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Original Paper

Activation of TRPV1 Prevents Salt-Induced Kidney Damage and Hypertension After Renal Ischemia-Reperfusion Injury in Rats

Shuang-Quan Yu[a,d] Shuangtao Ma[a] Donna H. Wang[a,b,c]

[a]Division of Nanomedicine and Molecular Intervention, Department of Medicine, Michigan State University, East Lansing, Michigan, [b]Neuroscience Program, Michigan State University, East Lansing, Michigan, [c]Cell and Molecular Biology Program, Michigan State University, East Lansing, Michigan, USA; [d]Youjiang Medical University for Nationalities, Guangxi, China

Key Words
Trpv1 • Blood pressure • Renal injury • Inflammation • Fibrosis

Abstract
Background/Aims: High-salt intake after recovery from renal ischemia-reperfusion (I/R) injury leads to hypertension with severe renal damage. Transient receptor potential vanilloid type 1 (TRPV1) channels have been involved in the regulation of inflammation and oxidative stress following ischemic organ injury. We tested the hypothesis that activation of TRPV1 conveys preconditioning protection to the kidney subjected to I/R. ***Methods:*** TRPV1 was activated or down-regulated by subcutaneous injection of a low (1mg/kg) or high (100mg/kg) dose of capsaicin, respectively, 3 hours before ischemia. Rats were fed a 0.4% NaCl diet for 5 weeks after I/R followed by a 4% NaCl diet for 4 more weeks in 4 groups: sham, I/R, I/R+high-dose capsaicin (HCap), and I/R+low-dose capsaicin (LCap). ***Results:*** Renal TRPV1 expression was decreased in I/R rats ($P<0.05$) and further reduced in I/R+HCap group ($P<0.05$) but unchanged in I/R+LCap rats compared with the sham group. Blood pressure were elevated in I/R rats ($P<0.05$) and further increased in I/R+HCap group ($P<0.05$) but unchanged in I/R+LCap rats compared with sham. Renal function was impaired in I/R rats ($P<0.05$) and further deteriorated in I/R+HCap group ($P<0.05$) but unchanged in I/R+LCap group. Renal inflammatory responses, oxidative stress, and renal collagen deposition were augmented in I/R rats (all $P<0.05$) and further intensified in I/R+HCap group (all $P<0.05$) but unchanged in I/R+LCap group. ***Conclusion:*** Activation of TRPV1 plays an anti-inflammatory and anti-oxidative stress role in preventing renal tissue damage and salt-induced hypertension after I/R injury, indicating that TRPV1 conveys preconditioning protection that may have therapeutic implication.

Donna H. Wang, MD, FAHA

Division of Nanomedicine and Molecular Intervention, Department of Medicine, Michigan State University, 788 Service Road, B316 Clinical Center, East Lansing, MI 48824 (USA)
Tel. +1-517-432-0797, Fax 1-517-432-1326, E-Mail donna.wang@hc.msu.edu

Introduction

Patients who survived from acute renal injury are at increased risk of developing high blood pressure (BP) [1]. Animal experiments exhibited a similar phenomenon in which rats, recovered from acute ischemia/reperfusion (I/R)-induced renal failure, develop renal damage and hypertension when subjected to high salt (HS) loading [2, 3]. Studies aimed at investigating the underlying mechanisms showed that immune suppression with mycophenolate mofetil, a suppressor of T cells and B cells, prevented salt-sensitive hypertension following recovery from acute renal I/R injury [4, 5], indicating that salt-sensitive hypertension in this model is dependent on inflammatory response.

Transient receptor potential vanilloid type 1 (TRPV1) is a non-selective cation channel located in sensory neurons that can be activated by noxious heat (>43˚C), proton, or vanilloid compounds [6, 7]. TRPV1 has been shown to play a key role in preventing the development of salt-sensitive hypertension [8]. It has been reported that TRPV1 positive sensory nerves counterbalance the prohypertensive effects of several neurohormonal systems to maintain normal BP when challenged with salt loading [9-17]. We also demonstrated that TRPV1 plays a protective role against cardiac and renal injury, which is independent on its BP lowering effects [18-20]. TRPV1 activation or depletion prevents or aggravates, respectively, myocardial damage induced by acute cardiac I/R or renal injury induced by deoxycorticosterone acetate-salt loading through suppressing or increasing inflammatory responses, respectively [18-24], which were consistent with results reported by other groups [25-30]. It has also been shown that activation of TRPV1 conveys an anti-inflammatory effect [18-24], which may underlie TRPV1-mediated organ protection under pathological conditions.

Given that renal I/R injury may impair renal sensory nerves expressing TRPV1 that has been shown to play a role in mediating inflammatory processes [18-24], we hypothesized that activation of TRPV1 conveys preconditioning protection to the kidney subjected to acute I/R injury and prevents HS-induced hypertension and renal damage. In the present study, we tested the hypothesis from both ends by activating or downregulating TRPV1, i.e., a low dose of capsaicin (a TRPV1 agonist) was applied prior to I/R to activate TRPV1 as preconditioning stimulation; and a high dose of capsaicin was applied to down-regulate TRPV1. To reveal underlying mechanisms, we also examined the changes in renal function, inflammatory response, and oxidative stress.

Materials and Methods

Animals

Male Wistar rats weighing 175-200g (Charles River Laboratory; Wilmington, MA, USA) were housed on a cycle of 12-hr light and 12-hr darkness. Food and water were available *ad libitum*. Rats were fed a low-sodium diet (0.4% NaCl by weight, Dyets, Bethlehem, PA, USA) for six weeks: from one week before receiving renal I/R to 5 weeks after the I/R procedure. Thereafter, rats were fed a high-sodium diet (4% NaCl by weight, Dyets) for 4 weeks. All experiments were approved by the Institutional Animal Care and Use Committee of Michigan State University and were performed in accordance with the guidelines and regulations of Animal Care Program of Michigan State University.

Treatment with capsaicin

Low dose of capsaicin (LCap, 1 mg/kg) or high dose capsaicin (HCap, 100 mg/kg) was administered subcutaneously 3 hours before renal ischemia in rats anesthetized with ketamine/xylazine (85/5 mg/kg, intraperitoneally). Therefore, rats were divided into 4 groups: Sham, I/R, I/R+HCap, I/R+LCap.

Renal I/R procedure

Renal I/R was induced by clamping the renal artery of both kidneys in anesthetized rats. After 40-minute ischemia, the clamps were removed and the incision was closed. The rats were administered antibiotics (penicillin and streptomycin).

Measurement of BP, water intake, and urine excretion

For the measurement of systolic BP, rats were trained to be accustomed to the measuring condition for 5 days before the testing day to minimize the effect of stress on BP. The value of systolic BP of conscious rats was the average of 9 separate measurements using the tail cuff method (Hatteras Instruments SC1000 Blood Pressure Analysis System, Cary, NC, USA). For the measurement of mean arterial pressure (MAP), a PE-50 catheter was cannulated into the right carotid artery of rats anesthetized with ketamine/xylazine and connected with pressure transducer and recorder (Gould Instruments, Cleveland, OH, USA). Three hours later, the MAP was obtained on fully awake and unstrained rats. 24-hour water intake and urine excretion were determined using metabolic cages.

Assays of creatinine, urea, and 8-isoprostane

Plasma and urine creatinine concentrations were assayed using a kit (K625-100, Creatinine assay kit, BioVision, Mountain View, CA, USA). Plasma concentrations of urea were determined using a kit (K375-100, urea assay kit, BioVision). Urinary 8-isoprostane level was determined using an EIA kit (516351, 8-isoprostane EIA kit, Cayman Chemical, Ann Arbor, MI, USA).

Western blotting

Sample was homogenized and sonicated in 2ml of 10mmol/L Tris buffer (pH 7.6) containing 0.5mmol/L $MgCl_2$, 5mmol/L NaCl, and protease inhibitors. Homogenates were centrifuged at 500g for 5min at 4°C. The supernatant was added with 10μl of 0.5mol/L EDTA and 100μl of 10% Triton X-100, incubated on ice for 45min, and centrifuged at 22, 000g for 30min at 4°C. The supernatant was saved as loading samples. 20mg/ml of proteins were electrophoresed on SDS-PAGE gels [7.5% for TRPV1, 10% for tumor necrosis factor (TNF)-α, connective tissue growth factor (CTGF), interleukin (IL)-1β] and transferred to PVDF membrane (162-0180, Bio-Rad Laboratories, Hercules, CA, USA). Membranes were incubated with rabbit anti-TRPV1 antibody (1:1000, RA10110, Neuromics, Edina, MN, USA), mouse anti-TNF-α antibody (1:500, T-3198, Sigma-Aldrich, St. Louis, MO. USA), mouse anti-IL-1β antibody (1:200, sc-74138, Santa Cruz Biotechnology, Santa Cruz, CA, USA), rabbit anti-CTGF antibody (1:200, sc-25440), rabbit anti-collagen I antibody (1:200, sc-8784), or rabbit anti-collagen IV antibody (1:200, sc-11360), at 4°C overnight, followed by incubation with HRP-donkey anti-rabbit IgG (1:10, 000, 711-035-152, Jackson ImmunoResearch Laboratories, West Grove, PA, USA) or HRP-donkey anti-mouse IgG (1:10, 000, 711-035-151, Jackson ImmunoResearch Laboratories) for 2h at room temperature. The immunoreactive bands were visualized by ECL reagents (RPN 2106, Amersham, GE Healthcare, Piscataway, NJ, USA) and a film (Kodak® X-Omat LS film, Eastman Kodak company, Rochester, NY, USA). The intensity of the bands was determined by using ImageJ (NIH, Bethesda, MD, USA). The protein loading was normalized by β-actin (1:2, 000, sc-69879).

Immunofluorescence staining

Rats were anesthetized by ketamine/xylazine and perfused transcardially by a fixative 4% paraformaldehyde in PBS. The kidneys were harvested and cut into sections (40μm for TRPV1 staining, 5μm for macrophage staining). The sections were incubated with rabbit anti-TRPV1 antibody (1:500, AB5566, Millipore, Billerica, MA, USA) or mouse anti-CD68 monoclonal antibody (1:100, MCA341R, AbD Serotec, Kidlington, UK) at 4°C overnight, then incubated with Rhodamine Red (TM)-X donkey anti-rabbit IgG (1:100, 711-295-152, Jackson ImmunoResearch Laboratories) or Rhodamine Red (TM)-X donkey anti-mouse IgG (1:100, 715-295-152, Jackson ImmunoResearch Laboratories) for 1h at room temperature, mounted with Vectashield mounting medium (H-1400, Vector Laboratories, Burlingame, CA, USA). Images were taken with a fluorescent microscope (Olympus BX41 model, Olympus Optical Co. Ltd, Tokyo, Japan; Olympus MicroSuiteTM-Basic software, Olympus Soft Imaging Solutions GmbH, Münster, Germany). For the quantification of CD68-positive macrophage staining, 10 coronal sections through the renal hilus of each kidney at interval of 20μm were selected for staining. For each section, 10 fields of view from cortex and medulla each were chosen randomly for counting the number of macrophages. The value was expressed as macrophage number per square millimeter.

Staining of collagen deposition

Rats were perfused transcardially with 4% paraformaldehyde. The kidneys were harvested and cut into sections of 5μm. The staining procedure was performed using a kit (Gomori's One-Step Trichrome stain kit, 9176A, Newcomer Supply Inc, Middleton, WI, USA).

Drugs

Capsaicin (M2028, Sigma-Aldrich) was dissolved in saline including 0.1% ethanol.

Statistical analysis

All data were expressed as mean±SE. Unpaired Student's *t*-test was used to analyze the differences between two groups. One-way ANOVA followed by a Bonferroni adjustment for multiple comparisons was used to analyze the differences among groups. Differences at $P<0.05$ were considered statistically significant.

Results

TRPV1 was activated or down-regulated by subcutaneous injection of a low (1mg/kg) or high (100mg/kg) dose of capsaicin, respectively, 3 hours before I/R procedure. Rats were fed a 0.4% NaCl (LS) diet for 5 weeks after I/R followed by a 4% NaCl (HS) diet for 4 more weeks. There was no difference in body weight (data not shown) among all groups at any time point examined, indicating that general growth and condition of rats were not affected by I/R or dietary treatment.

Low dose of capsaicin prevented the down-regulation of renal TRPV1 after I/R

Immunohistochemistry staining showed that TRPV1 in both the cortex and the medulla of the kidney was weaker in I/R rats, and was weakest in I/R rats treated with HCap, but was unchanged in I/R rats treated with LCap compared to that of sham rats (Fig. 1a). Negative controls in which TRPV1 antibody was omitted showed no staining (data not shown). Consistently, Western blot analysis revealed that renal TRPV1 protein level was decreased in I/R rats ($P<0.05$) and further reduced in I/R+HCap rats ($P<0.05$) but unchanged in I/R+LCap rats compared to sham rats (sham: 0.45±0.03, I/R: 0.22±0.02, I/R+HCap: 0.12±0.02, I/R+LCap: 0.38±0.05) (Fig. 1b and 1c).

Low dose of capsaicin prevented HS intake-induced BP elevation in I/R rats

Next we examined the effects of manipulation of renal TRPV1 on BP. Systolic BP was similar among all groups when fed LS diet but showed gradual differences among groups after loading with HS. Systolic BP was significantly elevated in I/R rats compared to sham rats ($P<0.05$), and further increased in rats treated with I/R+HCap ($P<0.05$) (Fig. 2a). The increase of systolic BP in I/R rats induced by HS loading was prevented by pretreatment with low dose of capsaicin in I/R+LCap group (Fig. 2a). We obtained similar results in the measurement of MAP (sham: 113±2, I/R: 124±2, I/R+HCap: 134±2, I/R+LCap: 115±2 mmHg, Fig. 2b).

Low dose of capsaicin prevented HS intake-induced renal dysfunction in I/R rats

There was no significant change in the ratio of urine/water intake among groups during feeding with LS diet while the ratio of urine/water intake showed gradual differences after loading with HS. The ratio of urine excretion/water intake was lower in I/R rats compared to sham rats ($P<0.05$), and further decreased in rats treated with I/R+HCap ($P<0.05$), while the decrease of the ratio of urine excretion/water intake in I/R rats induced by HS loading was prevented in I/R+HCap group (sham: 0.77±0.02, I/R: 0.67±0.04, I/R+HCap: 0.53±0.02, I/R+LCap: 0.77±0.03; Fig. 3a). The renal function, in terms of the creatinine clearance and plasma urea and creatinine levels, was impaired in I/R rats (all $P<0.05$) and further dete-

riorated in I/R+HCap rats (all $P<0.05$) but unchanged in I/R+LCap rats compared to sham rats at one day after I/R procedure (Fig. 3b-3d). The renal function recovered after 5-week of LS treatment (Fig. 3b-3d). However, when the diet was switched from LS to HS, the similar pattern of changes in the levels of creatinine clearance and plasma urea and creatinine among groups was observed at 4 weeks after HS treatment (for creatinine clearance, sham: 0.53±0.07, I/R: 0.25±0.04, I/R+HCap: 0.13±0.02, I/R+LCap: 0.44±0.05 ml/min/100gbwt; for plasma urea, sham: 6±0, I/R: 12±1, I/R+HCap: 21±2, I/R+LCap: 8±1mM; for plasma creatinine, sham: 0.56±0.08, I/R: 1.11±0.13, I/R+HCap: 1.78±0.20, I/R+LCap: 0.57±0.07 mg/100 mL; Fig. 3b-3d).

Low dose of capsaicin prevented HS intake-induced renal inflammation in I/R rats

To further determine the relationship between TRPV1 and renal function, we examined the expression of inflammatory cytokines and infiltration of macrophages in kidney tissue. We found the levels of TNF-α and IL-1β in the kidney were augmented in I/R rats (both $P<0.05$) and further intensified in I/R+HCap rats (both $P<0.05$) but unchanged in I/R+LCap rats compared to sham rats 4 weeks after HS treatment (TNF-α, sham: 0.24±0.01, I/R: 0.36±0.03, I/R+HCap: 0.49±0.04, I/R+LCap: 0.27±0.02; IL-1β, sham: 0.28±0.03, I/R: 0.42±0.04, I/R+HCap: 0.57±0.05, I/R+LCap: 0.27±0.04; Fig. 4a-4d). We also examined the macrophage infiltration in kidney tissue at the end of the experiment. Macrophage infiltration was more in the renal cortex and medulla in I/R rats than sham rats ($P<0.05$), and intensified in I/R+HCap rats ($P<0.05$) (Fig. 5a and 5b). In contrast, there was no difference in renal macrophage infiltration between I/R+LCap rats and sham rats (renal cortex, sham: 10±1, I/R: 33±3, I/R+HCap: 57±5, I/R+LCap: 14±2 cells/mm^2; renal medulla, sham: 13±2, I/R: 39±4, I/R+HCap: 61±6, I/R+LCap: 18±3 cells/mm^2; Fig. 5a and 5b).

Low dose of capsaicin prevented HS intake-induced renal oxidative stress in I/R rats

The level of urinary 8-isoprostane was significantly increased in I/R rats ($P<0.05$) and further elevated in I/R+HCap rats ($P<0.05$) but unchanged in I/R+LCap rats compared to sham rats at one day after I/R procedure (Fig. 6). The changes in urinary 8-isoprostane level between groups disappeared 5 weeks after I/R injury (Fig. 6). However, when the diet was switched from LS to HS, the similar pattern of changes in the level of urinary 8-isoprostane reappeared (sham: 11±2, I/R: 18±2, I/R+HCap: 25±2, I/R+LCap: 12±1 ng/day; Fig. 6).

Low dose of capsaicin prevented HS intake-induced renal fibrosis in I/R rats

CTGF and collagen are markers of renal fibrosis. Western blot revealed that the levels of CTGF, collage I, and collagen IV were increased in I/R rats (all $P<0.05$) and further elevated in I/R+HCap rats (all $P<0.05$) but unchanged in I/R+LCap rats compared to sham rats (CTGF, sham: 0.24±0.02, I/R: 0.38±0.04, I/R+HCap: 0.53±0.04, I/R+LCap: 0.27±0.02; collagen I, sham: 0.22±0.03, I/R: 0.38±0.04, I/R+HCap: 0.64±0.06, I/R+LCap: 0.27±0.03; collagen IV, sham: 0.28±0.04, I/R: 0.49±0.02, I/R+HCap: 0.67±0.04, I/R+LCap: 0.34±0.04; Fig. 7a-7f). Gomori one-step trichrome staining showed that collagen in renal cortex and medulla was obvious in I/R+HCap group (Fig. 8).

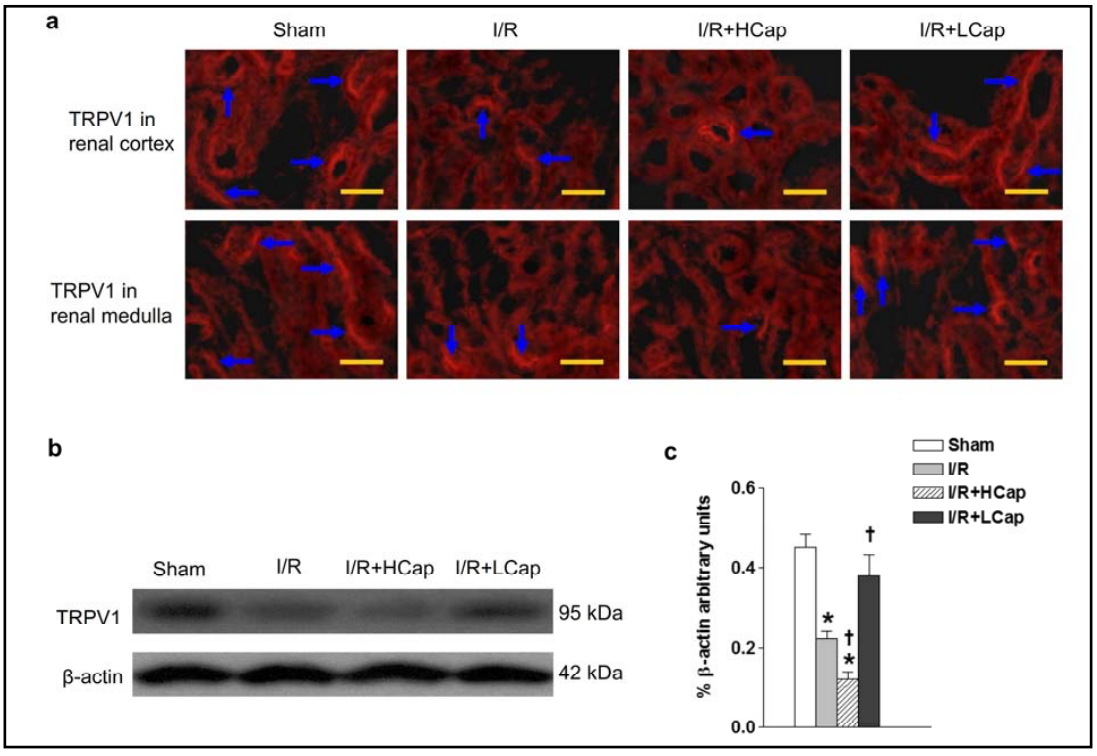
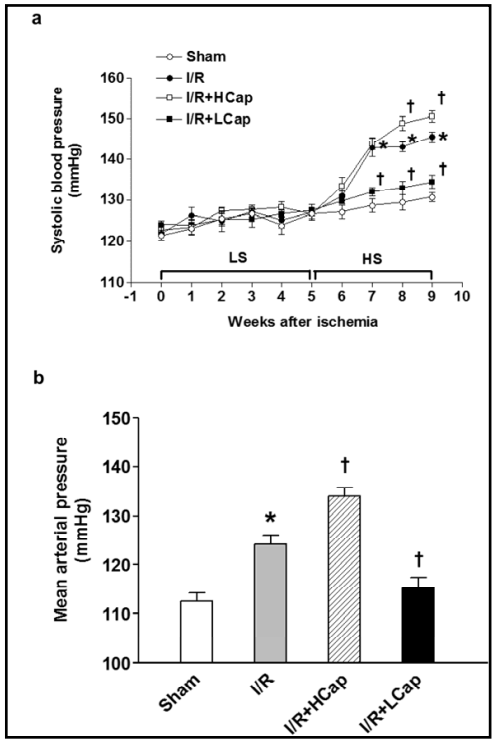


Fig. 1. Effect of renal ischemia/reperfusion (I/R) and capsaicin pretreatment on the expression of renal TRPV1. Immunohistochemistry staining (a), representative Western blot (b) and quantification (c) of TRPV1 in renal tissue from rats in sham, I/R injury, I/R with pretreatment of a low dose of capsaicin (I/R+LCap), and I/R with pretreatment of a high dose of capsaicin (I/R+HCap) groups with HS diet for 4 weeks. Values are mean±SE (n=7 to 8). *P<0.05 compared with sham group; †P<0.05 compared with I/R group. Arrows indicate TRPV1 staining fibers. Scale bars, 50μm.

Fig. 2. Effect of I/R, capsaicin pretreatment and high salt loading on blood pressure in rats. Systolic blood pressure measured once a week before and after I/R (a) and mean arterial pressure measured at 4 weeks after high salt loading (b) in rats in sham, I/R injury, I/R+LCap, and I/R+HCap groups. Values are mean±SE (n=6 to 8). *P<0.05 compared with the sham group; †P<0.05 compared with the I/R group.



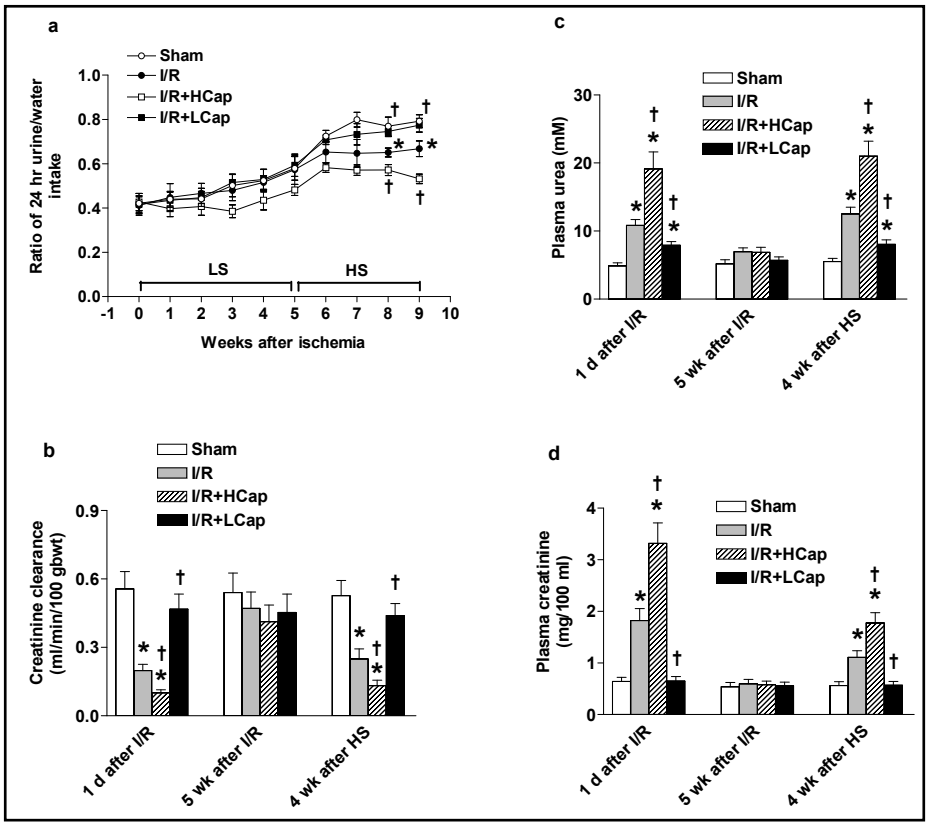


Fig. 3. Effect of I/R, capsaicin pretreatment and high salt loading on renal function. 24-hour ratio of urine/water intake measured once a week before and after I/R (a), and creatinine clearance (b) and plasma urea (c) and creatinine (d) measured at 1 day after I/R, 5-week after I/R, and 4-week after high salt loading in rats of sham, I/R injury, I/R+LCap, and I/R+HCap groups. Values are mean±SE (n=6-8). *P<0.05 compared with the sham group; †P<0.05 compared with the I/R group.

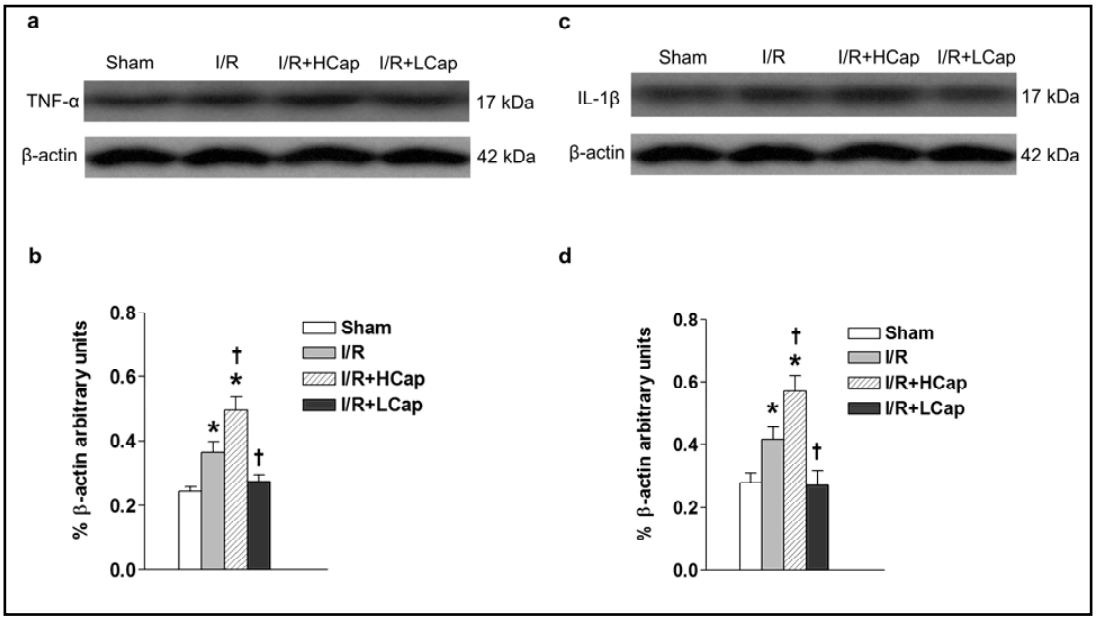


Fig. 4. Effect of I/R, capsaicin pretreatment and high salt loading on renal inflammation. Western blotting for the expression of TNF-α (a, b) and IL-1β (c, d) in the kidney from rats in sham, I/R injury, I/R+LCap, and I/R+HCap groups with HS diet for 4 weeks. Values are mean±SE (n=5). *P<0.05 compared with the sham group; †P<0.05 compared with the I/R group.

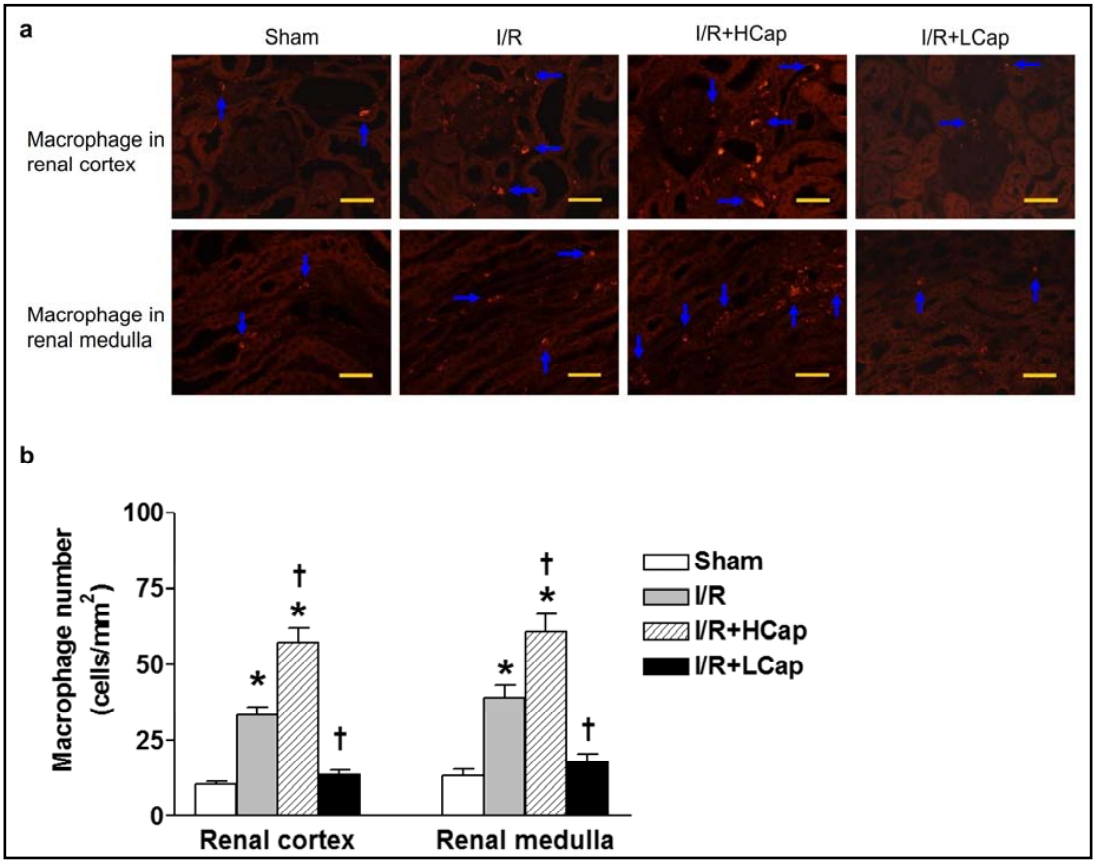
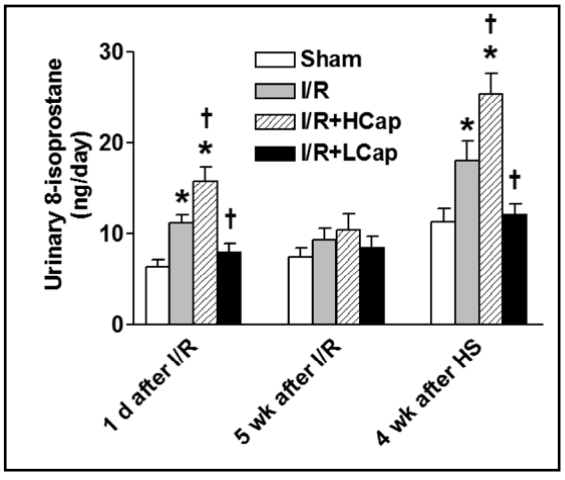


Fig. 5. Effect of I/R, capsaicin pretreatment and high salt loading on renal macrophage infiltration. Immunohistochemistry staining (a) and quantification results (b) of macrophage infiltration in the renal cortex and renal medulla of rats in sham, I/R injury, I/R+LCap, and I/R+HCap groups with HS diet for 4 weeks. Arrows indicate macrophages. Scale bars, 50μm.

Fig. 6. Effect of I/R, capsaicin pretreatment and high salt loading on oxidative stress. Urinary 8-isoprostane level measured at 1 day after I/R, 5-week after I/R, and 4-week after high salt loading in rats of sham, I/R injury, I/R+LCap, and I/R+HCap groups. Values are mean±SE (n=6). *P<0.05 compared with the sham group; †P<0.05 compared with the I/R group.



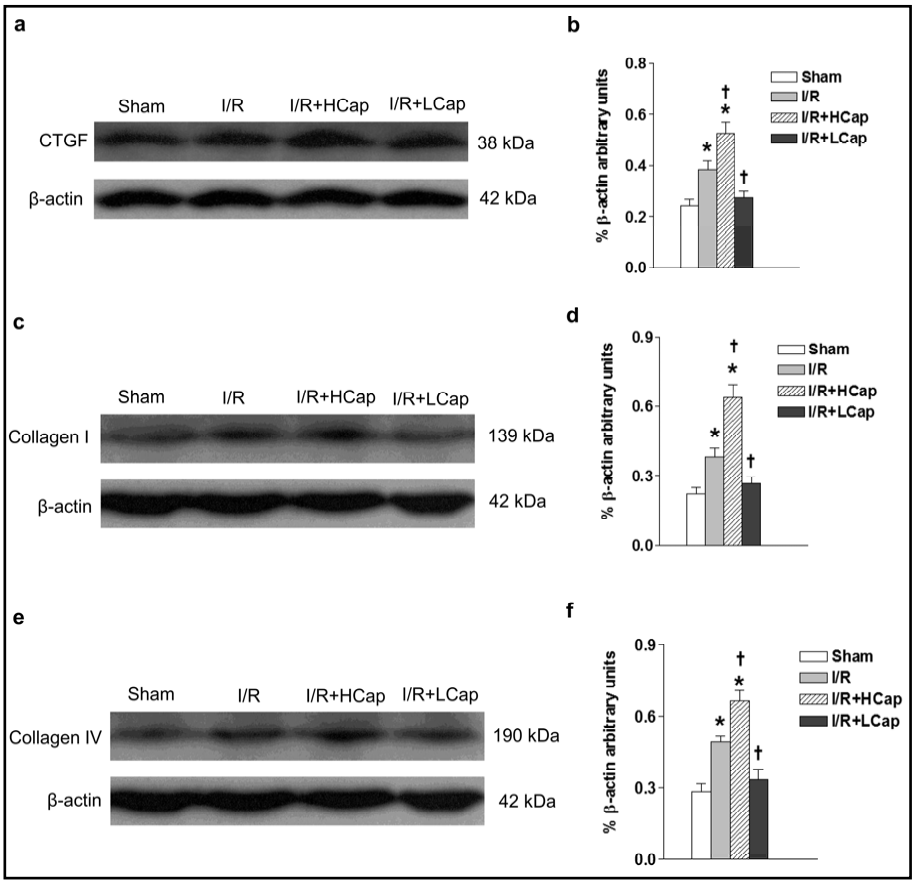


Fig. 7. Effect of I/R, capsaicin pretreatment and high salt loading on collagen expression. Western blotting of CTGF (a, b), collagen I (c, d), and collagen IV (e, f) in the kidney of rats from sham, I/R injury, I/R+LCap, and I/R+HCap groups with HS diet for 4 weeks. Values are mean±SE (n=5). *P<0.05 compared with the sham group; †P<0.05 compared with the I/R group.

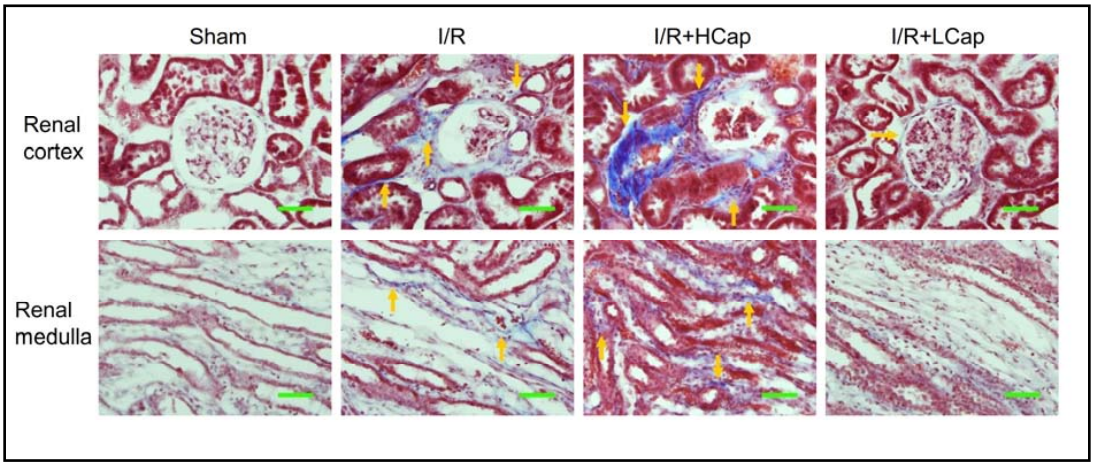


Fig. 8. Effect of I/R, capsaicin pretreatment and high salt loading on renal fibrosis. Gomori one-step trichrome staining shows collagen staining (indicated by arrows) in the renal cortex and renal medulla of rats from sham, I/R injury, I/R+LCap, and I/R+HCap groups after with HS diet for 4 weeks. Scale bars, 50μm.

Discussion

This study shows that HS intake-induced elevation of BP, renal dysfunction, inflammation, oxidative stress, and fibrosis in I/R rats were prevented or exaggerated by a low dose of capsaicin or a high dose of capsaicin, respectively.

Evidence from patients and animal models shows that acute renal failure not only has high acute fatality rate but also has long-term detrimental effects [31]. The renal function does not recover completely following I/R overtime, resulting in the development of hypertension with secondary renal disease when facing challenges such as HS loading [2-5, 31]. Thus, development of strategies to prevent or ameliorate long-term effects of acute renal injury is of clinical significance. Accumulating studies showed that TRPV1 plays a role in BP regulation and tissue protection [20, 24], which are consistent with the finding in the present study that confirms the potential protective role of TRPV1 in HS-induced hypertension and renal damage after I/R.

We examined the effects of TRPV1 with approaches from both ends, i.e., activation of TRPV1 by a low dose of capsaicin and downregulation of TRPV1 by a high dose of capsaicin. Low dose of capsaicin has been widely used to activate TRPV1 and was regarded to convey preconditioning protection to organs [25-30]. We have shown that activation of TRPV1 by its agonist, N-oleoyldopamine, exhibited protection against I/R-induced injury in heart [18]. In contrast, high dose of capsaicin has been used to eradicate the TRPV1 permanently [9-11, 17]. Indeed, TRPV1 in the kidney was markedly reduced by a high dose of capsaicin treatment in the present study, demonstrating that the strategy of TRPV1 removal was successful. The mechanism underlying the upregulation of TRPV1 by the injection of a low dose of capsaicin is still not clear. It might be due to the improvement of renal injury induced by activating TRPV1.

Without altering TRPV1 levels, the rats following I/R developed hypertension when the diets were shifted from LS to HS, which was consistent with the data reported previously [3]. However, when TRPV1 was activated prior to renal ischemia, elevation of BP in I/R rats induced by HS intake was prevented. On the contrary, when TRPV1 was downregulated prior to renal ischemia, BP was elevated even higher than rats subjected to I/R alone. These results suggest that TRPV1 conveys preconditioning protection to the kidney subjected to I/R, and prevents HS-induced hypertension with renal damage after I/R.

Next, we aimed to answer how TRPV1 conveys such preconditioning protection. Our previous studies showed that TRPV1 activation results in changes in renal function, inflammatory response, and ROS production [18-21, 23, 24]. In the present study, the levels of creatinine clearance and urinary urea were deteriorated one day after I/R but recovered to normal levels after 5-week LS treatment, which indicates that a great part of renal function recovered after initial renal failure following acute ischemia. Our data show that deterioration was prevented or exaggerated by activation or suppression of TRPV1, respectively, which is consistent to some extent with observations by other investigators [26-30]. Similar changes in creatinine clearance and urinary urea occurred again when the rats received 4 weeks of HS intake later. The changes in ratio of 24-hour urine excretion/water intake changed in the same pattern. These data support the notion that activation or suppression of TRPV1 prior to renal ischemia could prevent or exaggerate the loss of renal function during HS intake, respectively. Thus, TRPV1 causes parallel changes in renal function as that of BP in the face of HS challenge after renal I/R injury, suggesting that TRPV1-mediated kidney protection may be attributed to its anti-hypertensive effects.

At the end of 4-week of HS treatment, we found that the levels of pro-inflammatory cytokines, macrophage infiltration, and oxidative stress were augmented in I/R rats and further intensified in I/R rats with TRPV1 suppression but unchanged in I/R rats with TRPV1 activation. The augmentation of pro-inflammatory cytokines and superoxide may contribute to renal tissue damage [19, 21, 24]. Indeed, we observed that enhancement of renal fibrosis in I/R rats can be prevented by a low dose of capsaicin but intensified by a high dose of capsaicin.

Conclusion

Taken together, these results show a novel role of TRPV1 in the pre-conditioning protection of the kidney against I/R injury. After recovery from acute renal ischemia, HS-induced augmentation of inflammatory responses and oxidative stress may lead to re-injury of the kidney resulting in the loss of renal function, and as a result, development of hypertension. Activation of TRPV1 prior to I/R injury reduces inflammatory responses and oxidative stress, and therefore prevents I/R-induced renal injury, loss of renal function, and development of hypertension.

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Disclosure Statement

The authors declare they have no conflicts of interest.

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