressed as picograms of TNF-α or TGF-β1 per milligrams of protein. The TNF ELISA has a sensitivity of 13 pg/ml and a detection range up to 2,000 pg/ml, with an intra-assay imprecision of 2.7% and an interassay imprecision of 6.2%. The TGF-β1 ELISA has a sensitivity of 4.6 pg/ml and a detection range up to 8,000 pg/ml, with an intra-assay imprecision of 3.4% and an interassay imprecision of 8.4%.

Western blot analysis. Protein extracts from homogenized samples (50 μg/lane; at least 3 different samples/group) were electrophoresed into a 12% Tris-glycine gel and transferred to a nitrocellulose membrane. Immunoblotting was performed by incubating each membrane in 5% dry milk overnight at 4°C, followed by incubation with an anti-caspase 3 (1:200 rabbit polyclonal; Cell Signaling Technology, Beverly, MA), anti-caspase 8 (1:2,000 rabbit polyclonal; Stressgen Biotechnologies, Victoria, Canada), anti-caspase 9 (1:500 rabbit polyclonal; Cell Signaling Technology), or anti-α-SMA (1:100; Abcam, Cambridge, MA) antibody for 2 h. After being washed three times in T-PBS, each membrane was incubated for 1 h with a peroxidase-conjugated secondary antibody (1:10,000; StressGen). Equivalent protein loading for each lane was confirmed by stripping and reblotting each membrane for β-actin (Sigma, St. Louis, MO; primary
1:5,000 for 30 min at room temperature, secondary 1:5,000 for 30 min at room temperature). The analysis was repeated in triplicate to assure reproducibility of results. The membranes were developed using enhanced chemiluminescence (Amersham Pharmacia Biotech, Piscataway, NJ), and the density of each band was determined using the National Institutes of Health image analysis software and was expressed as a percentage of β-Actin density.

Terminal deoxynucleotidyl transferase dUTP-mediated nick-end labeling assay. Three transverse 6-μm renal tissue sections were prepared from each sample using a cryostat and fixed in 4% paraformaldehyde and 30% sucrose. With the use of a kit from Boehringer Mannheim, DNA strand breaks representative of apoptosis were detected in each tissue section using terminal deoxynucleotidyl transferase incorporation of fluorescein-dUTP. After cellular permeabilization with 0.1% Triton X for 2 min, the tissue sections were exposed to terminal deoxynucleotidyl transferase fluorescein labeling for 1 h. The tissue sections were then washed in PBS and exposed to a nuclear counterstain (10 μg/ml bis-benzimide) for 30 s. The specimens were mounted in an antiquenching medium (ProLong Antifade Kit; Molecular Probes, Eugene, OR) and maintained at −4°C until microscopic examination. The number of fluorescent nuclei were quantified per high powered field in each treatment group and compared. Samples were analyzed in triplicate. The characteristic morphologic features of apoptosis (i.e., nuclear condensation) were also correlated with nuclear fluorescence.

Apoptosis ELISA. A portion of the renal cortex from each kidney was homogenized in liquid nitrogen and resuspended in 4 vol of ice-cold 50 mM Tris-HCl (pH 7.4). The samples were sheared by passing them through a 19-gauge needle and agitated on ice for 30 min. Four volumes of 0.1% Triton X-100 were added to each sample, and the samples were agitated on ice for 60 min. The samples were then centrifuged at 13,000 rpm for 20 min at 4°C. A photometric enzyme-immunoassay for the quantitative determination of cytoplasmic histone-associated-DNA-fragments representative of apoptosis (Cell Death Detection ELISA Plus, Roche Diagnostics; Mannheim, Germany) was performed using 20 μl of supernatant from each sample as described by the manufacturer. The samples were tested in duplicate and compared with an untreated sample, and the results were expressed as optical density per milligrams of protein. The assay allows the specific detection of mono- and oligonucleosomes in as few as 5 × 10^2 cell equivalents per well.

α-SMA accumulation. Interstitial accumulation of α-SMA was evaluated by staining representative tissue sections with a monoclonal anti-α-SMA antibody (1A4 clone; DakoCytomation, Carpinteria, CA). Three transverse 6-μm sections were prepared from each sample, deparaffinized, and washed in TBS. The tissue sections were

**Fig. 3. Caspase-8, -9, and -3 activity after UUO. Western blot and graphic depiction of renal cortical 20-kDa cleaved caspase 8 expression (A), 38-kDa cleaved caspase 9 expression (B), and 17-kDa cleaved caspase 3 expression (C) in males, castrate males, females, and testosterone-supplemented oophorectomized females subjected to 3 days of UUO vs. sham operation.**
subjected to an avidin/biotin block for 10 min, rinsed in TBS, and then blocked with normal horse serum for 20 min. Sections were then incubated with diluted primary antibody (1:1,000) for 10 min and then washed with TBS and incubated with a biotinylated secondary antibody (1:500; DakoCytomation LSAB2 Kit) for 10 min. The sections were then incubated with streptavidin-horseradish peroxidase for 10 min, rinsed in TBS, dehydrated, and mounted.

GFR. Inulin clearance rates were used to measure total GFR in animals exposed to UUO as described by Qi et al. (39). FITC-labeled inulin (5%) was diluted in saline to a concentration of 20 mg/ml and heated to 45–50°C to dissolve in solution. FITC-inulin (7 mg) was then injected into the tail vein of each rat 48 h before the onset of obstruction (baseline) and 3 days after the onset of obstruction. Blood samples were obtained from the tail vein of each rat 10, 30, 60, and 120 min after the injection. The quantity of FITC-inulin in the serum of each blood sample was determined using a fluorometer, and the GFR (µl/min) was calculated by measuring the rate at which FITC-inulin was cleared from the bloodstream [absorbance early – absorbance late/absorbance (early + late) × 2,100].

**Statistical analysis.** Data are presented as means ± SE. Differences at the 95% confidence intervals were considered significant. The experimental groups were individually compared using a one-way ANOVA with post hoc Bonferroni-Dunn (JMP Statistical Software version 5.0, Berkeley, CA). A further validation of the statistical analysis was performed using an overall ANOVA for each examination and by adjusting for multiple comparisons in all pairs (MCA) using Tukey-Kramer honestly significant difference. A power analysis of significant findings ranged from 0.65–0.99.

**RESULTS**

**Serum testosterone levels.** Serum testosterone levels were drawn from animals in each treatment group and compared. M and OFT rats had significantly higher testosterone levels than CM or normal F rats (Fig. 1). Control levels of testosterone are consistent with prior observations in the literature (43, 49).

![Fig. 4. Renal tubular cell apoptosis after UUO. A: photographs of renal cortical tissue sections (magnification: ×400) demonstrating renal tubular cell apoptosis (terminal deoxynucleotidyl transferase dUTP-mediated nick-end labeling assay) in males, castrate males, females, and testosterone-supplemented oophorectomized females subjected to 3 days of UUO vs. sham operation. Nuclei are all stained blue with apoptotic nuclei counterstained green and identified with arrowheads. B: number of apoptotic nuclei per high powered field (×400). C: quantity of histone-associated DNA fragments (ELISA) in renal cortical tissue.](https://www.ajpendo.org/content/294/2/438/F7.png)
**Induction of TNF-α protein production.** Renal cortical tissue obtained from sham-operated animals revealed low levels of TNF-α production across all treatment groups (Fig. 2). TNF-α levels remained near baseline levels in CM and F after 3 days of UUO. In contrast, TNF-α levels were significantly increased in M and OFT in response to 3 days of UUO. TNF-α levels in M and OFT were also significantly higher than those observed in CM or F subjected to the same time course of UUO.

**Activation of caspase-8, -9, and -3.** Protein extracts from homogenized sham and obstructed renal samples were analyzed for caspase-8, -9, and -3 activity. Samples from sham-operated animals demonstrated low levels of caspase-8, -9, and -3 in each treatment group. Active caspase 8 expression was significantly higher in obstructed M and OFT renal samples compared with shams, and caspase 8 expression was significantly higher in M and OFT renal samples subjected to UUO than in CM and F exposed to the same degree of obstruction (Fig. 3A).

Active caspase 9 expression was similarly higher in M and OFT renal samples subjected to obstruction compared with sham-treated animals. Again, a significantly higher degree of caspase 9 expression was observed in obstructed M and OFT renal samples compared with CM and F samples (Fig. 3B).

Active caspase 3 expression was significantly higher in obstructed M, F, and OFT renal samples compared with shams, and significantly higher caspase 3 expression was detected in obstructed M and OFT renal samples compared with CM and F samples exposed to the same degree of renal obstruction (Fig. 3C).

**Renal tubular cell apoptosis.** Transverse renal tissue sections from each treatment group were stained for the presence of apoptotic nuclei (Fig. 4, A and B). The number of apoptotic nuclei increased significantly in M, F, and OFT renal samples subjected to UUO, and the extent of apoptosis in M renal samples was significantly higher than that observed among CM or F samples subjected to the same time course of UUO. While obstructed OFT renal samples also demonstrated significantly more apoptosis than F samples using a one-way comparison, this difference was not significant upon adjusting for multiple comparisons.

Renal cortical samples from each treatment group were also homogenized and analyzed quantitatively for cytoplasmic histone-associated DNA fragments, a marker of apoptosis (Fig. 4C). The quantity of cytoplasmic histone-associated DNA fragments increased significantly in response to obstruction in M and OFT renal samples, and levels were significantly higher than those observed among CM and F renal samples exposed to the same degree of obstruction.

**Induction of TGF-β1 protein production.** Renal cortical tissue obtained from sham-operated animals revealed low levels of TGF-β1 production across all treatment groups (Fig. 5). TGF-β1 levels were significantly higher in M and OFT samples exposed to UUO compared with sham-treated animals. TGF-β1 levels were also significantly higher in obstructed M samples than in CM or F samples subjected to the same degree of renal injury. While TGF-β1 levels were significantly higher in obstructed OFT samples compared with F samples using a one-way ANOVA, this difference was not significant upon adjusting for multiple comparisons.

**α-SMA accumulation.** Increased interstitial accumulation of α-SMA is an indicator of renal fibrosis during renal obstruction (16, 17). While sham-treated and obstructed F and CM samples only exhibited α-SMA staining in the wall of blood vessels (Fig. 6A), an increase in tubulointerstitial staining for α-SMA was detected in M and OFT renal samples exposed to 3 days of UUO. These observations were confirmed with Western blot analysis (Fig. 6B). A significant increase in the expression of α-SMA was detected in M and OFT renal samples exposed to UUO compared with sham-treated kidneys; however, α-SMA expression was significantly higher in obstructed M and OFT renal samples compared with obstructed CM or F samples subjected to the same degree of injury.

**Renal function.** GFR remained stable after UUO in F and CM rats (Fig. 7). In contrast, M and OFT rats demonstrated a reduction in GFR in response to 3 days of UUO. GFRs were significantly lower in obstructed M and OFT rats than in F rats exposed to the same duration of obstruction.

**DISCUSSION**

Despite advancements in urologic surgery, upper urinary tract obstruction remains an important cause of renal failure. The development of renal injury during obstruction is primarily a consequence of increased proinflammatory signaling and the subsequent release and activation of a number of profibrotic and proapoptotic mediators. While there is growing experimental evidence that proinflammatory signaling cascades are affected by gender (38, 46, 47) and clinical evidence of an increased male incidence and mortality rate with acute renal failure (7, 36), this is the first study to elucidate the injurious effects of testosterone during renal obstruction. Endogenous testosterone production in normal male rats and testosterone exogenously administered to oophorectomized females significantly increase TNF production and proapoptotic and profibrotic signaling during obstruction, which, in turn, results in an increase in apoptotic cell death, tubulointerstitial fibrosis, and renal dysfunction.

It has been well established in the literature that TNF-α is an important mediator of both ischemic and obstructive renal injury (9, 10, 16, 17, 26, 27, 30, 31). TNF-α upregulates proapoptotic signaling and stimulates apoptotic tubular cell death in the kidney during ischemia and obstruction (26, 27, 31). In addition, TNF-α has been implicated in the genesis of
renal tubulointerstitial fibrosis (16, 17) and has a significant role in immune cell recruitment and proinflammatory mediator production (11, 23, 32). Given the wide breadth of TNF-α involvement in obstructive renal injury, we investigated the effects of gender and testosterone on obstruction-induced TNF-α production, proapoptotic signaling, apoptosis, fibrosis, and renal dysfunction.

Our data reveal that obstruction-induced renal cortical TNF-α production is nearly doubled in males and testosterone-treated oophorectomized females compared with castrated males or normal females. Prior studies (28, 31) reveal that this level of TNF production can directly stimulate apoptosis, fibrosis, and proapoptotic and profibrotic signaling during renal obstruction. While the mechanisms for this response remain unclear, some evidence suggests that sex steroids may influence proximal aspects of proinflammatory signaling (38, 48). Wang et al. (48) observed that males display increased p38 mitogen-activated protein kinase activation and cytokine expression after myocardial ischemia-reperfusion compared with castrated males, and correlated these findings to an improvement in postischemic myocardial recovery. This is an important finding, considering that most gender differences in disease susceptibility have been attributed to the protective effects of estrogen (6, 14, 41). Similarly, Park et al. demonstrated that

Fig. 6. Renal cortical α-smooth muscle actin (α-SMA) accumulation after UUO. A: photographs of renal cortical tissue sections (magnification: ×200) demonstrating α-SMA accumulation in males, castrate males, females, and testosterone supplemented oophorectomized females subjected to 3 days of UUO vs. sham operation. α-SMA is stained brown and renal tubular cells are stained pink (T, tubule; G, glomerulus). Black arrowheads identify α-SMA accumulation within the wall of blood vessels. White arrows identify α-SMA accumulation with the tubulointerstitial space. B: Western blot and graphic depiction of renal cortical α-SMA activity.
testosterone reduces the activity of protective mediators, such as nitric oxide synthase, Akt, heat shock protein 27, and extracellular signal-related kinases, during renal ischemia-reperfusion (37, 38). Our observation that testosterone increases obstruction-induced renal TNF-α production supports these findings and provides one potential explanation for the injurious effect of testosterone on the kidney during obstruction.

Obstruction-induced renal TNF-α production has been demonstrated to increase proapoptotic signaling and apoptotic tubular cell death in the kidney. Upon TNF-α binding to TNFR1, TNF receptor 1-associated death domain (TRADD) can interact specifically with the death domain of TNFR1 and serve as a common platform for the activation of several different signaling molecules that stimulate caspase 8/10 and 3 activation and thereby commit the cell to apoptosis (8, 18). The direct stimulatory effect of TNF-α on caspase 8 and 3 activation and apoptotic cell death during renal obstruction has previously been described (31). The intrinsic (mitochondrial) pathway of apoptosis, on the other hand, involves disturbances in the mitochondrial membrane. Mitochondrial release of cytochrome c triggers apoptosis via caspase 9, and subsequently, caspase 3 activation, and is regulated in part by the Bcl-2 family of proteins (32). The anti-apoptotic Bcl-2 proteins (Bcl-2 and Bcl-xL) reside in the outer mitochondrial wall and serve to inhibit cytochrome c release, while the proapoptotic Bcl-2 proteins (Bad and Bax) reside in the cytosol and translocate to the mitochondria upon death signaling to facilitate cytochrome c release (32).

Our data reveal that apoptotic renal tubular cell death and active caspase-8, -9, and -3 expression are all significantly higher in males and testosterone-treated oophorectomized females subjected to UUO than in castrated males and females subjected to the same time course of obstruction. In fact, caspase activity and the degree of apoptosis remain close to baseline levels in castrated males and females during obstruction. The observation that testosterone promotes proapoptotic signaling and cell death is supported by previous work on renal tubular cells in vitro. At physiologic concentrations, testosterone induces apoptosis in renal tubular cells, an effect that is prevented with flutamide or estrogen pretreatment (46). Furthermore, the proapoptotic mediators Fas, Fas ligand, FADD, and Bax are all upregulated, and the anti-apoptotic Bcl-2 is downregulated, within 48 h of in vitro renal tubular cell exposure to testosterone (46). While the enhancement of proapoptotic signaling and apoptotic cell death during renal obstruction may be partially explained by increased TNF-α activity, the increase in active caspase 9 expression, a component of the intrinsic mitochondrial apoptotic pathway, suggests that other signaling mechanisms may also be involved.

The effect of gender and sex hormones on renal tubulointerstitial fibrosis has primarily been studied in the setting of chronic allograft rejection. Muller et al. (34) demonstrated that kidneys transplanted into ovariectomized, testosterone-treated females demonstrated increased interstitial fibrosis, glomerular sclerosis, proteinuria, and increased expression of fibronectin and TGF-β1 compared with estradiol treated ovariectomized females. Similarly, Antus et al. (2) found that kidneys transplanted into castrate male rats treated with testosterone exhibited increased proteinuria, profound glomerulosclerosis, and increased TGF-β1 and platelet-derived growth factor-A and -B expression, irrespective of donor gender, compared with estradiol or vehicle-treated castrated male rats. The authors further demonstrated that the adverse effects of androgens on chronic allograft nephropathy are mediated by dihydrotestosterone, as the histologic deterioration and expression of profibrotic mediators were inhibited by treatment with both the anti-androgen flutamide and the 5 alpha-reductase inhibitor finasteride (1). Male gender and testosterone have also been demonstrated to reduce the effect of cytoprotective proteins, such as heat shock protein 72, in renal ischemia-reperfusion injury (12), and to increase the expression of profibrotic mediators in an animal model of autosomal-dominant polycystic kidney disease (42).

Our data suggest that androgens also have a profibrotic effect during renal obstruction. We observed a significantly greater increase in active TGF-β1 production in males subjected to UUO compared with females and castrated male rats exposed to the same degree of injury. In addition, we observed that α-SMA accumulation, a marker of tubulointerstitial fibrosis during renal obstruction, was significantly more pronounced in obstructed males and testosterone-treated oophorectomized females than in females or castrated males. While the mechanism of the profibrotic effect of testosterone requires further investigation, these observations suggest that testosterone has broad ranging injurious properties, stimulating both proapoptotic and profibrotic signaling pathways during renal obstruction.

Finally and significantly, we correlated our observations of a testosterone-mediated increase in TNF-α production, proapoptotic signaling, apoptotic cell death, and fibrosis during obstruction to alterations in renal function. Due to concerns about the sensitivity and reliability of serum creatinine levels in a UUO model, we determined GFR pre- and post-UUO obstruction using inulin clearance. Inulin clearance is widely considered the “gold standard” marker of glomerular filtration, as it is freely filtered, not secreted, and not reabsorbed (15, 21). FITC labeling has provided a nonradioactive and extremely sensitive means of detecting minute amounts of inulin in serum and urine, which has been proven sensitive to a controlled reduction in nephrin mass and successful in monitoring GFR in conscious mice (5, 24, 29, 39). Using this technique, we have demonstrated that males and testosterone-treated oophorectomized females suffer a significant reduction in GFR in re-
sponse to UUO, while castrated males and females exhibit little change.

Upper urinary tract obstruction remains an important cause of renal dysfunction in children and adults. While sex steroids are known regulators of inflammation, this is the first study to demonstrate that the genders have a differing ability to tolerate obstructive renal injury. Historically, gender differences in disease susceptibility have been attributed to the protective effects of estrogen; however, this investigation reveals that testosterone has a significant effect on obstructive renal injury, stimulating TNF-α production; caspase-8, -9, and -3 activation; apoptotic cell death; tubulointerstitial fibrosis; and renal dysfunction. A greater understanding of the role of testosterone in proinflammatory, proapoptotic, and profibrotic signaling during obstructive renal injury may provide new therapeutic strategies to protect against renal dysfunction in the future.

GRANTS

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