Salt Intake Augments Hypotensive Effects of Transient Receptor Potential Vanilloid 4
Functional Significance and Implication

Feng Gao, Dexin Sui, R. Michael Garavito, R. Mark Worden, Donna H. Wang

Abstract—To test the hypothesis that activation of the transient receptor potential vanilloid 4 (TRPV4) channel conveys a hypotensive effect that is enhanced during salt load, male Wistar rats fed a normal-sodium (0.5%) or high-sodium (HS; 4%) diet for 3 weeks were given 4α-phorbol 12,13-didecanoate (4α-PDD), a specific TRPV4 activator, in the presence or absence of capsazepine, a selective TRPV1 blocker, ruthenium red, a TRPV4 blocker, or TRPV4 small hairpin RNA that selectively knockdowns TRPV4. 4α-PDD (1, 2.5, or 5 mg/kg IV) dose-dependently decreased mean arterial pressure (P<0.05). HS enhanced 4α-PDD–induced depressor effects as well as 4α-PDD–mediated release of calcitonin gene–related peptide and substance P (P<0.001). Ruthenium red markedly blunted (P<0.001), whereas capsazepine slightly attenuated (P<0.05) 4α-PDD–induced depressor effects in HS and normal-sodium diet rats. Ruthenium red alone increased baseline mean arterial pressure in both HS and normal-sodium diet rats with a greater magnitude in the former (P<0.05). Western blot analysis showed that HS increased TRPV4 expression in dorsal root ganglia and mesenteric arteries (P<0.05) but not the renal cortex and medulla. Gene-silencing approach revealed that TRPV4 small hairpin RNA downregulated TRPV4 expression leading to blunted 4α-PDD–induced hypotension (P<0.05). Thus, TRPV4 activation decreases blood pressure in rats given a normal-sodium diet. HS enhances TRPV4 expression in sensory nerves/mesenteric arteries and TRPV4-mediated depressor effects and calcitonin gene–related peptide/substance P release such that HS causes a greater increase in blood pressure when TRPV4 is blocked. Our data indicate that TRPV4 activation may constitute a compensatory mechanism in preventing salt-induced increases in blood pressure. (Hypertension. 2009;53:00-00.)

Key Words: salt intake ■ gene-targeting ■ gene-silencing ■ sensory nerves ■ blood pressure ■ transient receptor potential channel

The transient receptor potential (TRP) vanilloid 4 (also named Osm-9–like TRP channel 4, vanilloid receptor-related osmotically activated channel; vanilloid receptor–like channel 2, or TRP 12) receptor is a nonselective cation channel of the vanilloid subfamily of TRP channels. TRP vanilloid 4 (TRPV4) is broadly expressed in the heart, brain, liver, kidney, lung, trachea, placenta, salivary gland, and sensory neurons in the trigeminal ganglion and dorsal root ganglia (DRG).1 TRPV4 is 5 to 10× more permeable for Ca2+ than Na+ and can be activated by osmolarity, heat, mechanical stimulation, 4α-phorbol ester derivatives, and lipids, including endocannabinoids, arachidonic acid, and their metabolites.4,5 These stimuli promote TRPV4 channel opening by distinct pathways (eg, cell swelling activates TRPV4 by phospholipase A2–dependent formation of arachidonic acid and subsequent generation of 5,6′-epoxyeicosatrienoic acid via the cytochrome P450 epoxyenase-dependent pathway).4,5 In contrast, activation of TRPV4 evoked by phorbol esters and heat depends on an aromatic residue at the N terminus of the third transmembrane.6 TRPV4 may play a role in several physiological responses. As an osmoreceptor, TRPV4 is expressed in neurons of the circumventricular organs, where neurosensory cells are known to be responsive to systemic osmotic pressure.7 TRPV4 gene deletion leads to disturbed osmotic regulation in the face of hyperosmolarity.8 Expression of TRPV4 in the rat kidney is restricted to water-impermeant nephron segments, suggesting that TRPV4 is an osmotically responsive cation channel.9 Furthermore, TRPV4 may function in the transduction of osmolality/hypotonicity stimulation in airways in humans,10,11 of mechanical or temperature stimulation in Caenorhabditis elegans,12 and of thermal sensation in the hypothalamus in rodents.13,14 We have shown that TRP vanilloid 1 (TRPV1) channels play a key role in preventing salt-induced increases in blood pressure.15,16 However, the role of TRPV4 in modulation of

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From the Departments of Medicine (F.G., D.H.W.), Biochemistry and Molecular Biology (D.S., R.M.G.), Chemical Engineering and Materials Science (R.M.W.), Neuroscience Program (D.H.W.), and Cell and Molecular Biology Program (D.H.W.), Michigan State University, East Lansing.
Correspondence to Donna H. Wang, MD, FAHA, Department of Medicine, B316B Clinical Center, Michigan State University, East Lansing, MI 48824. E-mail donna.wang@ht.msu.edu
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blood pressure in the face of salt challenge is largely unknown. This study tests the hypotheses that TRPV4 activation leads to dose-dependent hypotension and that high salt intake enhances TRPV4-induced depressor effects as a mean to prevent salt-induced increases in blood pressure. Given the lack of selective channel blockers and its coexpression with TRPV1, the effect of TRPV4 activation or inhibition was examined using the best available pharmacological tools (ie, 4α-phorbol 12,13-didecanoate [4α-PDD] or ruthenium red [RuR], respectively). The specificity of 4α-PDD was examined in the presence or absence of TRPV1 or TRPV4 antagonists, and the specificity of RuR was tested in the presence or absence of TRPV1 or TRPV4 agonists. Finally, TRPV4 small hairpin RNA (shRNA) was used to specifically knockdown TRPV4 expression and the effect examined.

Methods

Preparation of Animals and Samples
Six-week-old male Wistar rats (Charles River Laboratory; Wilmington, Mass) were randomly assigned to a normal-sodium (NS) diet (0.5% NaCl by weight; Harlan Teklad) or a high-sodium (HS) diet (4% NaCl by weight) group and treated for 3 weeks. All rats drank water ad libitum throughout the experiment.

In addition to rats subject to acute experiments in which various agonists or antagonists were given, a subset of rats fed an NS or HS diet were euthanized by decapitation at the end of the third week without subjecting them to acute experiments. Blood was collected in EDTA tubes for plasma calcitonin gene–related peptide (CGRP) and substance P (SP) assays. The cervical, thoracic, and lumbar DRG, mesenteric resistance arteries (MA), and the renal cortex and medulla were dissected and collected for Western blot analysis.

Surgical Preparation
Rats were anesthetized with ketamine and xylazine (80 and 4 mg/kg IP, respectively) for implantation of vascular catheters, or with urethane (1.5 g/kg IP) when the animals were subject to capsaicin (CAP) injection. The left jugular vein and carotid artery were cannulated under anesthesia for administration of drugs and for monitoring of mean arterial pressure (MAP) and heart rate with a Statham 231D pressure transducer coupled to a Gould 2400 recorder (Gould Instruments, respectively). Baseline MAP and its response to various chemicals except for CAP were obtained 3 hours after surgery with the rats fully awake and unrestrained in their home cages.

Effects of TRPV4 Activation in the Presence or Absence of the TRPV1 or TRPV4 Blockade
To examine whether activation of TRPV4 leads to hypotension, rats fed an NS diet were given various doses (0, 1, 2, or 5 mg/kg IV bolus) of 4α-PDD in 4 groups (each group of rats for each dose). After observing a dose-dependent decrease in MAP, rats fed an NS or HS diet were randomly assigned to groups for injection of vehicle or 4α-PDD (2.5 mg/kg IV) alone or in combination with capsaicin (CAP; a TRPV1 receptor antagonist; 3 mg/kg IV), SB 366791 (a TRPV1 receptor antagonist; 2 mg/kg IP), or RuR (a TRPV4 channel blocker; 1 or 3 mg/kg IV). 4α-PDD at 2.5 mg/kg IV was administered 6, 8, 20, or 30 minutes after injection of CAPZ at 3 mg/kg IV, RuR at 1 mg/kg IV, RuR at 3 mg/kg IV, or SB 366791 at 2 mg/kg IP, respectively, and the drug administration dose and route were chosen according to previous studies. MAP was recorded for 30 minutes starting 10 minutes before and 20 minutes after 4α-PDD injection in all groups. Two different TRPV1 blockers, CAPZ and SB 366791, were used in light of their distinct potencies and mechanisms of actions. Additional groups of rats fed an NS or HS diet were given vehicle or RuR (1 or 3 mg/kg IV) alone to detect MAP responses to TRPV4 blockade.

Effects of TRPV1 Activation in the Presence or Absence of the TRPV1 or TRPV4 Blockade
To serve as controls of TRPV4 activation, rats fed an NS diet were randomly assigned to groups for administration of vehicle or CAP (30 μg/kg IV; a selective TRPV1 agonist) alone or in combination with SB 366791 (2 mg/kg IP) or RuR (1 and 3 mg/kg IV). CAP was injected 5, 8, 20, and 30 minutes after injection of vehicle; RuR was injected at 1 mg/kg or 3 mg/kg IV or SB 366791 at 2 mg/kg IP, respectively, and the peak changes in MAP occurred 1 to 2 minutes after injection of CAP recorded in all groups. The dose of CAP was chosen based on a previous study. Given that CAP is an irritant and causes pain in conscious rats, this protocol was performed in anesthetized rats as described previously.

Radioimmunoassay
A rabbit anti-rat CGRP radioimmunoassay kit and a rabbit anti-rat SP radioimmunoassay kit (Phoenix Pharmaceuticals) were used to determine CGRP and SP contents in plasma that was collected 6 minutes after 4α-PDD administration in all groups.

Western Blot Analysis
Western blot analysis was performed as described previously with the use of primary antibody targeted to TRPV4 (1:500; Alomone Labs, Jerusalem, Israel) and secondary antibody conjugated with horseradish peroxidase (1:800; Santa Cruz Biotechnology, Santa Cruz, CA). The membranes were developed using an ECL kit (Amersham Pharmacia Biotech) and exposed to films (Hyperfilm-ECL; Amersham Pharmacia Biotech). The films were scanned and analyzed with the use of the Image Quantity Program (Scion) to obtain integrated densitometric values. β-Actin was used to normalize protein loading on membranes.

Preparation and Systemic Application of the shRNA/Dendrimer Complex
A subset of rats fed an NS or HS diet was injected via the tail vein of TRPV4 shRNA/dendrimer complex or control shRNA/dendrimer complex at the beginning of the third week (ie, at the end of the second week), once per day, for 7 days (please see the online data supplement available at http://www.hypertensionaha.org). Plasma shRNAs (SureSilencing shRNA plasmid for rat TRPV4 with sequence) were purchased from SuperArray Bioscience Corporation (Frederick, Md). Generation 5 PAMAM dendrimers (Dendritech, Inc; Midland, Mich) were used as carriers of the plasmids and were dissolved in water (27.25%, w/v) and mixed with 1.6 mg/kg shRNA in 0.9% NaCl solution (total injection volume 1.6 mL) using a charge ratio of 7.

Quantitative Real-Time Polymerase Chain Reaction
Total tissue RNA was extracted using RNeasy Mini Kit (Qiagen) following the instructions provided by the supplier. Total RNA (0.5 μg) was used for first-strand cDNA synthesis with random hexamer primers and Superscript III RNase H− reverse transcriptase (Invitrogen) according to manufacturer protocol. Real-time polymerase chain reaction (PCR) primers for TRPV1, TRPV4, and 18SrRNA were obtained (please see online supplement). PCR reactions were performed with QuantiTect SYBR Green PCR Kit (Qiagen) using 3 μL of cDNA as the template in each 20-μL reaction mixture. PCR assays were performed with an Applied Biosystem 7900HT Sequence Detection System (ABI Prism). Data were also normalized with the quantity of 18S rRNA in individual samples to correct for sample variability.

Drugs
4α-PDD (LC Laboratories) or CAP (Sigma) was dissolved in ethanol (5% v/v), Tween-80 (5% v/v), and saline right before administration to animals. CAPZ (Sigma) or SB 366791 (Sigma) was dissolved in dimethyl sulfoxide (5% v/v), Tween-80 (10% v/v), and saline in the same manner as above. RuR (Sigma) was dissolved in saline.
were considered statistically significant at a Bonferroni adjustment for multiple comparisons. Differences among groups were analyzed using 1-way ANOVA followed by a Bonferroni adjustment for multiple comparisons. Differences among groups were analyzed by using the unpaired Student $t$ test. Differ-
ences between the 2 groups were analyzed by using the unpaired Student $t$ test. Differences were considered statistically significant at $P<0.05$.

**Statistical Analysis**

All values are expressed as means $\pm$ SE. Differences between the 2 groups were analyzed by using the unpaired Student $t$ test. Differences among groups were analyzed using 1-way ANOVA followed by a Bonferroni adjustment for multiple comparisons. Differences were considered statistically significant at $P<0.05$.

**Results**

**MAP Responses to Intravenous Administration of 4α-PDD at Various Doses**

Figure 1 shows that administration of 4α-PDD (1, 2.5, 5 mg/kg IV) caused a dose-dependent decrease in MAP and an increase in heart rate in NS diet rats, indicating that activation of TRPV4 led to a depressor effect on blood pressure and a normal functional baroreflex. The depressor effects reached the peak 6 to 8 minutes after administration. Given that the midrange dose of 4α-PDD (2.5 mg/kg) provided a robust yet not detrimental drop in MAP, it was chosen for the rest of the studies reported below.

**MAP Responses to TRPV4 Activation in the Presence or Absence of TRPV1 or TRPV4 Blockade**

There was no significant difference in baseline MAP between NS and HS diet groups of rats after 3-week dietary treatment (HS, 103±2 mm Hg versus NS, 94±4 mm Hg; $P>0.05$).

Figure 2 shows the peak changes of MAP that occurred 5 to 7 minutes after injection of 4α-PDD with or without other drugs. The magnitude of decrease in MAP induced by 2.5 mg/kg 4α-PDD IV was significantly greater in HS than NS diet rats, indicating that TRPV4 function is sensitized in rats fed an HS diet. Moreover, blockade of TRPV4 with RuR (1 mg/kg or 3 mg/kg IV) markedly blunted the depressor effect of 4α-PDD in rats fed an NS or HS diet. In contrast, blockade of TRPV1 with CAPZ but not SB 366791 weakly but significantly attenuated the depressor effect of 4α-PDD in rats fed an HS diet only. These data indicate that the depressor effect induced by 4α-PDD is mediated mainly by activation of TRPV4, but TRPV1 may also contribute to 4α-PDD–induced depressor action in the face of salt load.

**MAP Responses to Intravenous Administration of 4α-PDD at Various Doses**

Figure 1. Time-course responses of MAP (A) and heart rate (B) to bolus injection of 4α-PDD (1 mg/kg, 2.5 mg/kg, or 5 mg/kg IV) in conscious rats fed an NS diet. Vehicle indicates ethanol (5% v/v), Tween-80 (5% v/v), and saline, intravenous. Values are mean±SE ($n=5$ to 8). $^*P<0.05$ compared with the corresponding vehicle-treated value.

**MAP Responses to TRPV4 Activation in the Presence or Absence of TRPV1 or TRPV4 Blockade**

There was no significant difference in baseline MAP between NS and HS diet groups of rats after 3-week dietary treatment (HS, 103±2 mm Hg versus NS, 94±4 mm Hg; $P>0.05$).

Figure 2. Changes in MAP 5 to 7 minutes after bolus injection of 4α-PDD (2.5 mg/kg IV) with or without SB 366791 (2 mg/kg IP; a selective TRPV1 blocker), CAPZ (3 mg/kg IV; a selective TRPV1 blocker) and RuR (1 mg/kg and 3 mg/kg IV) in conscious rats fed an NS or HS diet. Vehicle indicates ethanol (5% v/v), Tween-80 (5% v/v), and saline, intravenous. Values are mean±SE ($n=5$ to 7). $^*P<0.05$ compared with the corresponding NS diet group; †$P<0.05$ compared with the corresponding vehicle-treated group; $^*P<0.05$ compared with the corresponding 4α-PDD-treated group; ‡$P<0.05$ compared with the SB- and CAPZ-treated groups.

**Figure 3. Mean blood pressure (MAP) responses to injection of RuR (1 mg/kg and 3 mg/kg IV) in conscious rats fed an NS or HS diet. Vehicle indicates intravenous saline. Values are mean±SE ($n=7$ to 10). $^*P<0.05$ compared with the corresponding vehicle-treated group; $^*P<0.05$ compared with the corresponding NS diet group.
To determine whether blockade of TRPV4 affects baseline blood pressure in HS rats, MAP responses to bolus injection of RuR (1 mg/kg or 3 mg/kg IV) were examined under the fully awake state of rats. The MAP elevation began immediately after administration of RuR and reached the peak in 3 to 6 minutes in both NS and HS diet rats. The pressor action of RuR at the doses of 1 mg/kg and 3 mg/kg IV lasted for 6 to 8 minutes and 15 to 20 minutes, respectively. The peak MAP responses to RuR at 3 mg/kg IV were elevated significantly in HS compared with NS diet rats (Figure 3).

### MAP Responses to TRPV1 Activation in the Presence or Absence of the TRPV1 or TRPV4 Blockade

The peak changes in MAP occurred 1 to 2 minutes after injection of CAP in all groups (Table). Although SB 366791 (2 mg/kg IP) effectively blocked CAP-induced depressor effects, RuR at 1 or 3 mg/kg was incapable of blockade of CAP-induced depressor effects. These findings are supported by a previous report and indicate that the pressor effect of RuR is attributable to blockade of TRPV4 but not TRPV1 channels.

### TRPV4 Protein Expression in DRG, MA, and the Kidney in Response to HS Intake

Figure 4 shows that there was no significant difference in TRPV4 expression in the renal cortex and medulla between NS and HS diet rats, but HS intake enhanced TRPV4 expression in DRG and MA ($P<0.05$). Elevated TRPV4 expression in DRG and MA may underlie, at least in part, enhanced depressor effects of TRPV4 observed in HS rats.

#### Table. Effects of CAP on MAP in the Presence or Absence of TRPV1 or TRPV4 Blockade in Urethane-Anesthetized Rats Fed an NS Diet

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>MAP, mm Hg</th>
<th>Baseline</th>
<th>After CAP</th>
<th>$\Delta$</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>115±3</td>
<td>113±3</td>
<td>$-2\pm3$</td>
<td></td>
</tr>
<tr>
<td>CAP</td>
<td>112±5</td>
<td>86±4*</td>
<td>$-26\pm2$</td>
<td></td>
</tr>
<tr>
<td>SB 366791 + CAP</td>
<td>110±3</td>
<td>108±3†</td>
<td>$-3\pm3$</td>
<td></td>
</tr>
<tr>
<td>1 mg/kg RuR + CAP</td>
<td>112±3</td>
<td>83±3‡</td>
<td>$-29\pm2$</td>
<td></td>
</tr>
<tr>
<td>3 mg/kg RuR + CAP</td>
<td>116±4</td>
<td>93±5*</td>
<td>$-23\pm1$</td>
<td></td>
</tr>
</tbody>
</table>

After baseline recording, MAP was recorded 1 to 2 minutes after CAP administration.

Values are mean±SE (n=4 to 6). CAP, 30 $\mu$g/kg IV; SB 366791, 2 mg/kg IP; RuR, 1 or 3 mg/kg IV; vehicle, ethanol (5% v/v), Tween-80 (5% v/v), and saline, intravenous.

*$P<0.05$ compared with the corresponding vehicle-treated group; †$P<0.05$ compared with the corresponding CAP-treated group; ‡$P<0.05$ compared with the corresponding SB-treated group.
Effects of TRPV4 shRNA Treatment on TRPV4 Expression and Function

The results of Western blot analysis indicated that TRPV4 shRNA treatment significantly downregulated TRPV4 protein expression in DRG by 29% in NS diet rats and 38% in HS diet rats, MA by 34% in NS diet rats and 41% in HS diet rats, and the renal medulla by 33% in NS diet rats (albeit $P>0.05$) and 52% in HS diet rats but not in the renal cortex in NS or HS diet rats (Figure 6). To ascertain TRPV4 mRNA expression levels, the renal medulla was used as an example and subjected to quantitative real-time PCR analysis. Consistent with the protein expression, TRPV4 mRNA expression in the renal medulla was reduced significantly in TRPV4 shRNA– compared with control shRNA–treated rats by 67% and 50% in NS and HS diet rats, respectively (Figure 7A). In contrast, TRPV4 shRNA treatment had no effect on TRPV1 mRNA expression in NS or HS diet rats (Figure 7B), confirming the specificity of TRPV4 shRNA in the suppression of TRPV4 but not TRPV1 expression.

There was no significant difference in baseline MAP between control shRNA– and TRPV4 shRNA–treated groups in NS diet (control shRNA, 87±3 mm Hg versus TRPV4 shRNA, 85±4 mm Hg; $P>0.05$) or HS diet (control shRNA, 93±4 mm Hg versus TRPV4 shRNA, 89±5 mm Hg; $P>0.05$) rats. However, downregulation of TRPV4 with TRPV4 shRNA significantly attenuated the depressor effects of 4α-PDD (2.5 mg/kg IV) in both NS and HS diet rats (Figure 8). These data indicate that TRPV4 shRNA specifically and effectively downregulates mRNA and protein expression of TRPV4 in NS and HS diet rats, resulting in attenuated depressor effects of TRPV4 observed in these rats.

Discussion

This study examines the role of TRPV4, a newly discovered osmosensor and mechanosensor, in salt-induced regulation of blood pressure. The data presented here show that: (1) 4α-PDD induces a dose-dependent decrease in blood pressure by activation of TRPV4 in rats fed an NS diet, and HS intake enhances 4α-PDD–induced depressor effects via mainly activation of TRPV4 as well as possibly TRPV1, (2) blockade of TRPV4 with RuR elevates baseline MAP in rats fed an NS diet, and HS intake sensitizes RuR-induced pressor effects, (3) HS upregulates TRPV4 expression in sensory nerves and mesenteric arteries and enhances TRPV4-mediated CGRP and SP release, and (4) gene delivery of TRPV4 shRNA in vivo downregulates mRNA and protein expression of TRPV4, leading to attenuated 4α-PDD–induced depressor effects. These data indicate for the first time that salt intake augments TRPV4–induced depressor effects, which may constitute a compensatory mechanism in preventing salt-induced increases in blood pressure.

It has been reported that, as a TRPV4 channel opener, 4α-PDD also weakly activates TRPV1. We therefore examined whether 4α-PDD–induced depressor effects were mediated by TRPV1 activation. Our results showed that blockade of TRPV1 weakly attenuated 4α-PDD–induced hypotension in HS rats only, whereas blockade of TRPV4 markedly blunted the fall of blood pressure induced by
These data indicate that 4α-PDD–induced depressor effects are predominantly mediated by TRPV4 activation during NS or HS intake, and that a component of the depressor effect of 4α-PDD is mediated by TRPV1 activation when HS is given, a finding supported by previous in vitro findings.18 Likewise, as a TRPV4 channel blocker, RuR may act on TRPV1 channels to affect its function. However, our data show that RuR had no effect on CAP-induced depressor effects, whereas SB 366791 effectively blocked CAP action. These data indicate that RuR action is TRPV1 independent, a result consistent with a previous report.29 Moreover, these findings indicate that the effect of RuR on preventing a 4α-PDD–induced fall in blood pressure is mediated by blockade of TRPV4.
Elevated TRPV4 expression by HS intake may constitute a compensatory effect in offsetting salt-induced increases in blood pressure. Our data show that blockade of TRPV4 with RuR elevated baseline MAP in both NS- and HS-treated rats, and that HS intake augmented pressor effects induced by RuR. Given that RuR effectively blunted 4α-PDD– but not CAP-induced hypotension, the pressor effects induced by RuR are probably mediated by blockade of TRPV4 but not TRPV1. These data indicated that TRPV4 possesses an antihypertensive effect, especially in the face of salt load. Furthermore, enhanced TRPV4 expression, TRPV4–mediated sensory neuropeptide release, and TRPV4–mediated depressor effects during HS intake may constitute a compensatory effect in offsetting salt-induced increases in blood pressure.

As an effective and specific tool to knockdown the target gene expression,54 TRPV4 shRNA combined with 5 PAMAM, the most used dendrimers for facilitating delivery of intact interfering RNAs into target cells/organisms in vivo,55 have been used in the current study to further identify whether the effect induced by 4α-PDD is mediated by TRPV4 activation. As a result, TRPV4 shRNAs effectively reduced TRPV4 expression in DRG sensory neurons, mesenteric arteries, and the renal medulla, leading to attenuated depressor effects evoked by 4α-PDD. A greater effect may be reached with more suppression of TRPV4 expression, but additional studies are necessary to confirm the notion. Nevertheless, these results further support the notion that TRPV4 mediates 4α-PDD–induced depressor effects and activation of TRPV4 conveys an antihypertensive effect.

**Perspectives**

The kidney and central nervous system are the 2 major sites for salt sensing in blood pressure regulation and hypertension.6,13 However, the mechanistic link between dietary salt and hypertension remains poorly understood. Several distinct mechanisms possibly involved in this process, including Cl− sensing in renal tubular fluids by Na+−K+−Cl− cotransporters, sensing of Na+ or osmolarity in cerebrospinal fluid by TRPV1, and osmolarity sensing in glial cells of supraoptic and paraventricular nuclei by volume-regulated anion channels.15,16,23,24,37,38 TRPV4 has been shown to be expressed in the circumventricular organs, the organum vasculosum of the lamina terminalis, and the subfornical organ, which sense and modulate osmotic pressure by feedback regulation.8 In addition, TRPV4 may affect salt sensitivity of blood pressure by regulating release of antidiuretic hormone and the subsequent osmoregulatory role in preventing development of salt-sensitive hypertension.8,10,11,19,20,38 Thus, TRPV4 may serve as a target for development of therapy treating hypertension, especially a salt-sensitive subpopula-
tion. Furthermore, in vivo delivery of gene in a format of nanoparticle may be a potential useful tool for downregulation of expression and function of specific genes and their corresponding proteins, leading to altered functions governed by these proteins to achieve therapeutic purposes.

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Disclosures

None.

References

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