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Segmental Regulation of Sodium and Water Excretion by TRPV1 Activation in the Kidney

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Abstract

Our previous studies show that activation of the transient receptor potential vanilloid type 1 (TRPV1) channels by a selective agonist, capsaicin (CAP), given unilaterally into the renal pelvis leads to increases in urine flow rate (Uflow) and urinary sodium excretion (UNa) bilaterally, albeit the mechanisms underlying enhanced renal excretory function are unknown. The present study was designed to determine the contribution of each of the renal segments to enhanced renal excretory function when TRPV1 expressed in sensory nerve fibers innervating the renal pelvis is activated. To accomplish the goal, LiCl was given intravenously to male Wistar rats while the left renal pelvis (LRP) was perfused with vehicle or CAP with or without a selective TRPV1 antagonist, capsazepine (CAPZ). Uflow and clearance of creatinine, lithium, sodium and water, either as filtered or fractionally, were determined in both kidneys. LRP perfusion of CAP at 2.4 nmol increased Uflow ($\mu\text{l}\cdot\text{min}^{-1}\text{g}^{-1}$) (ipsilaterally from 6.6 ± 0.6 to 14.6 ± 2.2 and contralaterally from 7.4 ± 0.7 to 13.9 ± 1.8 , $p < 0.05$) and UNa ($\mu\text{mol}\cdot\text{min}^{-1}\text{g}^{-1}$) (ipsilaterally from 0.6 ± 0.2 to 1.8 ± 0.3 and contralaterally from 0.7 ± 0.2 to 1.9 ± 0.4 , $p < 0.05$). Ipsilateral blockade of the TRPV1 with CAPZ at 24 nmol prevented CAP-induced increases in Uflow and UNa bilaterally. Creatinine, lithium, sodium and free water clearance ($\text{ml}\cdot\text{min}^{-1}$) were increased in CAP (1.47 ± 0.27 , 0.44 ± 0.05 , 0.026 ± 0.004 , 0.41 ± 0.05 , respectively) compared to vehicle (0.72 ± 0.12 , 0.25 ± 0.05 , 0.010 ± 0.001 , 0.24 ± 0.05), CAPZ + CAP (0.83 ± 0.13 , 0.24 ± 0.03 , 0.014 ± 0.002 , 0.23 ± 0.03) and CAPZ (0.88 ± 0.05 , 0.21 ± 0.01 , 0.010 ± 0.001 , 0.20 ± 0.01) groups ($p \leq 0.01$). Filtered sodium load, distal delivery of sodium and distal sodium reabsorption ($\mu\text{Eq}\cdot\text{min}^{-1}$) were also increased in CAP (202.2 ± 33.3 , 61.3 ± 7.4 , 57.6 ± 7.4 , respectively) compared to vehicle (97.7 ± 16.6 , 33.6 ± 5.8 , 32.2 ± 5.9), CAPZ + CAP (110.5 ± 16.3 , 32.5 ± 4.5 , 30.7 ± 4.3) and CAPZ (118.0 ± 4.5 , 27.9 ± 1.2 , 26.8 ± 1.2) groups ($p \leq 0.01$). In contrast, fractional lithium and sodium excretion, absolute proximal reabsorption, fractional proximal reabsorption, fractional distal sodium and water reabsorption were not different among groups.

Therefore, activation of the TRPV1 expressed in primary afferent nerves innervating the renal pelvis leads to diuresis and natriuresis in both kidneys. The TRPV1-induced sodium and water excretion appears to be mediated by increases in glomerular filtration rate and distal tubular delivery of sodium but not by suppression of renal proximal and distal tubular reabsorption, suggesting a key role of segmental regulation of renal function by TRPV1-positive primary sensory nerves in the maintenance of sodium and water homeostasis.

Keywords

TRPV1; glomerular filtration rate; tubular reabsorption; natriuresis; sensory nerves; renal pelvis

INTRODUCTION

Sodium and water homeostasis is maintained under the physiological condition and impaired in disease states such as hypertension and heart failure. One of the therapeutic strategies for these diseases is to restore the impaired sodium and water homeostasis. Given that the kidney is a key organ in the regulation of water and sodium excretion, it has been a target for defining the pathogenesis of a number of cardiovascular diseases as well as for drug development.

It has been shown that the renal pelvis is heavily innervated with thin neurofilament- and neuron-specific enolase (NSE)-immunoreactive nerve fibers.¹ These nerve fibers form a two-dimensional network with the transverse connections, which mainly distribute within the submucosal layer of the renal pelvic wall. A subset of these nerve fibers makes up sensory nerves that contain the transient receptor potential vanilloid type 1 (TRPV1) channels. These TRPV1-positive sensory nerves have their free terminal endings distributed in the mucous layer and close to the epithelial cells of the renal pelvis.² Given that the TRPV1 can be activated by polymodal stimuli including heat, low pH, lipid metabolites, and vanilloid compounds, the renal pelvis richly innervated by TRPV1-positive sensory nerves may act as a sensory organ sensing mechano- and chemo-stimulations imposed onto the renal pelvis, leading to modulation of renal excretory function and diuresis and natriuresis responses.^{3,4}

Our previous study showed that activation of the TRPV1 expressed in sensory nerve endings innervating the unilateral renal pelvis by its selective agonist, capsaicin (CAP), induces bilateral diuresis and natriuresis.⁵ TRPV1-mediated bilateral diuresis and natriuresis were abolished by blockade of the TRPV1 with its selective receptor antagonist, capsazepine (CAPZ), given ipsilaterally into the renal pelvis or by ipsilateral renal denervation.⁵ These results indicate that renal afferent as well as efferent nerves play a key role in the regulation of sodium and water excretion via an inhibitory renorenal reflex mechanism.⁴

Renal sympathetic innervation controls at least three neuroeffectors in the kidney, i.e., blood vessels, renal tubules, and juxtaglomerular granular cells.⁶ Previous studies showed that unilateral renal denervation leads to a higher rate of sodium excretion from the denervated kidney than from the contralateral innervated kidney.⁷ Moreover, it has been shown that decreases in renal sympathetic nerve activity (RSNA) lead to diuresis and natriuresis in the presence^{4,8} or absence of changes in glomerular filtration rate (GFR) and renal blood flow (RBF),⁹ whereas increases in RSNA lead to an anti-natriuresis in the absence of significant change in GFR.¹⁰

Although our previous data show that activation of the TRPV1 leads to diuresis and natriuresis, the mechanisms underlying enhanced renal excretory function are unknown. The present study was designed to determine the contribution of each of the renal segments to enhanced renal excretory function when TRPV1 expressed in sensory nerve fibers innervating the renal pelvis is activated. The potential mechanisms and implications of the study are discussed.

METHODS

Animal groups and protocols

All experiments were approved by the Institutional Animal Care and Use Committee. Male Wistar rats weighing 294 ± 5 g (Charles River Laboratories; Wilmington, MA) were housed in the animal facility for 1 wk before experiments and randomly assigned to four groups for the following treatments: (1) control (vehicle), 0.18 % of ethanol and Tween 80 in saline given via left renal pelvis perfusion (LRPP); (2) capsaicin (CAP) given at 2.4 nmol (12.2ng/ μ l or 0.04 nmol/ μ l) via LRPP; (3) capsazepine (CAPZ, a selective TRPV1 antagonist) given at 24 nmol (150.8ng/ μ l or 0.4 nmol/ μ l) via LRPP before CAP perfusion (CAPZ+CAP); (4) CAPZ

given at 24 nmol via LRPP. It has been shown that 2.4 nmol CAP given via LRPP but not intravenously leads to bilateral diuresis and natriuresis, which can be prevented by CAPZ given at 24 nmol ipsilaterally.⁵

Experimental procedure

All rats were intraperitoneally administered pentobarbital sodium, 50 mg·kg⁻¹, and maintained with an intravenous infusion of 10 mg·kg⁻¹·hr⁻¹ at 50 μl·min⁻¹. The potent pentobarbital sodium was selected to make sure that it was still effective 1.5 h after the end of the surgery so that renal pelvis perfusion of CAP, an irritant and pain causing compound, could be conducted. Catheters were placed in the right jugular vein (RJV) for administration of drugs, and in the right carotid artery for monitoring mean arterial pressure (MAP) with a Statham 231D pressure transducer coupled to a Gould 2400s recorder (Gould Instrument Systems, Valley View, Ohio, USA). Polyethylene (PE-50) catheters were inserted into both ureters via midline incision. A fine outlet tube of MD-2000 (ID 0.18/OD 0.22 mm, BASi, West Lafayette, IN 47906, USA) was placed inside the PE-50 catheter with its tip in the renal pelvis during a 3-min perfusion of drug at rate of 20 μl·min⁻¹ that did not change renal pelvis pressure.⁸

The experiment started approximately 1.5 h after the end of the surgery. Protocols for LRPP contained two 3- minute periods: CAPZ was perfused in the first 3 – minute period, CAP in the second 3 – minute period. In the case when CAP or CAPZ was perfused alone, the other period was perfused with vehicle. In controls, vehicle was perfused in both periods without perfusion of CAP or CAPZ. Urine samples were collected for 30 minutes before and after experimental protocols for analysis of urine sodium, lithium, and creatinine. At the end of the experiment, blood samples were collected for analysis of hematocrit (Hct), total protein (TP), and plasma concentrations of sodium, lithium, and creatinine. For intravenous administration of Li⁺, a priming dose of 0.3 μmol LiCl·g⁻¹ (per gram of body weight) was given for 30 minutes and a dose of 0.04 μmol LiCl·g⁻¹·hr⁻¹ was used for continuous intravenous infusion. These doses of IV administration of Li⁺ produced plasma Li⁺ concentrations at a range of 0.15–0.30 mmol·L⁻¹ at the time of the experiment.¹¹

Creatinine assay

Plasma and urine creatinine concentrations were determined with the use of an improved Jaffe creatinine assay kit (BioAssay Systems, CA). Briefly, the samples and creatinine standards were added to a plate and incubated with working reagent supplied by the manufacturer for 20 min. The plate was read at 490 nm by an absorbance microplate reader (μ Quant, Bio-IEK Instrument, Inc.).

Analysis of lithium

Plasma and urine lithium concentrations were determined with the use of a flame photometer (Model IL 943, Instrumentation Laboratory). Briefly, plasma and urine were deproteinized by addition of equal amounts of 0.3 N ZnSO₄ and 0.3 N Ba(OH)₂. After vortexing thoroughly, samples were centrifuged at 3,000 × g for 15 min at 4°C. The supernatant was filtered with a large filter tube (Millipore, UFC40HV00; 0.45 μm, Bedford, MA) followed by centrifugation at 3,000 × g for 15 min at 4°C. The filtered supernatant was dried with a vacuum centrifuge at 4°C. The dried pellet was reconstituted in distilled water. After mixing thoroughly, samples were centrifuged at 15,300 × g for 10 min at 4°C. The clear supernatant was used for lithium measurement, and the concentration of lithium was determined with a standard curve.

Analysis of sodium, hematocrit, and total protein

Plasma and urine sodium concentrations were determined with the use of a flame photometer (Model IL 943, Instrumentation Laboratory). Plasma was deproteinized before measurement

of sodium. Hematocrit was determined by collecting blood in EDTA tubes subjecting subsequently to centrifugation at $1,800 \times g$ for 30 min. Total protein of plasma was determined by the use of BCA protein assay (Pierce, Rockford, IL). Briefly, the samples and protein standards were added to a plate and incubated with working reagent supplied by the manufacturer for 30 min. The plate was read at 562 nm by an absorbance microplate reader (μ Quant, Bio-IEK Instrument, Inc.).

Calculation

The clearances of creatinine (C_{Cr} , used as a measure of glomerular filtration rate, GFR), lithium (C_{Li}), and sodium (C_{Na}) were calculated with the standard expression:

$$C_x = (U_x/P_x)V,$$

where U_x and P_x are urine and plasma concentrations, respectively, of the substance x , and V is the urine flow rate. Fractional excretion of lithium (FE_{Li}) and sodium (FE_{Na}) were calculated as C_{Li}/GFR and C_{Na}/GFR . The following parameters were derived according to Boer and colleagues:¹² Filtered sodium load (FL_{Na}) was calculated as $P_{Na} \times C_{Cr}$, where P_{Na} is the plasma concentration of sodium; distal delivery of sodium (DD_{Na}) was calculated as $C_{Li} \times P_{Na}$. DD_{Na} was also calculated from the formula of $(C_{H_2O} + C_{Na}) \times P_{Na}$, where C_{H_2O} and C_{Na} are free water and sodium clearances, respectively.¹³ When deducting the two equations for DD_{Na} , free water clearance equals to $C_{Li} - C_{Na}$. Absolute proximal reabsorption (APR) was calculated as $C_{Cr} - C_{Li}$, where C_{Cr} and C_{Li} are creatinine and lithium clearances, respectively; Fractional proximal reabsorption (FPR) was calculated as $[(C_{Cr} - C_{Li})/C_{Cr}] \times 100$; Distal sodium reabsorption (DR_{Na}) was calculated as $DD_{Na} - U_{Na} V$, where $U_{Na} V$ is urine sodium excretion;¹⁴ Fractional distal sodium reabsorption (FDR_{Na}) was calculated as $[(C_{Li} - C_{Na})/C_{Li}] \times 100$; Fractional distal water reabsorption (FDR_{H_2O}) was calculated as $[(C_{Li} - UV)/C_{Li}] \times 100$, where UV is urine volume.¹⁵ Considering that tubular reabsorption of filtered lithium occurs largely in the proximal tubules and that its reabsorption at more distal nephron sites is limited,¹⁶ it should be noted that lithium is assumed to be reabsorbed in the proximal tubules in parallel with sodium and water, and that it is neither secreted nor reabsorbed beyond the proximal tubule. Finally, it should be noted that throughout the paper, the expression “distal tubule” indicates all segments of the renal tubules beyond the proximal segment.

Statistical analysis

All values are expressed as means \pm SE. The differences among groups were analyzed using one-way or two-way ANOVA followed by the Tukey-Kramer multiple comparison tests. Comparisons of MAP before and after administration of drugs were performed by the use of a paired t-test. Differences were considered statistically significant at $p < 0.05$.

Drugs

Capsaicin (Sigma) was dissolved in ethanol (5% v/v), Tween 80 (5% v/v), and saline to make a stock solution of 65 nmol/ μ L and was further diluted in saline to a concentration of 0.04 nmol/ μ L to be perfused into the renal pelvis at a rate of 20 μ L \cdot min⁻¹ within the 3 min period. Capsazepine (Calbiochem, San Diego, California, USA) was dissolved in DMSO (10% v/v), Tween 80 (10% v/v), and saline to make a stock solution of 53 nmol/ μ L, and was further diluted in saline in the same manner before renal pelvis perfusion.

RESULTS

MAP and plasma levels of ions and other parameters

There was no significant difference of MAP at the baseline levels among four experimental groups (Table 1). Unilateral renal pelvic perfusion of CAP, CAPZ, or the combination of the two did not alter MAP from their baseline levels (Table 1). Moreover, hematocrit (Hct) and plasma concentrations of total protein (TP), sodium ($[Na^+]_p$), creatinine ($[Cr]_p$), and lithium ($[Li^+]_p$) were not significantly different among four experimental groups at the end of the experiments (Table 2).

Effects of CAPZ on CAP-induced diuresis and natriuresis

CAP given via LRPP significantly increased bilateral urine flow rate (Figures 1a and 1b) and urine sodium excretion (Figures 1c and 1d) of kidneys. The increases in Uflow and UNa of both kidneys induced by CAP given via LRPP were abolished by blockade of the TRPV1 with CAPZ (Figures 1a–1d). CAPZ given alone via LRPP did not alter bilateral Uflow and UNa (Figures 1a–1d).

Effect of TRPV1-activation on clearances of creatinine, lithium, sodium, and free water

Clearances of creatinine (C_{Cr}), lithium (C_{Li}), sodium (C_{Na}), and free water (C_{H_2O}) significantly increased when TRPV1 in the left renal pelvis was activated by CAP (Figures 2a–2d). The increases in C_{Cr} , C_{Li} , C_{Na} and C_{H_2O} induced by CAP given via LRPP were abolished by blockade of the TRPV1 with CAPZ (Figures 2a–2d). In contrast, both fractional excretion of lithium (FE_{Li}) and sodium (FE_{Na}) were not significantly different among groups (Table 2).

Effect of TRPV1-activation on filtered sodium load and distal delivery of sodium

Activation of the TRPV1 in the left renal pelvis induced a significant increase in both of filtered sodium load (FL_{Na}) and distal delivery of sodium (DD_{Na}), which was abolished by blockade of the TRPV1 with CAPZ (Figures 3a–3b).

Effect of TRPV1-activation on renal tubular reabsorption

Although both absolute proximal reabsorption (APR) and fractional proximal reabsorption (FPR) were not significantly different among groups (Table 2), there is a tendency that APR was higher in the CAP group compared to the vehicle group (Table 2). Activation of the TRPV1 in the left renal pelvis induced a significant increase in distal sodium reabsorption (DR_{Na}), which was abolished by blockade of the TRPV1 with CAPZ (Figure 3c). In contrast, both of fractional distal sodium (FDR_{Na}) and water (FDR_{H_2O}) reabsorption were not significantly different among groups (Table 2).

DISCUSSION

The results of the present study showed that activation of the TRPV1 by its selective agonist, CAP, given into the renal pelvis unilaterally increased urine flow rate (Uflow) and urinary sodium excretion (UNa) bilaterally without changing blood pressure. Accompanying diuresis and natriuresis induced by activation of the TRPV1 in the unilateral renal pelvis, clearances of creatinine (C_{Cr}), lithium (C_{Li}), sodium (C_{Na}), and free water (C_{H_2O}), as well as filtered sodium load (FL_{Na}), distal delivery of sodium (DD_{Na}), and distal sodium reabsorption (DR_{Na}) were increased. In contrast, fractional excretion of lithium (FE_{Li}) and sodium (FE_{Na}), absolute proximal reabsorption (APR), fractional proximal reabsorption (FPR), and fractional distal sodium (FDR_{Na}) and water (FDR_{H_2O}) reabsorption were not altered by TRPV1 activation. Furthermore, blockade of the TRPV1 by its selective antagonist, CAPZ, abolished CAP-induced increases in Uflow, U_{Na} , C_{Cr} , C_{Li} , C_{Na} , C_{H_2O} , FL_{Na} , DD_{Na} , and DR_{Na} . Therefore, on

the basis of the results obtained in the present study, it is reasonable to conclude that the TRPV1-induced sodium and water excretion appears to be mediated by increases in the glomerular filtration rate (GFR) and distal delivery of sodium, but not by suppression of renal proximal and distal tubular reabsorption.

Renal excretory function is mainly determined by the following three factors: renal blood flow, GFR, and renal tubule reabsorption. The present study showed that activation of the TRPV1 in the unilateral renal pelvis induced bilateral diuresis and natriuresis with marked increases in GFR, indicating that TRPV1-positive sensory nerves innervating the renal pelvis play an important role in the regulation of renal excretion function via modulation of glomerular function. A previous study showed that ipsilateral obstruction of urine flow or elevation of pressure in the renal pelvis activated renal mechanosensitive neurons,⁸ resulting in an increase in ipsilateral afferent renal nerve activity and subsequent contralateral diuresis and natriuresis with an increase in GFR. The latter effect was mediated by contralateral inhibition of efferent renal nerve activity, a phenomenon known as the contralateral inhibitory renorenal reflex.⁴ Therefore, the renal pelvis heavily innervated by sensory nerves may act as a sensory organ detecting a variety of stimuli imposed on the renal pelvis, resulting in alterations in renal excretory function via the renorenal reflex. Our findings indicate that the TRPV1, expressed in sensory nerves innervating the renal pelvis, may serve as a molecular detector sensing changes in physical and/or chemical factors¹⁷ in the renal pelvis to maintain water and sodium homeostasis via modulating renal function.

Given that filtered lithium is largely reabsorbed in the proximal tubule and is assumed to be neither secreted nor reabsorbed beyond the proximal tubule, lithium clearance has been used as an index of proximal tubular function.¹⁶ We found that, although activation of the TRPV1 increased clearance of lithium as twice as much of that of controls, fractional excretion of lithium was not altered. These findings indicate that CAP-induced diuresis and natriuresis were the result of enhanced GFR rather than decreased reabsorption in renal proximal tubules. Although absolute proximal reabsorption and fractional proximal reabsorption were not statistically altered by activation of the TRPV1 in the renal pelvis, there was a tendency that absolute proximal reabsorption was increased by capsaicin compared to that of vehicles. Future experiments using isolated renal tubule perfusion may help clarifying the role of capsaicin in mediating proximal tubular function.

We found that while activation of the TRPV1 in the renal pelvis increased GFR and filtered sodium load without changing reabsorption function of the proximal tubules, distal delivery of sodium was markedly increased. Given the limitation of the method, "distal tubules" here refer to all segments of the renal tubules beyond the proximal segment which includes the loop of Henle, distal segments, and collecting ducts. Although distal tubular reabsorption was enhanced by activation of the TRPV1 in the renal pelvis as indicated by increased distal sodium reabsorption, fractional distal sodium and water reabsorption was not altered. These results indicate that sodium transport from the lumen to the basal lateral side of epithelial cells in distal tubules might not be increased, but net sodium reabsorption in distal tubules was enhanced as a result of the dynamics of secretion and reabsorption in these segments. Nonetheless, enhanced distal sodium reabsorption was unable to reverse diuresis and natriuresis effects of TRPV1 activation, resulting in enhanced renal excretory function.

The TRPV1-induced diuresis and natriuresis were specific given that its effect could be abolished by its selective antagonist CAPZ. Moreover, blockade of the TRPV1 with CAPZ prevented TRPV1-induced increases in GFR, distal delivery of sodium, and distal sodium reabsorption. Although it is likely that TRPV1-positive sensory nerves innervating neuroeffectors in the kidney including vasculatures, tubules, and juxtaglomerular granular cells may directly modulate the function of these effectors, the fact that renal excretory function in

both kidneys was affected to the same extent when the TRPV1 expressed in the unilateral renal pelvis was activated indicates that the renal nerve reflex was operating. Indeed, our previous study⁵ indicated that bilateral diuresis and natriuresis caused by unilateral activation of TRPV1 expressed in the renal pelvis could be prevented by ipsilateral renal denervation. This indicates involvement of the renal nerve reflex consisting of enhanced afferent renal nerve activity via activation of the TRPV1 expressed in these nerves, contralateral suppression of efferent renal nerve activity, and enhancement of the excretory function of neuroeffectors innervated by efferent renal nerves (sympathetic nerves). Although further studies are needed to elucidate how TRPV1 positive-sensory nerves interact with sympathetic nerves innervating the kidney, our data suggest that activation of the TRPV1 expressed in the renal pelvis enhances renal excretory function possibly via inhibition of renal sympathetic nerve activity.

In conclusion, the results of the present study show that activation of the TRPV1 expressed in the unilateral renal pelvis leads to bilateral diuresis and natriuresis, which are likely the result of increased glomerular filtration rate and distal tubular delivery of sodium rather than suppression of renal proximal and distal tubular reabsorption. These data suggest that the TRPV1 may play a key role in segmental regulation of renal function and in maintenance of sodium and water homeostasis under physiological and pathophysiological conditions. The significance of TRPV1 mediated renal excretory function merits further future investigation of its role in hypertensive animal models.

Perspectives

Our data indicate that the TRPV1 may serve as a molecular sensor detecting changes in physical and chemical parameters in the renal pelvis leading to alteration of renal excretory function to maintain water and sodium homeostasis. It follows that changes in TRPV1 expression or function in the renal pelvis may alter renal excretion function via modulating the glomerular filtration rate and distal tubular delivery of sodium. It is tempting to speculate that, in a number of chronic cardiovascular diseases, e.g, heart failure and hypertension, dysfunctional TRPV1 contributes to disturbed sodium/water homeostasis and blood pressure regulation. If so, future development of novel compounds targeting the TRPV1 may prove to be beneficial in the treatment of these diseases.

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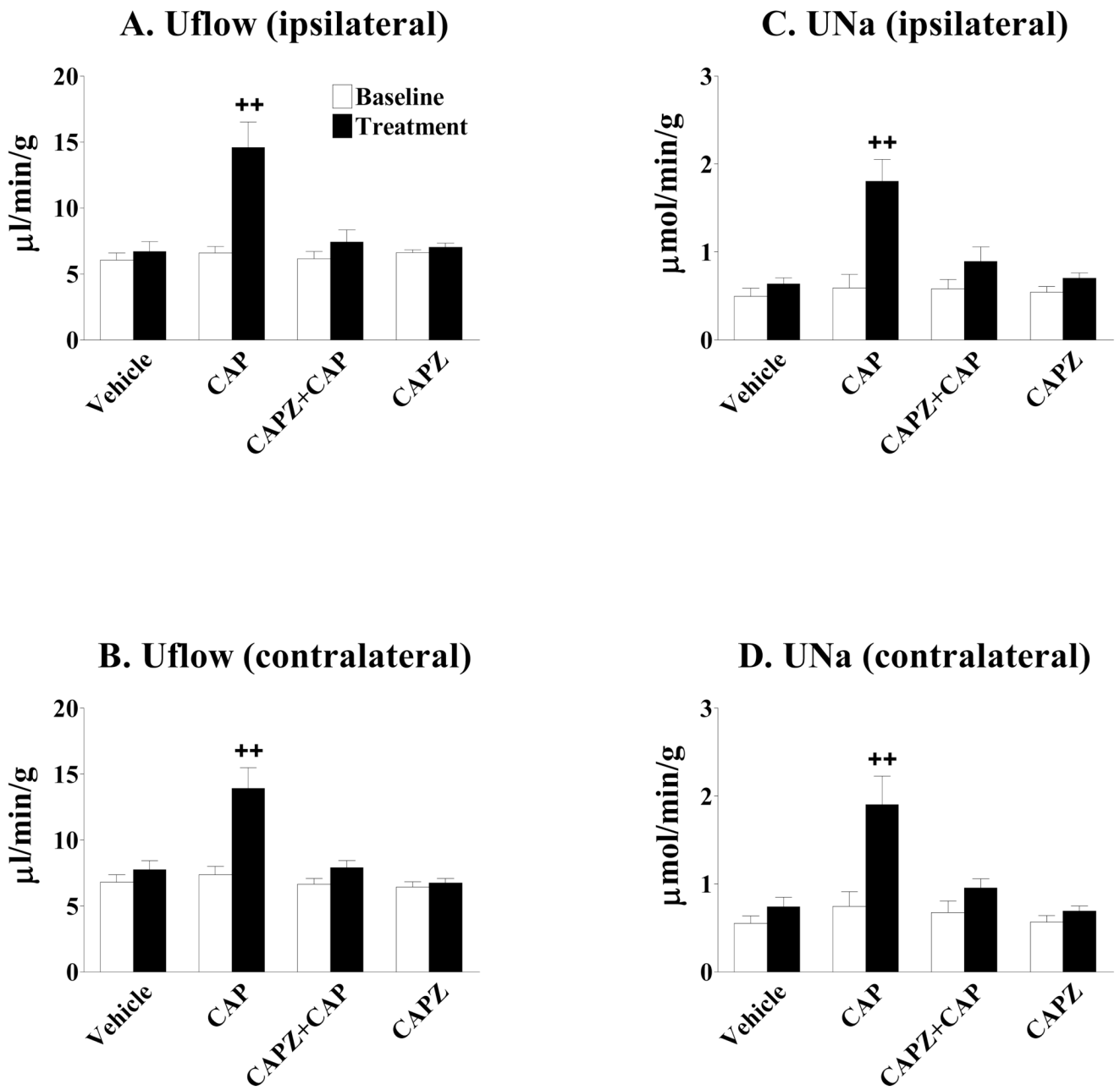


Figure 1.

Effects of capsazepine (CAPZ) on capsaicin (CAP)-induced diuresis and natriuresis. The increases in the urinary flow rate (Uflow) and urinary sodium excretion (UNa) of both kidneys induced by CAP given via left renal pelvis perfusion (LRPP) were abolished by blockade of the TRPV1 with CAPZ. (n= 5–6 rats). ++ p < 0.01 vs baseline in the same group and baseline and treatment in Vehicle, CAPZ + CAP, and CAPZ groups.

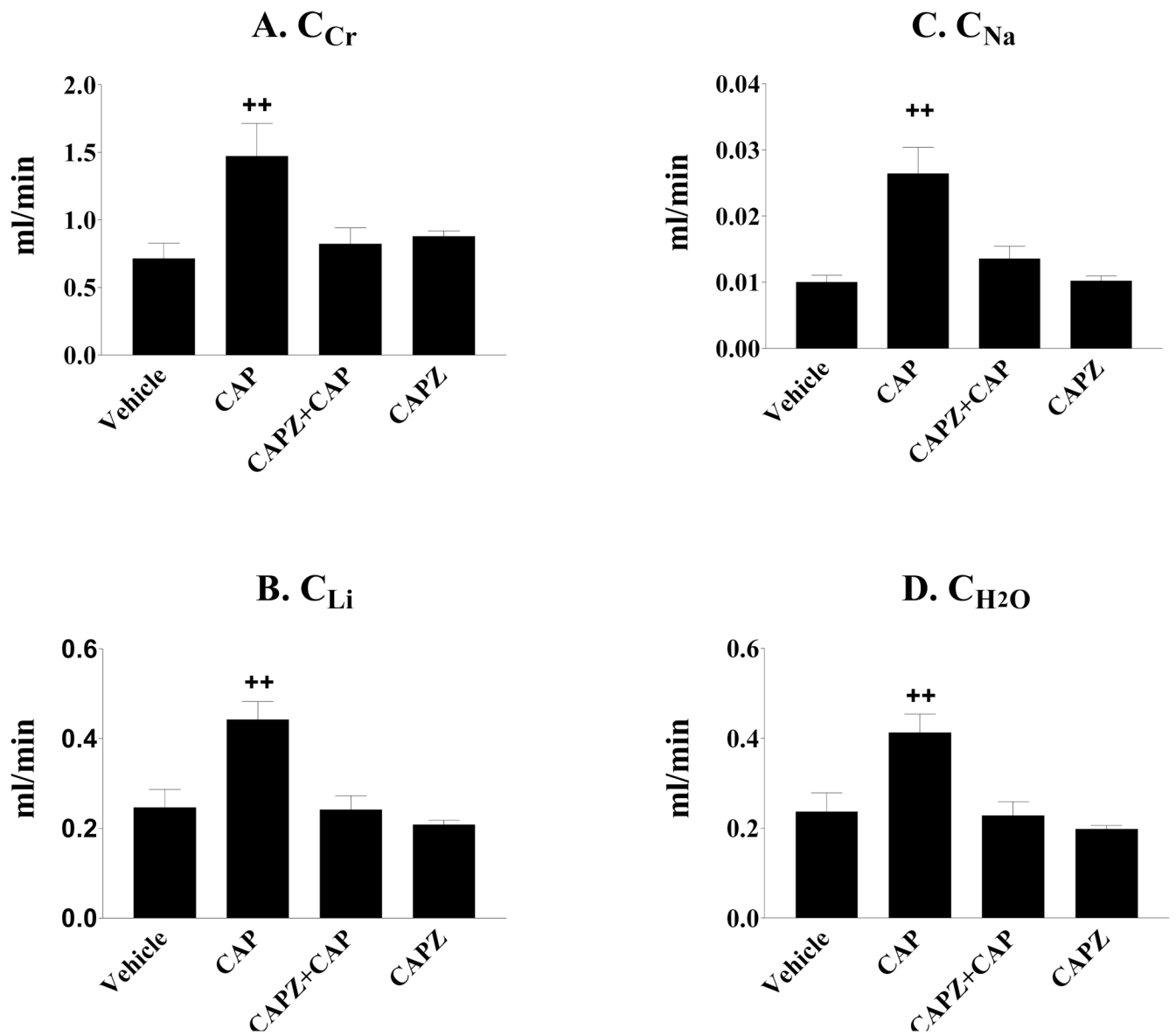


Figure 2. Effects of capsaicin (CAP) given via left renal pelvis perfusion (LRPP) on clearances of creatinine (C_{Cr}), lithium (C_{Li}), sodium (C_{Na}) and free water (C_{H_2O}). CAP significantly increased C_{Cr} (A), C_{Li} (B), C_{Na} (C), and C_{H_2O} (D) by activation of the TRPV1 in the renal pelvis and these effects of CAP were abolished by blockade of the TRPV1 with capsazepine (CAPZ). (n= 5–6 rats). ++ p < 0.01 vs Vehicle, CAPZ + CAP, and CAPZ groups.

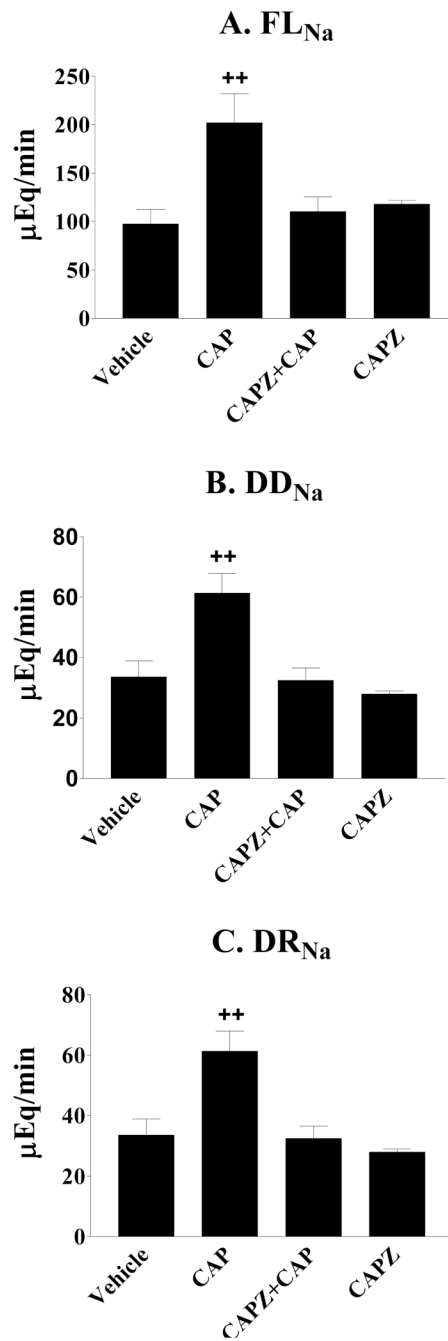


Figure 3.

Effects of capsaicin (CAP) given via left renal pelvis perfusion (LRPP) on filtered sodium load (FL_{Na}), distal delivery of sodium (DD_{Na}) and distal sodium reabsorption (DR_{Na}). CAP significantly increased FL_{Na} (A), DD_{Na} (B) and DR_{Na} (C) by activation of the TRPV1 in the renal pelvis and these effects were abolished by blockade of the TRPV1 with capsazepine (CAPZ) ($n=5-6$ rats). ++ $p < 0.01$ vs Vehicle, CAPZ + CAP, and CAPZ groups.

Table 1

MAP (mmHg) before and after the treatment

Groups	Baseline (mmHg)	Treatment (mmHg)
Vehicle	125 ± 1	125 ± 1
CAP	121 ± 4	121 ± 4
CAPZ+CAP	124 ± 4	122 ± 4
CAPZ	123 ± 3	121 ± 2

Values are expressed as mean ± SE, n= 5–6 rats.

Table 2
Plasma parameters and renal function in response to the treatment

	Vehicle	CAP	CAPZ + CAP	CAPZ
Hct, %	44.8±0.9	43.9±0.7	45.0±0.7	45.0±0.8
TP, mg·ml ⁻¹	58.1±5.5	59.9±4.7	53.2±5.8	63.3±0.9
[Na ⁺] _p , mmol·L ⁻¹	134.7±2.1	137.6±4.4	134.9±1.7	134.8±1.8
[Cr] _p , mg/dL ⁻¹	0.68±0.08	0.59±0.03	0.66±0.09	0.57±0.04
[Li ⁺] _p , mmol·L ⁻¹	0.24±0.04	0.26±0.01	0.24±0.02	0.25±0.02
FE _{Li} , %	40±11	34±8	32±6	24±1
FE _{Na} , %	1.6±0.3	2.1±0.4	1.9±0.4	1.2±0.1
APR, ml·min ⁻¹	0.5±0.1	1.0±0.3	0.6±0.1	0.7±0.1
FPR, %	60±11	66±8	68±6	76±1
FDR _{Na} , %	95±1	94±1	94±1	95±1
FDR _{H₂O} , %	94±1.1	94±0.3	93±0.4	93±0.5

Values are expressed as mean ± SE, n = 5–6 rats. ++ p ≤ 0.01 vs Vehicle, CAPZ + CAP and CAPZ groups. Hct, hematocrit; TP, total protein; [Na⁺]_p, plasma sodium concentration; [Cr]_p, plasma creatinine concentration; [Li⁺]_p, plasma lithium concentration; GFR, glomerular filtration rate; FE_{Li}, fractional excretion of lithium; FE_{Na}, fractional excretion of sodium; APR, absolute proximal reabsorption; FPR, fractional proximal reabsorption; FDR_{Na}, fractional distal sodium reabsorption; FDR_{H₂O}, fractional distal water reabsorption.