Impairment in Function and Expression of Transient Receptor Potential Vanilloid Type 4 in Dahl Salt-Sensitive Rats

Significance and Mechanism

Feng Gao, Donna H. Wang

Abstract—To examine the role of transient receptor potential vanilloid type 4 (TRPV4) channels in the development of salt-sensitive hypertension, male Dahl salt-sensitive (DS) and -resistant (DR) rats were fed a low-salt (LS) or high-salt (HS) diet for 3 weeks. DS-HS but not DR-HS rats developed hypertension. 4α-Phorbol-12,13-didecanoate (a selective TRPV4 activator; 2.5 mg/kg IV) decreased mean arterial pressure in all of the groups with the greatest effects in DR-HS and the least in DS-HS rats (P<0.05). Depressor effects of 4α-phorbol-12,13-didecanoate but not dihydrocapsaicin (a selective TRPV1 agonist; 30 μg/kg IV) were abolished by ruthenium red (a TRPV4 antagonist; 3 mg/kg IV) in all of the groups. Blockade of TRPV4 with ruthenium red increased mean arterial pressure in DR-HS rats only (P<0.05). TRPV4 protein contents were decreased in the renal cortex, medulla, and dorsal root ganglia in DS-HS compared with DS-LS rats but increased in dorsal root ganglia and mesenteric arteries in DR-HS compared with DR-LS rats (P<0.05). Mean arterial pressure responses to blockade of small- and large-/intermediate-conductance Ca\(^{2+}\)-activated K\(^+\) channels (Maxi channels) with apamin and charybdotoxin, respectively, were examined. Apamin (100 μg/kg) plus charybdotoxin (100 μg/kg) abolished 4α-phorbol-12,13-didecanoate–induced hypotension in DR-LS, DR-HS, and DS-LS rats only. Thus, HS-induced enhancement of TRPV4 function and expression in sensory neurons and resistant vessels in DR rats may prevent salt-induced hypertension possibly via activation of Maxi channels given that blockade of TRPV4 elevates mean arterial pressure. In contrast, HS-induced suppression of TRPV4 function and expression in sensory neurons and kidneys in DS rats may contribute to increased salt sensitivity. (Hypertension. 2010;55:00-00.)

Key Words: Dahl salt-sensitive hypertension ■ TRP channels ■ TRPV4 ■ TRPV1 ■ Ca\(^{2+}\)-activated K\(^+\) channels

As a major risk factor for cardiovascular disease, sodium plays an important role in the pathogenesis and therapy of hypertension that affects 25% to 35% of the world population >18 years of age. The increment in blood pressure driven by a salt load is characteristic of salt-sensitive hypertension, a condition affecting more than two thirds of individuals with essential hypertension who are older than 60 years. Various lines of evidence suggest that black patients are more salt sensitive than whites, which may be because of a tendency to retain sodium in the kidney, although a complete explanation for the difference has yet to be developed. It has been proposed that the kidney and the central nervous system are the 2 major sites for salt sensing, but the underlying molecular mechanisms are largely unclear. As a genetic model of salt-sensitive hypertension mimicking that of humans, Dahl-salt sensitive (DS) hypertensive rats have been extensively used for the study of molecular mechanisms mediating increased salt sensitivity.

The transient receptor potential (TRP) vanilloid subtype (V) 4, a member of the TRP family, is a nonselective cationic channel. TRPV4 can be activated by a wide variety of stimuli, including thermal, physical, and chemical stimuli, such as the synthetic agonists 4α-phorbol-12,13-didecanoate (4α-PDD) and GSK1016790A, the endocannabinoid anandamide, or the arachidonic acid metabolite epoxyeicosatrienoic acid. In deed, broad expression of TRPV4 in various tissues including the heart, liver, lung, spleen, kidney, sympathetic ganglia, dorsal root ganglia (DRG), and trigeminal ganglia suggests a polynodal role of TRPV4 in diverse cell functions. Specifically, TRPV4 expresses in neurons of the circumventricular organs, including the organum vasculosum of the lamina terminalis and the subfornical organ, that sense and modulate osmotic pressure by feedback regulation. Furthermore, expression of TRPV4 in the rat kidney is restricted to water-impermeant nephron segment. All of the evidence support the osmosensitive nature of TRPV4, indicating that
TRPV4 may play a key role in the regulation of sodium and water homeostasis and that dysfunction of TRPV4 may contribute to the development of salt-sensitive hypertension.

We have shown that function and expression of TRPV1, a highly homologous channel of TRPV4, are impaired in DS rats, rendering these rats disadvantageous in terms of blood pressure regulation because of the weakening of the protective effect of TRPV1 in the face of salt load. Similar to TRPV1, TRPV4 plays a compensatory role in preventing salt-induced increases in blood pressure in Wistar rats. However, it is unknown whether altered expression and function of TRPV4 constitute a potential molecular mechanism contributing to increased salt sensitivity in a genetically predisposed hypertensive model. Accordingly, the present study was designed to examine this possibility. Blood pressure responses to a selective TRPV4 agonist, 4α-PDD, or a TRPV4 antagonist, ruthenium red (RuR), were assessed with or without blockade of the small- and large-intermediate-conductance Ca2+-activated K+ channels (Maxi channels) with apamin and charybdotoxin, respectively, in DS and Dahl-salt resistant (DR) rats fed a low-salt (LS) or high-salt (HS) diet. Previous reports indicate that RuR is an effective blocker of TRPV4 but not TRPV1 in rats, and Maxi channels are likely involved in TRPV4 action. Differential expression and regulation of TRPV4 in the kidney, mesenteric resistance arteries (MAs), and sensory neurons in response to LS or HS intake were also determined in DS and DR rats.

Methods
Preparation of Animals and Samples
All of the experiments were approved by the Institutional Animals Care and Use Committee. Experiments were performed using male DR and DS rats (Charles River Laboratory, Wilmington, MA). All of the rats (5 weeks old) housed in the animal facility 1 week before the experiments were randomly assigned to an LS (0.15% of NaCl by weight; Harlan Teklad) or HS (4% of NaCl by weight; Harlan Teklad) diet for 3 weeks and grouped as DRLS, DRHS, DSLS, and DSHS. The rats were anesthetized with ketamine and xylazine (80 and 4 mg/kg, IP, respectively) for implantation of vascular catheters or to normalize protein loading on membranes.

Western Blot Analysis
Membrane proteins were extracted as described previously, and 20 μg of proteins were used for Western blot analysis. The mesenteric arteries from 2 rats were pooled together and used as 1 sample. Western blot analysis was performed with the use of the Blood Pressure Analysis System (Hatteras Instruments) before dietary treatment and at the end of each week after dietary treatment.

To examine the effectiveness of RuR in blockade of TRPV4 but not TRPV1, rats were IV injected with 30 μg/kg of DHC, a selective TRPV4 agonist, alone or in combination with 3 mg/kg of RuR. The dose of DHC was chosen on the basis of previous studies showing specific and effective activation of TRPV4. DHC was administered 20 minutes after intravenous injection of RuR. In light of the fact that DHC is an irritant and causes pain in conscious rats, this protocol was performed under anesthesia, as described above.

MAP Responses to TRPV4 Blockade Alone
To determine whether blockade of TRPV4 conveyed significant changes in MAP, rats were subjected to IV injection of RuR at 3 mg/kg. Baseline MAP and its response to RuR were obtained 3 hours after surgery with the rats fully awake and unrestrained.

Immunohistochemistry
MAs were placed in liquid nitrogen and embedded in OTC compound. Freshly frozen samples were sectioned at 20 μm on a Leica CM1850 Cryostat (Leica Microsystems Inc), placed on 3-aminoethoxy silane–coated slides, fixed in acetone for 15 minutes, washed in saline, incubated in 0.1% Triton X-100 in PBS for 20 minutes, and then incubated in 5% sheep serum (Chemicon International) in PBS for 30 minutes. The sections were subsequently incubated in rabbit antirat TRPV4 (1:200, Alomone Laboratories) for 1 hour at room temperature, washed in PBS, and incubated in goat antirabbit Cy3 (1:50, Jackson ImmunoResearch) for 1 hour at room temperature. The sections were then incubated in alkaline phosphatase–conjugated secondary antibody (Jackson ImmunoResearch) for 1 hour at room temperature. The sections were then washed in PBS and incubated in nitroblue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate (both from Roche) for 20 minutes. The sections were then washed in water and examined. Negative controls were performed by omission of the primary antibody.
temperature. The slides were viewed under a Zeiss Pascal Confocal Laser Scanning Microscope using 543-nm laser. Negative controls from DRHS rats were performed by omission of primary antibodies, which showed no specific immunoreactivity.

**Drugs**

Both 4α-PDD (LC Laboratories) and DHC (Sigma) were dissolved using the same vehicle, that is, ethanol (5% vol/vol), Tween-80 (5% vol/vol), and saline. RuR (Sigma), apamin (Sigma), and charybdo-toxin (Sigma) were dissolved in saline.

**Statistical Analysis**

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

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### Results

**Baseline MAP in DS and DR Rats**

Before dietary treatment, there was no significant difference in systolic blood pressure between DS and DR rats, and HS treatment significantly increased the systolic blood pressure in DS rats compared with DR rats (Figure 1). The increase in systolic blood pressure was confirmed by elevated baseline MAP in conscious DSLS (164±5 mm Hg; P<0.05) compared with DSLS (107±4 mm Hg), DRLS (106±3 mm Hg), and DRHS (110±4 mm Hg) rats, consistent with the fact that blood pressure is sensitive to HS intake in DS rats.

**Effects of TRPV4 Activation in the Presence or Absence of TRPV4 Blockade**

As a selective TRPV4 activator, 2.5 mg/kg of 4α-PDD opened TRPV4 channels and decreased MAP in all 4 of the groups (Figure 2A through 2D). The depressor effect of MAP began at 2 to 3 minutes, reached the lowest points at 4 to 7 minutes, and lasted for 15 to 25 minutes after 4α-PDD administration. The magnitude of the decreases in MAP induced by 4α-PDD was the biggest in DRHS rats (−39±1 mm Hg; P<0.05) and the shallowest in DSLS rats (−14±2 mm Hg; P<0.05) rats compared with DSLS (−30±2 mm Hg) and DRLS (−31±2 mm Hg) rats (Figure 2E), indicating that enhanced TRPV4 function occurs in DR rats fed an HS diet and that diminished function of TRPV4 takes place in DS rats fed an HS diet. IV bolus preadministration of 3 mg/kg of RuR abolished 4α-PDD–induced hypotensive effects in all of the groups (DRLS: −5±3 mm Hg; DRHS: −6±2 mm Hg; DSLS: −5±2 mm Hg; DSHS: −4±2 mm Hg; Figure 2), indicating that RuR is an effective antagonist of TRPV4 in all of the settings.

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**Figure 1.** Time course of systolic blood pressure in conscious DR or DS rats measured by the tail-cuff method. Values are mean±SE (n=5 to 7). *P<0.05 vs the corresponding DSLS group.

**Figure 2.** Responses of MAP to bolus administration of 4α-PDD (2.5 mg/kg, IV) with or without TRPV4 blockade (RuR, 3 mg/kg, IV) in conscious DR or DS rats. A through D, Time course responses of MAP to bolus administration of 4α-PDD with or without RuR in conscious DR or DS rats. E, Peak responses of MAP to bolus administration of 4α-PDD with or without RuR in conscious DR or DS rats. Values are mean±SE (n=4 to 7). *P<0.05 compared with the corresponding 4α-PDD–treated group. †P<0.05 compared with the corresponding DRLS group. ‡P<0.05 compared with the corresponding DSLS group.
Effects of TRPV1 Activation in the Presence or Absence of TRPV4 Blockade

DHC (30 μg/kg, IV), a selective TRPV1 agonist, evoked a triphasic MAP response and reached the lowest points 1 to 3 minutes after its administration, consistent with the previous reports. The degree of the decreases in MAP induced by DHC was greater in DRHS rats compared with DRLS, DSLS, or DSHS rats (Table 1). RuR (3 mg/kg, IV) weakly but significantly attenuated the depressor effect of DHC in DRHS and DSHS rats, indicating somewhat attenuated function of TRPV1 by RuR under certain conditions (Table 1).

Effects of Blockade of TRPV4

In response to IV bolus administration of 3 mg/kg of RuR, MAP elevated immediately and reached the peak 2 to 5 minutes after administration in all of the groups (Figure 3). The pressor effect of RuR lasted for 15 to 20 minutes. Changes of MAP were bigger in DRHS (15 ± 2 mm Hg; P < 0.05) rats compared with the other 3 groups (DRLS: 7 ± 1 mm Hg; DSLS: 7 ± 1 mm Hg; DSHS: 4 ± 2 mm Hg), indicating that TRPV4 plays a compensatory role in preventing salt-induced elevation of blood pressure in DR rats and that this counterbalancing effect of TRPV4 is impaired in DS rats.

Expression and Regulation of TRPV4 in the Kidney, DRG, and MA

A clear single band representing TRPV4 protein was observed by Western blot analysis. The data showed that HS treatment decreased TRPV4 expression in the kidneys of DS rats (renal cortex: DSLS: 0.509 ± 0.035% versus DSHS, 0.355 ± 0.020% of β-actin arbitrary, P < 0.05; renal medulla: DSLS: 0.341 ± 0.047% versus DSHS, 0.114 ± 0.020% of β-actin arbitrary, P < 0.05), but it had no effect in the kidneys of DR rats (renal cortex: DRLS: 0.563 ± 0.034% versus DRHS, 0.581 ± 0.024% of β-actin arbitrary, P > 0.05; renal medulla: DRLS: 0.441 ± 0.017% versus DRHS, 0.451 ± 0.040% of β-actin arbitrary, P > 0.05). In DRG (Figure 5), HS treatment enhanced TRPV4 expression in DR rats (DRLS: 0.284 ± 0.041% versus DRHS, 0.673 ± 0.058% of β-actin arbitrary; P < 0.05) but decreased TRPV4 expression in DS rats (DSLS: 0.518 ± 0.012% versus DSHS, 0.220 ± 0.046% of β-actin arbitrary; P < 0.05). In the MA (Figure 5), HS treatment enhanced TRPV4 expression in both DR (DRLS: 0.108 ± 0.011% versus DRHS, 0.173 ± 0.013% of β-actin arbitrary; P < 0.05) and DS (DSLS: 0.164 ± 0.022% versus DSHS: 0.034% of β-actin arbitrary; P < 0.05 compared with the corresponding DHC-treated group. Absence of TRPV4 Blockade

Table 1. Effects of DHC on MAP in the Presence or Absence of TRPV4 Blockade in Pentobarbital-Anesthetized DR or DS Rats Fed an LS or HS Diet for 3 Weeks

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Change of MAP, mm Hg</th>
<th>DRLS</th>
<th>DRHS</th>
<th>DSLS</th>
<th>DSHS</th>
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</thead>
<tbody>
<tr>
<td>DHC</td>
<td>−28 ± 3</td>
<td>−39 ± 3*</td>
<td>−28 ± 4</td>
<td>−27 ± 1</td>
<td></td>
</tr>
<tr>
<td>RuR + DHC</td>
<td>−21 ± 2</td>
<td>−31 ± 1†</td>
<td>−22 ± 1</td>
<td>−23 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE (n = 4 to 5).

*P < 0.05 compared with the corresponding DRLS group.
†P < 0.05 compared with the corresponding DHC-treated group.

Effects of TRPV4 Activation in the Presence or Absence of Blockade of Maxi Channels

Blockade of Maxi channels with combinational administration of apamin (100 μg/kg, IV) and charybdotoxin (100 μg/kg, IV) blocked 4α-PDD–induced hypotensive effects in all of the groups (DRLS: −10 ± 1 mm Hg; DRHS: −13 ± 2 mm Hg; DSLS: −10 ± 2 mm Hg; DSHS: −7 ± 2 mm Hg, and the 4α-PDD alone groups were the same as in Figure 2). These results indicate a key role of Maxi channels in TRPV4-mediated hypotensive effects (Figure 7).
Discussion

This study was designed to test the hypothesis that impaired function and expression of TRPV4 channels occur in DS rats in the face of salt load, which contributes to the development of hypertension in this genetically predisposed strain that mimics human salt-sensitive hypertension. Our data show the following: (1) activation of TRPV4 conveys a similar degree of depressor effects in DR and DS rats on an LS diet, and the depressor effect of TRPV4 is enhanced in DR but diminished in DS rats in response to HS intake; (2) baseline blood pressure is markedly elevated in DR but not DS rats fed an HS diet when TRPV4 is blocked; (3) TRPV4 is differentially regulated in DR and DS rats by salt, that is, HS intake upregulates or maintains a steady state of TRPV4 expression in DRG and the renal cortex/medulla, respectively, in DR rats, whereas HS diet when TRPV4 is blocked; (4) blockade of the Maxi channels impedes the hypotensive effects induced by 4α-PDD in DR and DS rats fed an LS or HS diet. Taken together, these data show for the first time that TRPV4 function and expression are suppressed in response to salt load in DS rats, which may serve as a potential mechanism underlying increased salt sensitivity of arterial pressure in DS rats.

Although 4α-PDD is a potent hypotensive agent via its known effects on opening TRPV4 channels, it may also weakly activate TRPV1. However, the depressor effects of 4α-PDD are predominantly mediated by activation of TRPV4 but not TRPV1 at the dose used in the present study given that blockade of TRPV4 but not TRPV1 abolishes 4α-PDD-induced hypotensive effects. TRPV4 has been showed to be extensively expressed in smooth muscle cells and endothelial cells of blood vessels and can be activated by various endogenous vasoactive agents, including endocannabinoids, arachidonic acid, and its metabolite epoxyeicosatrienoic acids, leading to vasodilation or vasoconstriction depending on specific vascular beds. Interestingly, activation of TRPV4 conveys a similar degree of depressor effects in DR and DS rats fed an LS diet, indicating that TRPV4 function is intact in DS rats without salt challenge. In contrast, TRPV4 function is altered in an opposite direction in DR and DS rats in response to salt load, that is, the depressor effect of TRPV4 is enhanced in DR but diminished in DS rats in response to HS intake. These results may have at least the following implications. First, enhanced TRPV4 function in DR rats may be a compensatory response to HS intake to counteract salt-
induced increases in blood pressure. On the other hand, diminished TRPV4 function occurs in DS rats in response to salt load, indicating that there may be a genetic predisposition of salt-induced impairment of TRPV4 contributing to increased salt sensitivity of arterial pressure in this strain.

Given the lack of highly specific TRPV4 antagonists, RuR has been used as a pharmacological tool to block TRPV4. The specific issue relevant to the present study is the fact that TRPV4 coexpresses with TRPV1, a known cardiovascular regulator. Therefore, specificity of RuR was examined. Our results show that RuR abolishes the hypotensive effects induced by 4α-PDD in both DR and DS rats fed an LS or HS diet but only weakly attenuates DHC-induced depressor effects in DR rats fed an HS diet. These results indicate that blockade of 4α-PDD–induced hypotension by RuR is mainly mediated by antagonizing TRPV4 instead of TRPV1, a result consistent with previous reports.

Direct examination of protein expression of TRPV4 reveals differential expression in DR and DS rats, which may underlie distinct functional responses of TRPV4 in DR and DS rats fed an HS diet. HS intake upregulates or maintains a steady state of TRPV4 expression in sensory neurons or the renal cortex/medulla, respectively, in DR rats, whereas HS intake downregulates TRPV4 expression in sensory neurons and the renal cortex/medulla in DS rats. Thus, it is conceivable that upregulated TRPV4 expression leads to robust depressor effects in response to 4α-PDD–induced activation of TRPV4, whereas blockade of TRPV4 with RuR elevates baseline MAP in DR rats fed an HS diet. In contrast, suppressed TRPV4 expression results in dim or a lack of responses of blood pressure when TRPV4 is activated or blocked in DS rats on an HS diet. Interestingly, HS intake upregulates TRPV4 expression in mesenteric arteries, especially in endothelial cells of these vessels in both DR and DS rats, indicating that HS-induced impairment in TRPV4 expression in DS rats is tissue specific. Furthermore, whereas DOCA-salt–hypertensive rats have similar blood pressure as that of DS rats on an HS diet, TRPV4 expression in sensory neurons, kidneys, or MAs is not altered by DOCA-salt treatment. Theses results indicate that salt-induced impairment in TRPV4 expression in DS rats is model specific and that abnormalities in TRPV4 expression may not be the consequence but potentially the cause of elevated blood pressure in DS rats. Moreover, the lack of elevated TRPV4 expression in DOCA salt rats may contribute, at least in part, to increased blood pressure, given that compensatory upregulation of TRPV4 appears to prevent salt-induced increases in blood pressure in DR rats or Wistar rats.

<table>
<thead>
<tr>
<th>Tissues Examined</th>
<th>Sprague-Dawley</th>
<th>DOCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cortex</td>
<td>0.741±0.035</td>
<td>0.894±0.075</td>
</tr>
<tr>
<td>Renal medulla</td>
<td>0.401±0.040</td>
<td>0.417±0.046</td>
</tr>
<tr>
<td>DRG</td>
<td>0.433±0.056</td>
<td>0.385±0.023</td>
</tr>
<tr>
<td>MA</td>
<td>0.860±0.055</td>
<td>1.009±0.054</td>
</tr>
</tbody>
</table>

Values are mean±SE (n=4 to 5).

To determine the potential downstream pathway(s) mediating TRPV4 action in DR and DS rats, Maxi channel function was examined. Vascular responses to TRPV4 activation are mainly mediated by endothelium-derived hyperpolarizing factors (EDHFs). EDHF opens Maxi channels, leading to hyperpolarization of endothelial cells and the subsequent vasodilation. We have recently studied the relation between TRPV4 and EDHF in Wistar rats by using inhibitors specific for 3 major endothelium-dependent pathways, including indomethacin, Nω-nitro-arginine, and combination of apamin and charybdotoxin, to block the 4α-PDD–induced depressor effect. The results showed that administration of apamin plus charybdotoxin inhibits the hypotensive effect induced by TRPV4 activation in DR and DS rats, indicating that TRPV4-mediated depressor effects are largely endothelium- and Maxi channel–dependent. Endothelial dysfunction, known
to occur in DS rats as well as other salt-dependent hypertensive models, including DOCA-salt hypertensive rats, has been linked to impaired EDHF-induced vasodilatation. EDHF-induced vasodilatation is particularly critical in resistance arteries, making EDHF a key determinant in controlling vascular resistance. Decreased generation of EDHFs has also been shown to contribute to impairment of endothelium-dependent vasodilatation in hypertension. Thus, impaired endothelial function with disturbed EDHF release and/or action would lead to diminished function of Maxi channels.

Taking together previous results on TRPV1 with the data presented in the current study, there are similarities and differences in the function and expression between TRPV1 and TRPV4 in DR and DS rats. HS intake upregulates TRPV1 in kidneys and MAs and TRPV4 in sensory neurons in DR rats, leading to augmented depressor effects when these channels are blocked. On the other hand, HS intake suppresses TRPV1 in kidneys and mesenteric arteries and TRPV4 in kidneys and sensory neurons in DS rats, resulting in attenuated depressor effects when these channels are activated, which may constitute an impaired compensatory mechanism in the face of salt load. Although TRPV1-mediated vasodilatation appears to be largely CGRP dependent, TRPV4-induced hypotension is likely mediated by the activation of Maxi channels.

Perspectives

With more than half of hypertensives being salt sensitive, increased attention to strategies that target specifically in reducing salt sensitivity, particularly in high-risk individuals, is urgently needed. It has been reported that salt intake restriction decreases systolic and diastolic blood pressures in both hypertensive and normotensive individuals, with a bigger magnitude in the hypertensive group. However, the molecular mechanisms underlying salt-dependent regulation of blood pressure remain to be defined. Several powerful endocrine/paracrine/autocrine systems or factors have been implicated to be involved, which include but are not limited to the renin-angiotensin system, the endothelin system, transforming growth factor-β, nuclear factor-κB, and TRPV1.

The data from the present study provide further evidence that salt intake would enhance TRPV4 expression and function to counterbalance salt-induced elevation in blood pressure in a salt-resistant strain of rats. On the other hand, loss of function of TRPV4, at least in part, occurs in a salt-sensitive strain in response to salt load, which may be a potential molecular mechanism for increased salt sensitivity in this strain. It follows that protecting or enhancing TRPV4 expression and function may be therapeutic in treating salt-dependent hypertension.

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Disclosures

None.

References


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