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RESEARCH ARTICLE

TRPV1 Activation Prevents Renal Ischemia-Reperfusion Injury-Induced Increase in Salt Sensitivity by Suppressing Renal Sympathetic Nerve Activity

Shuang-Quan Yu[1,4], Shuangtao Ma[1] and Donna H. Wang[1,2,3,*]

[1]*Division of Nanomedicine and Molecular Intervention, Department of Medicine Michigan State University, East Lansing, Michigan, MI 48824, USA;* [2]*Neuroscience Program, Michigan State University, East Lansing, Michigan, MI 48824, USA;* [3]*Cell & Molecular Biology Program, Michigan State University, East Lansing, Michigan, MI 48824, USA;* [4]*Youjiang Medical University for Nationalities, Guaongxi, China*

Abstract: ***Background*:** Salt sensitivity is increased following renal Ischemia-Reperfusion (I/R) injury. We tested the hypothesis that high salt intake induced increase in Renal Sympathetic Nerve Activity (RSNA) after renal I/R can be prevented by activation of Transient Receptor Potential Vanilloid 1 (TRPV1).

***Methods*:** Rats were fed a 0.4% NaCl diet for 5 weeks after renal I/R, followed by a 4% NaCl diet for 4 more weeks in four groups: sham, I/R, I/R +High Dose Capsaicin (HDC), and I/R+Low Dose Capsaicin (LDC). The low (1mg/kg) or high (100mg/kg) dose of capsaicin was injected subcutaneously before I/R to activate or desensitize TRPV1, respectively.

***Results*:** Systolic blood pressure was gradually elevated after fed on a high-salt diet in the I/R and I/R+HDC groups but not in the I/R+LDC group, with a greater increase in the I/R+HDC group. Renal function was impaired in the I/R group and was further deteriorated in the I/R+HDC group but was unchanged in the I/R+LDC group. At the end of high salt treatment, afferent renal nerve activity in response to unilateral intra-pelvic administration of capsaicin was decreased in the I/R group and was further suppressed in the I/R+HDC group but was unchanged in the I/R+LDC group. RSNA in response to intrathecal administration of muscimol, a selective agonist of GABA-A receptors, was augmented in the I/R group and further intensified in the I/R+HDC group but was unchanged in the I/R+LDC group. Similarly, urinary norepinephrine levels were increased in the I/R group and were further elevated in the I/R+HDC group but unchanged in the I/R+LDC group.

***Conclusion*:** These data suggest that TRPV1 activation prevents renal I/R injury-induced increase in salt sensitivity by suppressing RSNA.

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1. INTRODUCTION

Acute renal failure is associated with high mortality. Although survived patients apparently recover from acute renal failure, some patients progressively develop chronic renal failure after renal Ischemia-Reperfusion (I/R) injury [1, 2]. This process was well-mimicked in animal studies [3-6], and they found that post-ischemic rats developed salt-sensitive hypertension [4]. Renal Sympathetic Nerve Activity (RSNA) plays a critical role in salt sensitivity of blood pressure [7-9]. However, RSNA was not examined in these studies. If altered, RSNA may contribute to the increased salt sensitivity in postischemic rats. An increase in RSNA not only plays a key role in the occurrence of hypertension but also contributes to the development of chronic renal failure [10, 11]. In the present study, we examined whether RSNA is increased in response to high salt intake in rats which had recovered from renal ischemic damage and if so, what kind of measures can be taken to prevent the increased sympathetic drive and hypertension.

Transient Receptor Potential Vanilloid type 1 (TRPV1) is a nonselective cation channel expressed in sensory neurons innervating peripheral organs including the kidney [12-14]. The role of TRPV1 in the development of salt-sensitive hypertension has been shown in many studies [15-23]. It has been reported that RSNA was suppressed when TRPV1-mediated Afferent Renal Nerve Activity (ARNA) was increased [24-28], suggesting that intact expression and function of

*Address correspondence to this author at the Division of Nanomedicine and Molecular Intervention, Department of Medicine, Michigan State University, 788 Service Road, East Lansing, MI 48824, United States;
E-mail: wangdo@msu.edu

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TRPV1 channels in renal sensory nerves are necessary and may contribute to the suppression of enhanced sympathetic drive and prevention of salt-induced hypertension in rats which have recovered from renal ischemic injury. Our recent study demonstrated that activation of TRPV1 plays an anti-inflammatory and anti-oxidative role in preventing renal tissue damage and salt-induced hypertension after renal I/R injury [29], while the present study focused on the role of renal sympathetic nerves.

The present study was conducted to address three questions: 1) whether renal TRPV1 expression and TRPV1-mediated ARNA were decreased after renal I/R; 2) whether RSNA is enhanced by feeding with high-salt diet in rats after recovered from renal ischemic injury; and 3) whether protection of renal TRPV1-positive afferent renal nerves leads to the suppression of heightened RSNA and results in the prevention of high salt-induced renal injury and hypertension in rats recovered from renal ischemic damage. In the present study, TRPV1 activation prior to renal I/R was achieved by the application of low-dose capsaicin, a TRPV1 agonist, while TRPV1 suppression before renal I/R was achieved by the application of high-dose capsaicin. Similar strategies of using low doses of TRPV1 agonists and high doses of TRPV1 agonists to activate and down-regulate TRPV1, respectively, have been used in our previous studies [15-23, 30] and by other groups [31-36].

2. MATERIALS AND METHODS

2.1. Animals

Male Wistar rats (175-200 g, Charles River Laboratory; Wilmington, Massachusetts, USA) were housed on a 12-hour light and 12-hour darkness cycle with free access to food and water. Rats were fed a low-sodium diet (0.4% NaCl, Diets, Bethlehem, Pennsylvania, USA) from one week before the surgery of renal I/R injury to 5 weeks after the surgery, followed by a high-sodium diet (4% NaCl, Diets, Bethlehem, Pennsylvania, USA) for 4 weeks. The application of all drugs and procedures on the rats in the study was approved in advance by the Institutional Animals Care and Use Committee of Michigan State University.

2.2. Renal Ischemia/Reperfusion (I/R) Injury

The bilateral renal arteries of ketamine/xylazine anesthetized rats were clamped for 40 minutes. Thereafter the clamping was released, and the incision was closed. The rats were injected with penicillin and streptomycin to prevent infection.

2.3. Treatments with Capsaicin

Rats were administered (s.c.) with a Low Dose of Capsaicin (LDC, 1 mg/kg) or a High Dose Capsaicin (HDC, 100 mg/kg) 3 hours before renal ischemia. There were 4 groups in the study: sham, I/R, I/R+HDC, I/R+LDC.

2.4. Measurement of Blood Pressure, Water Intake and Urine Excretion

Systolic blood pressure of conscious rats was measured using the tail cuff method (Hatteras Instruments SC1000 Blood Pressure Analysis System, Cary, North Carolina, USA). Mean arterial pressure of fully awake rats was measured *via* the catheter implanted into the right carotid artery of ketamine/xylazine-anesthetized rats at 3 hours after the implantation. The 24-hour water intake and urine excretion were measured using metabolic cages.

2.5. Assays of Urea and Creatinine

The concentrations of creatinine in the plasma and urine were assayed using the kit (K625-100, BioVision, California, USA). The concentration of urea in the plasma was determined using the kit (K375-100, BioVision, California, USA).

2.6. Western Blotting

The kidney tissue was homogenized in 2 mL of 10 mmol/L Tris buffer (pH 7.6) containing 0.5 mmol/L $MgCl_2$, 50 mmol/L NaCl, and protease inhibitors. After spinning the kidney homogenates at 500 g for 5 min at 4°C, the supernatant was added with 10 μL of 0.5 mol/L EDTA and 100 μL of 10% Triton X-100, incubated on ice for 45 min and was spun at 22,000 g for 30 min at 4°C. The supernatant was electrophoresed at the protein concentration of 30 mg/mL on 7.5% SDS-PAGE gel and transferred to PVDF membranes (162-0180, Bio-Rad Laboratories, Hercules, California, USA). The TRPV1 antibody was from Neuromics (1:1000, RA10110, Neuromics, Edina, Minnesota, USA). The secondary antibody HRP-donkey anti-rabbit IgG was from Jackson (1:10,000, 711-035-152, Jackson ImmunoResearch Laboratories, West Grove, Pennsylvania, USA). The immunoreactive bands were visualized by ECL reagents (RPN 2106, Amersham, GE Healthcare, Piscataway, New Jersey, USA) and the band intensity was quantified by using ImageJ (NIH, Bethesda, Maryland, USA). β-actin (1:2,000, sc-69879, Santa Cruz Biotechnology, Santa Cruz, California, USA) was used to normalize the protein loading.

2.7. Recording of ARNA and RSNA

Recording of the activity of the renal nerve was performed as described previously [24-28]. Briefly, the rat was anesthetized with ketamine/xylazine. The renal nerve branch was exposed and sectioned. Its proximal and distal part was placed on stainless steel electrodes for the recording of RSNA and ARNA, respectively. The nerve was fixed to the electrodes by applying silicone elastomer (Kwik-Cast™, World Precision Instruments, Sarasota, Florida. USA). The signals were amplified and filtered by a pre-amplifier (Model P511, Grass Technologies, West Warwick, Rhode Island, USA) and recorded by a recorder (Gould Instruments, Cleveland, Ohio, USA). Renal nerve activity was integrated over l-s intervals (P3 Plus software) and was expressed in percentage change compared to its basal value. The background activity (when the renal nerve bundle was crushed) was subtracted from all values of renal nerve activity. For recording of ARNA, the sensory nerve was activated by intra-pelvic administration of capsaicin (4 μM, 20 μL/min for 3 min) *via* a catheter (PE50) implanted into the pelvis; for recording of RSNA, the sympathetic nerve was suppressed by intrathecal administration of muscimol (3 nmol/kg) *via* a catheter

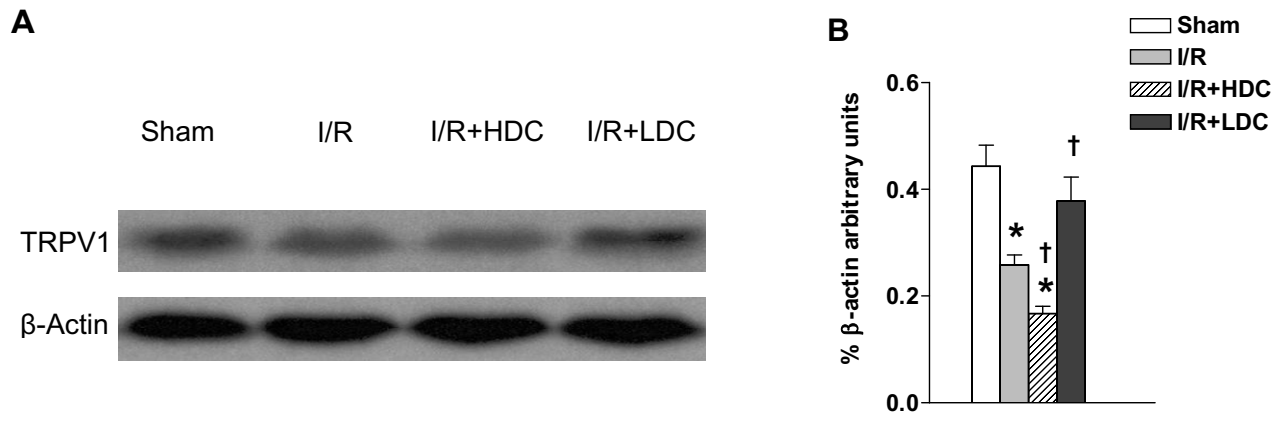

Fig. (1). Representative Western blots showing TRPV1 expression in the kidney 4 weeks after high-salt feeding in rats with renal ischemia-reperfusion (I/R) injury and capsaicin pre-treatment (**A**). (**B**) Quantification results (% β-actin arbitrary units). Values are mean ± SE (n = 5). *p<0.05 compared with the sham group; †p<0.05 compared with the I/R group.

(PE10) implanted into the subarachnoid space 3 days in advance. The methods of catheter implantation into the pelvis and the subarachnoid space were described previously [12, 13, 33].

2.8. Urinary Norepinephrine (NE) Assay

Five milliliters of urine was stored at -80°C with the addition of 50 μL of 6 N HCl for preservation. Urinary NE concentrations were measured by an EIA kit (40-734-350002, GenWay Biotech, San Diego, California, USA). For comparison of NE levels among groups, the values were standardized as an excretion rate per day (ng/day).

2.9. Drugs

Capsaicin (M2028, Sigma-Aldrich, St. Louis, Missouri, USA) was dissolved in saline including 0.1% ethanol. Muscimol (M1523, Sigma-Aldrich, St. Louis, Missouri, USA) was dissolved in saline.

2.10. Statistical Analysis

All data were expressed as mean ± SE. Differences among groups were compared by one-way ANOVA followed by Tukey-Kramer multiple comparison test. Differences between two groups were analyzed by using the unpaired Student's *t*-test and were considered statistically significant at $p<0.05$.

3. RESULTS

3.1. Low-dose Capsaicin Prevented I/R-induced Down-regulation of Renal TRPV1

Western blot analysis revealed that TRPV1 protein expression in the kidney was decreased in I/R rats, and was further reduced in I/R rats treated with High-Dose Capsaicin (HDC), but unchanged in I/R rats treated with Low-Dose Capsaicin (LDC) compared to that of sham rats (sham: 0.44 ± 0.04 *vs*. I/R: 0.26 ± 0.02 *vs*. I/R+HDC: 0.17 ± 0.01 *vs*. I/R+LDC: 0.38 ± 0.05, $p<0.05$, Fig. **1**).

3.2. Low-dose Capsaicin Prevented High-salt Diet-induced Hypertension in I/R Rats

To explore whether there was a correlation between changes in TRPV1 expression and blood pressure, we measured systolic blood pressure once a week during the whole experiment period and MAP at the end of 4 weeks of high salt loading. Compared with I/R alone, down-regulation of renal TRPV1 induced by high-dose capsaicin treatment was parallel with higher blood pressure. In contrast, activation of TRPV1 induced by low-dose capsaicin prevented high-salt diet-induced elevation of systolic blood pressure and mean arterial pressure (sham: 113 ± 3 *vs*. I/R: 124±2 *vs*. I/R+HDC: 135 ± 1 *vs*. I/R+LDC: 115 ± 1 mmHg, $p<0.05$, Fig. **2**).

3.3. Low-dose Capsaicin Ameliorated Renal Function in I/R Rats

Compared with sham rats, renal function was impaired in I/R rats after high-salt diet treatment. Down-regulation of TRPV1 by high-dose capsaicin further deteriorated the renal function, whereas activation of TRPV1 by low-dose capsaicin ameliorated renal function (ratio of 24-hour urine excretion/water intake, sham: 0.77 ± 0.02, I/R: 0.68 ± 0.03, I/R+HDC: 0.56 ± 0.03, I/R+LDC: 0.77 ± 0.03, $p<0.05$; creatinine clearance, sham: 0.53 ± 0.06, I/R: 0.28 ± 0.02, I/R+HDC: 0.18 ± 0.01, I/R+LDC: 0.47 ± 0.05 mL/min/100gbwt, $p<0.05$; plasma urea, sham: 7.5 ± 1, I/R: 14 ± 1, I/R+HDC: 23 ± 4, I/R+LDC: 8 ± 1 mM, $p<0.05$, Fig. **3**).

3.4. Low-dose Capsaicin Prevented Increase in RSNA Induced by I/R

To answer the question of whether the changes in renal function are due to the changes in RSNA, we examined RSNA and levels of urine NE. RSNA was judged by watching the RSNA response to the suppression of the spinal GABA-A receptor by intrathecal injection of muscimol (3 nmol/kg), a selective activator of GABA-A receptors. Intrathecal injection of muscimol caused a decrease in RSNA in sham rats. The decrease in RSNA was greater in I/R rats

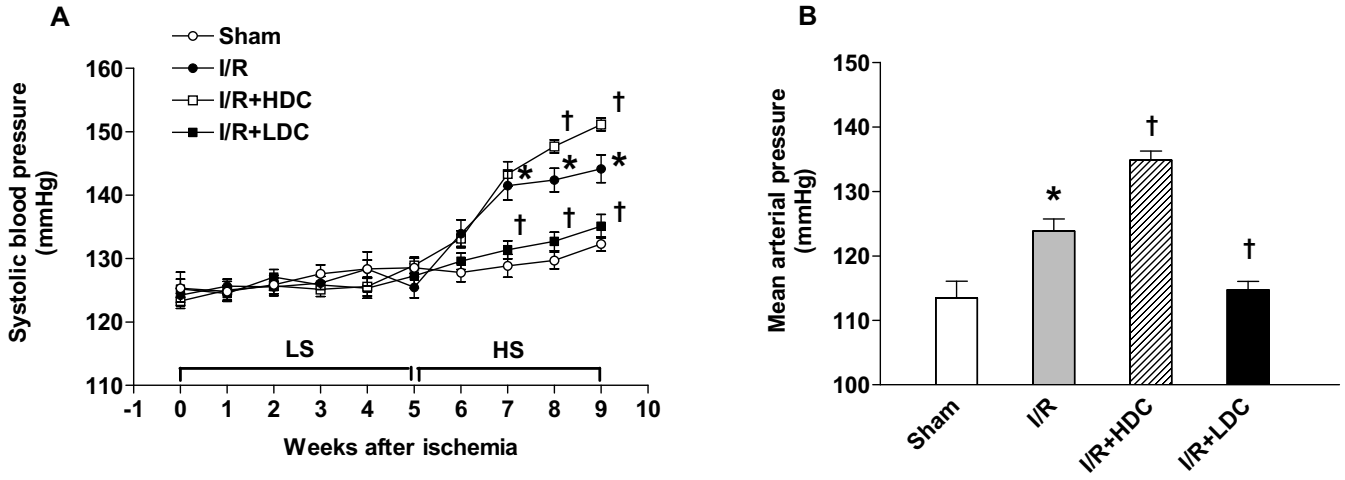

Fig. (2). Effects of ischemia/reperfusion (I/R), capsaicin pre-treatment and high salt feeding on blood pressure in rats. (**A**) Systolic blood pressure was measured once a week before and after I/R. (**B**) Mean arterial pressure (MAP) was measured at 9 weeks after I/R or at 4 weeks after high salt loading. Values are mean ± SE (n = 5-7). *p<0.05 compared with the sham group; †p<0.05 compared with the I/R group.

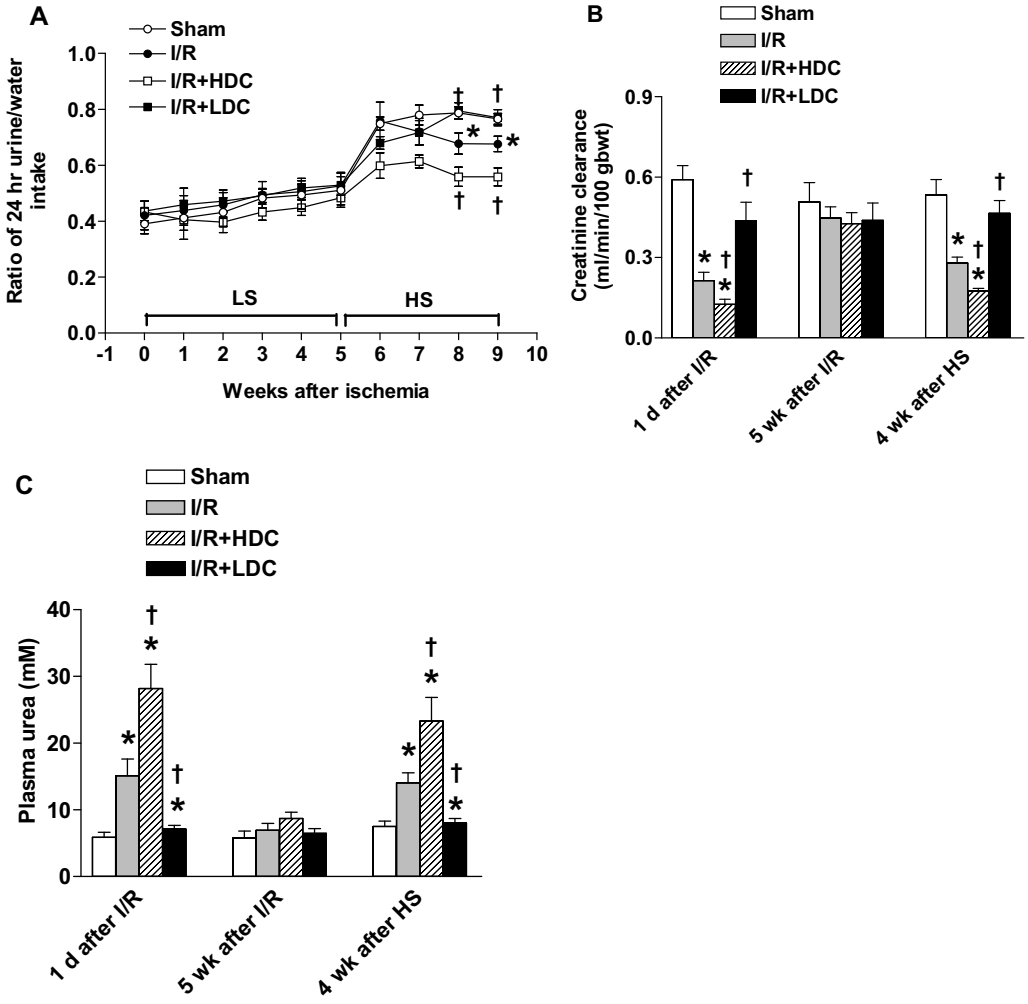

Fig. (3). Effects of I/R, capsaicin pretreatment and high-salt feeding on the 24-hour ratio of urine/water intake (**A**), creatinine clearance (**B**) and plasma urea (**C**) in rats. Values are mean ± SE (n = 6-8). *p<0.05 compared with the sham group; †p<0.05 compared with the I/R group.

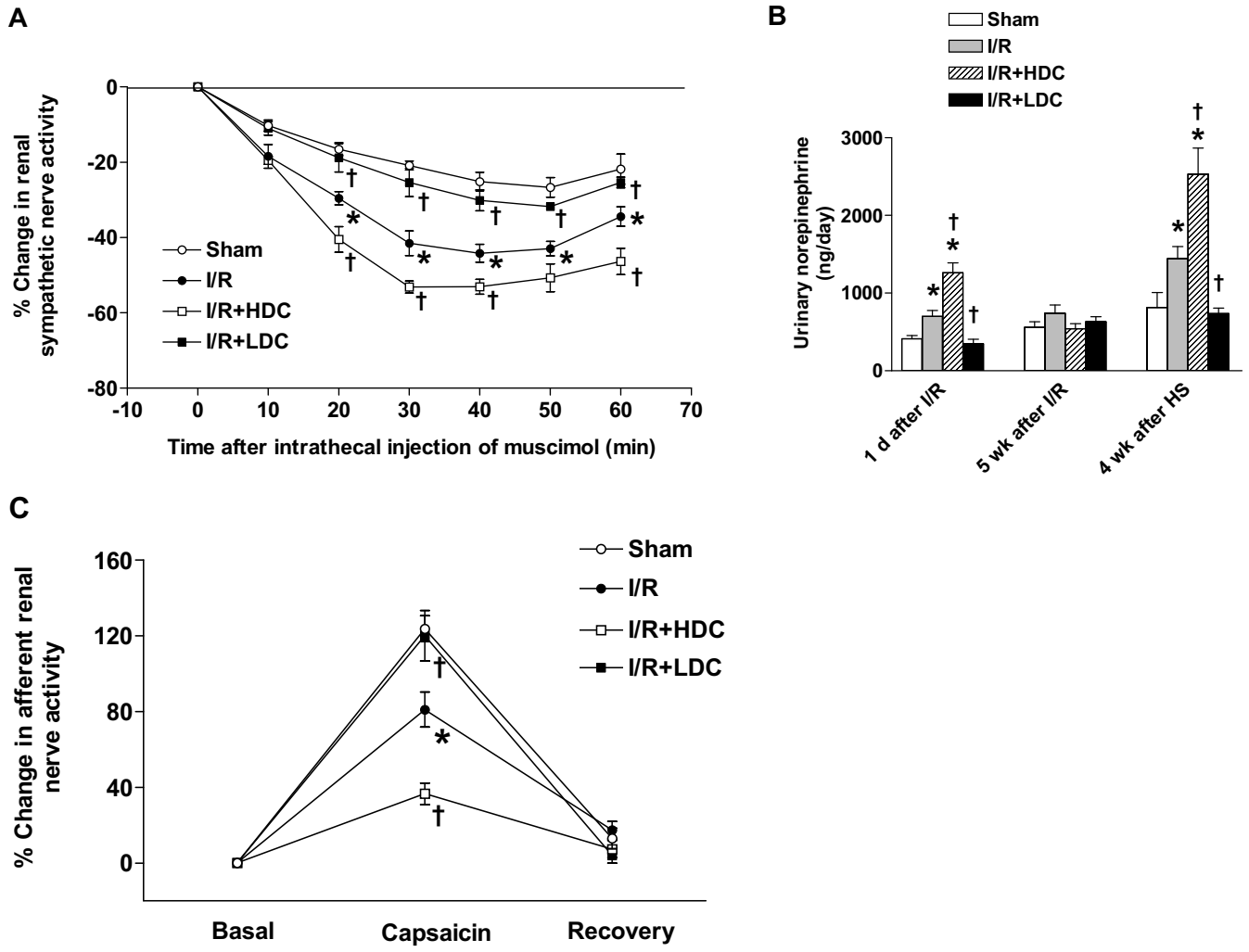

Fig. (4). Sympathetic and afferent renal nerve activity. (**A**) Renal sympathetic nerve activity after intrathecal injection of muscimol at the end of the experiments. (**B**) Urinary norepinephrine levels before and 4 weeks after high salt loading in rats with I/R and capsaicin pretreatment. (**C**) Afferent renal nerve activity after intra-pelvis injection of capsaicin. Values are mean ± SE (n = 5-6). *p<0.05 compared with the sham group; †p<0.05 compared with the I/R group.

and much greater in I/R+HD rats but almost unchanged in I/R+LDC rats compared to sham rats (sham: -21 ± 1 *vs*. I/R: -42 ± 3 vs. I/R+HDC: -53 ± 2 *vs*. I/R+LDC: -25 ± 4%, p<0.05, Fig. **4A**). Consistently, the urine NE levels were increased in I/R and further elevated in I/R+HDC but unchanged in I/R+LDC (sham: 785 ± 98 *vs*. I/R: 1311 ± 98 *vs*. I/R+HDC: 1731 ± 140 *vs*. I/R+LDC: 1018 ± 85 ng/day, p<0.05, Fig. **4B**).

3.5. Low-dose Capsaicin Prevented the Decrease in ARNA Induced by I/R

It is known that a decrease in ARNA leads to an increase in RSNA. Changes in renal TRPV1 by the administration of a high or low dose of capsaicin might produce corresponding changes in ARNA. In the present study, we measured changes in ARNA after stimulating the TRPV1-positive afferent renal nerves using intra-pelvic perfusion of capsaicin (4 μM, 20 μL/min for 3 min). ARNA was decreased in I/R and further suppressed in I/R+HDC but was unchanged in I/R+LDC (sham: 123 ± 7 *vs*. I/R: 81 ± 9 *vs*. I/R+HDC: 37 ± 6 *vs*. I/R+LDC: 120 ± 13%, p<0.05, Fig. **4C**).

4. DISCUSSION

Our data show that low-dose capsaicin treatment prior to renal ischemia prevented decreases in TRPV1 expression and ARNA, abolished augmentation in RSNA and urine NE levels and prevented renal dysfunction and hypertension in I/R rats fed a high-salt diet. In contrast, high-dose capsaicin pre-treatment led to exaggerated impairment in the expression and function of TRPV1-positive renal sensory nerves accompanied by further heightened RSNA, renal dysfunction and hypertension.

Renal TRPV1 levels in I/R rats measured 4 weeks after high-salt treatment were decreased compared to sham rats. It has been shown that renal TRPV1 levels were increased when a high-salt diet was given, thus it is unlikely that high-salt intake alone is the cause for renal TRPV1 downregulation [37-39]. It has also been shown that ARNA was decreased 24 hours after renal I/R, indicating that renal sensory nerves including TRPV1-positive nerve fibers were impaired at the early stage after I/R [40, 41]. Our data show that renal

TRPV1 levels as well as TRPV1-mediated ARNA were still low 9 weeks after I/R, suggesting that TRPV1-positive fibers were not regenerated over the period after being impaired by I/R. The lasting degenerative effects on TRPV1-positive sensory nerves by I/R appear as effective as that induced by pharmacological interventions [15-23, 35].

Although renal functional parameters including the ratio of urine excretion to water intake, creatinine clearance, and plasma urea were restored to within the normal limits 5 weeks after I/R, renal injury may not fully recover from renal I/R injury over the period. It has been reported that there were renal concentration defect and a reduction in peritubular capillaries in the recovered kidneys despite apparently normal renal tubular morphology and creatinine levels after I/R [3-6]. It appears that incomplete renal tissue recovery from I/R injury including renal TRPV1 downregulation was insufficient in inducing hypertension or in enhancing RSNA as seen for the first 5-week period before a high-salt diet was given. In contrast, RSNA, urine NE levels, and blood pressure were elevated when a high-salt diet was given to rats after I/R with decreased renal TRPV1 levels and suppressed TRPV1-mediated ARNA. These data suggest that impaired TRPV1 alone is insufficient to induce renal disorders but can contribute to heightened RSNA, renal injury and hypertension when combined with high-salt intake after I/R. These results are consistent with previous findings showing that degeneration of TRPV1-positive sensory nerves exacerbates rat hypertension when fed a high but not low sodium diet [15-23].

The heightened renal sympathetic drive may contribute to the development of hypertension by stimulating renin release and increasing vasoconstriction and sodium and water retention [15-17]. It has been shown that activation of TRPV1-positive renal sensory nerves suppressed RSNA [24-28]. Enhanced RSNA in the present study could be the result of attenuated inhibitory effects of TRPV1-positive renal afferent nerves on RSNA due to decreased TRPV1 levels after I/R. This notion is supported by the data from high or low dose capsaicin pre-treatment. Compared with I/R rats, high-dose capsaicin pre-treatment caused more profound decreases in renal TRPV1 levels as well as TRPV1-mediated ARNA, which is consistent with previous findings [15-23, 31, 35, 36]. The mechanism underlying degeneration or impairment of TRPV1-positive sensory nerves might be cytotoxic effects due to sustained and large amount of calcium influx into neurons when TRPV1 channels are maximally opened by high-dose capsaicin [42]. When renal TRPV1 levels and TRPV1-mediated ARNA were further deceased by high-dose capsaicin, elevated RSNA was observed in high-salt diet-fed I/R rats.

In contrast, renal TRPV1 levels and TRPV1-mediated ARNA in rats pretreated with a low dose of capsaicin were not decreased after I/R, suggesting that low-dose capsaicin given prior to renal ischemia protects TRPV1-positive renal sensory nerves from I/R injury. As a result, heightened RSNA was prevented due to normalization of expression and function of TRPV1-postive renal sensory nerves induced by low-dose capsaicin prior to I/R. It has been shown that pre-treatment with a low dose of TRPV1 agonists protects against I/R-induced renal injury, and the protective mechanism might be that TRPV1 activation-induced CGRP release in the kidney promotes endothelial prostaglandin I2 production, inhibits production of pro-inflammatory cytokines including tumor necrosis factor-α and interleukin (IL)-6, attenuates neutrophil infiltration, superoxide production, and nitric oxide production, and enhances expression of anti-inflammatory cytokine including IL-10 [31-36]. Indeed, prevention of TRPV1 downregulation by low-dose capsaicin pre-treatment led to normalization of renal function and blood pressure in I/R rats fed a high-salt diet. These data demonstrate that intact expression and function of TRPV1 play a compensatory role against RSNA enhancement, renal dysfunction, and hypertension in I/R rats fed a high-salt diet.

While low-dose capsaicin may protect against renal ischemic injury *via* CGRP release from TRPV1-positive renal sensory nerves, high-dose capsaicin was also likely to induce acute transient CGRP release before degeneration of TRPV1-positive renal sensory nerves induced by capsaicin or renal ischemic injury. However, our data show that high-dose capsaicin was incapable of protecting against renal injury; rather it exaggerated renal injury induced by I/R followed by high-salt intake. We would like to point out that we used 4% high salt diet to accelerate the effects in rats, which may not represent a typical diet in humans. In general, these data indicate that, in the absence of intact TRPV1-positive renal sensory nerves due to high-dose capsaicin pre-treatment, counter-regulatory effects against renal ischemia and salt-induced injury are lost, leading to aggravated renal impairment and hypertension,

CONCLUSION

In conclusion, our data indicate that activation of TRPV1 prior to renal I/R injury protects TRPV1-positive renal sensory nerves and prevents salt-induced RSNA enhancement and salt-sensitive hypertension after I/R.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All experimental procedures were approved by the Animal Care and Use Committee of Michigan State University, USA.

HUMAN AND ANIMAL RIGHTS

No humans were used in the study. The research was conducted in accordance with the ethical standards. All care and use of laboratory animals were followed and conform to NIH guidelines.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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