The long-term regulation of blood pressure rests on renal and nonrenal mechanisms and depends on a delicate balance between vasoconstrictor and vasodilator hormones and humoral agents, as well as those factors that act to increase or decrease renal sodium transport. Hypertension develops when this balance is disrupted and abnormalities in the regulation of ion transport intrinsic and extrinsic to the kidney have been proposed to cause essential hypertension. Pressure natriuresis is a key component in the regulation of body fluid volume. In all forms of hypertension, there is a shift of the renal pressure natriuresis curve that requires increased arterial pressure to maintain normal sodium and water balance.

The genetic causes of essential hypertension have been difficult to identify. More than one gene is undoubtedly involved because Mendelian dominant and recessive traits are not readily discernible in hypertensive subjects, except in those rare cases of monogenic hypertension. Moreover, in hypertensive persons, it is likely that risk-predisposing genes are engaged in a complex network of gene–gene and gene–environment interactions.1 2

High salt (NaCl) consumption contributes to the development of hypertension and is considered to be an independent risk factor for vascular remodeling, cardiac hypertrophy, and stroke. Salt sensitivity is defined as a fall in blood pressure during salt restriction and a rise during salt repletion/supplementation.3 Salt sensitivity and resistance have a large variety of determinants, including genetic factors, race/ethnicity, age, body mass, and diet. Hypertension and salt sensitivity of blood pressure are 2 conditions of which the etiologies are still elusive because of the complex influences of genes, environment, and behavior.

Recently, the transient receptor potential vanilloid 1, or TRPV1, has been identified as a factor having a role in the complex response to increases in salt intake. TRPV1 belongs to the transient receptor potential superfamily of nonselective cation channels with relatively low Ca2+ selectivity over Na+, that are expressed in a variety of tissues, including the nervous and cardiovascular systems, the kidney, and the liver.4 TRPV1 receptors are located in primary sensory neurons with cell bodies in the dorsal root and trigeminal ganglia, which coexpress sensory neuropeptides, including substance P and calcitonin gene–related peptide (CGRP).

Importantly, their fibers innervate all vascular beds, including those in kidney and heart, among other organs. Activation of TRPV1 by vanilloids, heat, PIP2, H+, and anandamide, the endogenous ligand of the cannabinoid receptor CB1, elicits electric signals reaching the central nervous system as well as facilitates the release of CGRP and substance P from peripheral nerve endings, resulting in potent vasodilation in many vascular beds. Extensive work by Wang et al5 demonstrated a novel role, mediated by TRPV1 receptors, of sensory nerves in regulating blood pressure homeostasis as well as the interaction between sensory nerves and neurohormonal systems controlling blood pressure, including the sympathetic nervous system, the renin-angiotensin system, endothelin, and oxidative stress. Using several models, evidence has been gathered supporting the notion that affrent renal nerves are important in preventing salt-induced increases in blood pressure by mechanisms that include direct regulation of sympathetic nerve activity at the level of the spinal cord and thus modulation of cardiovascular function, and CGRP inhibition of sympathetic tone.6 7

In this issue of Hypertension, Gao et al8 report on their identification of TRPV4 as another receptor belonging to the vanilloid subfamily of transient receptor potential channels that is also involved in blood pressure regulation. TRPV4 is activated by physical and chemical stimuli, including osmolarity, heat, mechanical stimulation, 4α-phorbol ester derivatives, and endogenous lipids such as endocannabinoids that promote channel opening by distinct pathways. It is expressed in the endothelium, where it contributes to intracellular Ca2+ homeostasis and regulation of cell volume, and in a variety of tissues of the cardiovascular system or related to cardiovascular regulation. They show that activation of TRPV4 decreases blood pressure in rats fed a normal-salt diet and had a more marked effect in rats on a high-salt diet. Conversely, administration of a TRPV4 channel blocker that increases blood pressure in rats on a normal-salt diet has a greater effect in animals fed a high-salt diet. In an elegant experiment, the authors effectively reduced TRVP4 expression in sensory neurons and mesenteric arteries using TRPV4 small hairpin RNA (shRNA), resulting in the attenuation of the depressor effects of channel activation.

These results provide the first evidence of a previously unknown role of TRPV4 in cardiovascular function and blood pressure regulation during salt loading. In particular, these studies indicate a possible role of TRPV4 in salt-sensitive hypertension, suggesting that TRPV4 functions as part of the compensatory mechanisms operative in the regulation of salt-induced elevations in blood pressure, probably by mediating depressor effects through both TRPV4-mediated sensory neuropeptide release and TRPV4-mediated nitric oxide–dependent vasorelaxation.9 One other
interesting suggestion of this study is that of an interaction between TRPV1 and TRPV4, which is indicated by the effects on CGRP and substance P release, in which both channels seem to participate. Both channels are highly homologous and coexpress in key organs, but their interaction has been difficult to define because of the lack of selective channel blockers.

Most hypertension research has been focused on increases in prohypertensive system activity and much less on the antihypertensive counter-regulatory pathways. Thus, identification of counter-regulatory systems may open venues for development of new therapies. However, regulating TRPV4 channels to modify blood pressure may not be an easy task because it has been reported recently that a potent and selective TRPV4 agonist produces dramatic and complex cardiovascular effects associated with endothelial barrier failure.10

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References


Sensing Salt Intake
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In the version of the editorial commentary, “Sensing Salt Intake,” by Armando and Jose that was posted online on December 15, 2008 (DOI: 10.1161/HYPERTENSIONAHA.108.125310), an error occurred. The title of the article should be “Sensing Salt Intake” rather than “Sensoring Salt Intake.” The error is corrected in the current online version and the final version of the article published in the February 2009 issue. (Armando I, Jose PA. Sensing salt intake. Hypertension. 2009;53:118–119.)

The publisher regrets the error.