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TRPV in hypertension, inflammation, and end organ damage: an imminent target of therapy for cardiovascular disease?

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Abstract

Purpose of review—The possible role of several neurohormonal factors in pathogenesis of hypertension has been studied extensively both in humans and experimental animal models. However, controversial data from some of previous studies are indecisive and call for reassessment and development of new targets. This mini-review presents some of the most recent findings about the role of transient receptor potential vanilloid type 1 (TRPV1) channels in development of hypertension and its pathology.

Recent findings—TRPV1, activated by novel endovanilloids or altered pH, temperature, and/or local hemodynamics, may serve as a distinct molecular sensor detecting sodium and water balance and may play a role in preventing salt-induced hypertension and tissue damage. Impairment of the TRPV1 system may contribute to increased salt sensitivity, inflammation, and end organ damage.

Summary—Emerging evidence indicates that TRPV1 plays a key role in cardiovascular health and disease by acting as a sensor and regulator of cardiovascular homeostasis and a protector against cardiovascular injury. Given the huge population who suffers from cardiovascular disease, the study of the TRPV1 system may improve our understanding of pathogenesis of several common cardiovascular disorders and may lead to development of therapy for hypertension, inflammation, and organ damage.

Keywords

transient receptor potential channels; endovanilloids; hypertension; renal injury; myocardial infarction; inflammation

Introduction

The recently discovered transient receptor potential (TRP) superfamily of ion channels, especially the TRPV (vanilloid) subfamily, is intimately involved in a broad array of sensory pathways and respond to environmental stimuli including altered pH, temperature, mechanical and osmotic stress, intra- and extracellular messengers, as well as altered levels of lipid metabolites. All of these changes may involve or result in cardiovascular regulation. This mini-review focuses on the most recent findings about the role of TRPV1 in cardiovascular health and disease, with highlights on TRPV1 as a sensor and regulator of cardiovascular homeostasis and a protector against cardiovascular injury.

Characterization of TRPV1

The TRPV subfamily, consisting TRPV1-6, has been implicated in thermosensation (TRPV1-4) [1], osmosensation (TRPV4) [2], and calcium reabsorption in the kidney and the gastrointestinal tract (TRPV5, 6) [3]. In addition to well recognized roles in pain- and thermosensation [4,5], TRPV1 participates in apoptosis [6], regulation of bladder function [7], taste [8], and neurogenic inflammation [9]. Emerging evidence shows that TRPV1 also plays a key role in the regulation of salt and water homeostasis and blood pressure [10–14].

TRPV1 is mainly localized to primary sensory neurons in the dorsal root ganglia (DRG) as well as in the trigeminal and nodose ganglia [4]. These primary afferent neurons co-express sensory neuropeptides including trkA, IB4, substance P (SP), and/or calcitonin gene-related peptide (CGRP) among others, and their myelinated A δ fibers or unmyelinated C fibers innervate a wide variety of tissues including virtually all vascular beds. [15–19]. In rats, TRPV1 protein and/or mRNA have been detected in the kidney [20], bladder [21], urothelium [21, 22], heart [23,24], stomach [25], mast cells [26], pulmonary arterial and aortic smooth muscle [27], spleen and CNS [20]. In humans, TRPV1 expression was found in epidermal keratinocytes [28,29], mast cells [30], epithelial cells of hair follicle [29], sweat glands [29], sebaceous glands [29], bladder urothelium [31], kidney [32], cerebral cortex [32], cerebellum [32], and hypothalamus [33] among others. The ever growing list of organs and tissues expressing TRPV1 has led to the discovery of novel functions of this channel that has wide implications for health and disease [29,34,35].

TRPV1 is a polymodal integrator of noxious stimuli and can be activated by numerous biological or synthetic compounds or modalities that may be categorized to three classes including receptor-induced activation, ligand-induced activation, and direct activation [36]. Receptor-induced activation refers to the activation of isoforms of phospholipase C through the activity of G-protein coupled receptors and receptor tyrosine-kinases. As a result, phosphatidylinositol-4,5-bisphosphate (PIP₂) is hydrolyzed into diacylglycerol and inositol-3,4,5-trisphosphate (IP₃), products which can modulate TRPV1 function. Furthermore, specific isoforms of PKA and PKC are activated that can modulate the channel's status through phosphorylation events [37–53]. For example, ATP potentiates TRPV1 activity through its interaction with P2Y receptors in a PKC-dependent pathway [54]. Ligand-induced activation, the most commonly studied form of activation of TRPV1 proteins, refers to the binding of either exogenous or endogenous small organic molecules, inorganic ions (such as H⁺), or products of lipid or nucleotide metabolism to the channel (either extra- or intracellularly) in a way that causes a conformational change in the channel that opens the pore to allow influx of cations [54–77]. Finally, direct activation refers to mechanical stimuli or changes in temperature ($\geq 43^{\circ}\text{C}$) [4,75].

Capsaicin and anandamide (arachidonoyl ethanolamide), a vanilloid-like compound that is a potent agonist at the TRPV1 receptor, have been most widely studied and used in the biochemical and pharmacological characterization of TRPV1 [56–60]. Many other ligands have been discovered or synthesized that are activators of TRPV1. These include but are not limited to methanandamide [61,62], N-arachidonoyl-dopamine (NADA) [63,64], resiniferatoxin (RTX), rinvanil and its derivatives [65], 2-aminoethoxydiphenyl borate (2-APB) [66,67], the peripheral satiety factor oleoylethanolamide [68], N-Oleoylethanolamine [69], ethanol [70–72], as well as several lipoxygenase products [73]: 12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, 15-(S)-HETE, leukotriene B₄, and a cytochrome P450 product 20-HETE [74].

A class of compounds that is known to inhibit TRPV1 channel activation includes capsazepine and ruthenium red (RR) [78], as well as the high-affinity iodo-resiniferatoxin [79], thiazole

carboxamides [80], A-425619 [81,82], AMG 9810 [83], and N-Acylvanillamines such as arvanil [84]. These compounds or newer classes of agonists or antagonists of TRPV1 yet to be developed may confer therapeutic potentials once the role of TRPV1 is better understood.

TRPV1 as a Sensor in Cardiovascular Health

TRPV1 has been implicated in many aspects of physiological regulation as well as in cardiovascular regulation [10–14,85–117]. Given the complex interplay of neurohormonal systems in vivo, it is currently uncertain as to how stresses, such as rises in sodium intake or intraluminal pressure, lead to activation of TRPV1. Thus it is of great interest to understand how the receptor senses the chemical and mechanical environment in the vasculature and kidney and integrates altered environmental stimuli to lead to cardiovascular protection.

If TRPV1 may act as a sensor, the question remains as to what are the endogenous ligands in the CNS and peripheral sites that TRPV1 detects. Several endogenous candidates have been identified including anandamide, lipoxygenase and cytochrome P450 products of arachidonic acid, and N-arachidonoyldopamine [74,118]. We have shown that high salt intake increases plasma anandamide levels analyzed by liquid chromatography/electrospray tandem mass spectrometry and that blockade of the TRPV1 increases mean arterial pressure in high salt treated rats, indicating that TRPV1 may act as a molecular target for salt-induced elevation of endovanilloid compounds to regulate blood pressure [112**]. Future studies would be fruitful if focusing on determining the roles of each endogenous ligands of TRPV1 in the pathophysiological state, a process which in all likelihood will lead to the discovery of new candidates for endogenous activation of TRPV1.

It is inconclusive and seemingly controversial in terms of the role of TRPV1 as a mechanosensor. No evidence is available supporting the direct activation of TRPV1 via sheer stress generated by the flow in the lumen of blood vessels. However, TRPV1 may be activated indirectly by altered transmural pressure through the production of 20-hydroxyeicosatetraenoic acid (20-HETE), a known activator of TRPV1 that causes the release of SP when it binds to the TRPV1 expressed on sensory C-fibers [74]. TRPV1 may act as a mechanoreceptor and causes SP release and sensory activation in rat kidneys considering the fact that blockade of TRPV1 in the renal pelvis prevents intrapelvic pressure (at 20 mmHg but not 50 mmHg)-dependent activation of afferent renal nerve activity and diuresis/natriuresis [119**]. The absence of TRPV1 in the urothelium inhibits mechanically evoked purinergic signaling given the fact that bladder urothelial cells from wild type but not TRPV1 null mice respond to a hypotonic stimulus with a release of ATP [120]. It may also be possible that TRPV1 coassembles with distinct mechanosensitive TRPV subtypes or other proteins in the bladder [16]. In contrast to the peripheral response in which TRPV1 seems to be activated by the hypotonic stimulus, TRPV1 expressed in the CNS has an antidiuresis effect by triggering the release of arginine-vasopressin (AVP) in response to serum hyperosmolality [121]. AVP-releasing neurons in the supraoptic nucleus (SON) of the hypothalamus of wild type but not TRPV1 knockout mice shrink in response to a hyperosmotic stimulus, activating a stretch-inhibited osmosensory transduction channel [122]. This would lead to depolarization that contributes to cellular excitation and AVP release.

TRPV1 and Renal Excretory Function

In addition to the afferent function, TRPV1-positive neurons also have an efferent motor function. Binding of agonists to TRPV1 causes the opening of the cation channel that leads to the influx of sodium and calcium ions [123–127]. While sodium influx is high enough to depolarize the neuron and lead to an afferent impulse conduction, calcium influx is required for the release of neuropeptides from sensory nerve endings [88,128]. At least 12 different types of transmitters have been identified in TRPV1-positive sensory neurons that can be

released alone or with other peptides. These neuropeptides include SP, neurokinin A, neuropeptide K, eledoisin-like peptide, somatostatin, vasoactive intestinal polypeptide, cholecystikinin-octapeptide, CGRP, galanin, corticotrophin-releasing factor, arginine vasopressin, and bombesin-like peptides [128].

TRPV1 activation by local and/or systemic chemical (e.g., changes in concentrations of ions or endocrine/paracrine/autocrine factors) or mechanical (e.g. changes in pressure) stimuli may cause the release of neuropeptides such as SP and CGRP to mediate a response. SP and CGRP have been shown to have direct and indirect effects on tubular ion transport in the kidney, likely contributing to natriuretic and diuretic actions [129–132]. Moreover, there appears to have a cross-talk between TRPV1, neurokinin 1 (NK1) receptors, and CGRP receptors to regulate afferent renal nerve activity. Our data showed that NK1 activation induced by SP release upon TRPV1 activation governs TRPV1-mediated increases in afferent renal nerve activity and natriuresis, whereas CGRP action is TRPV1-dependent [111**]

Degeneration of TRPV1-positive sensory nerves accompanying with depletion of sensory neurotransmitters inhibited natriuresis and increased blood pressure in rats fed a high salt diet [10,86–90,96–100,104,105], indicating that TRPV1 and/or sensory neuropeptides normally function to increase natriuresis and diuresis in response to high salt intake. Indeed, our subsequent studies indicate that TRPV1 present in a subpopulation of sensory nerves innervating the kidney is responsible for capsaicin-induced diuresis and natriuresis when capsaicin was administered into the renal pelvis [91].

Several TRPV1 splice variants have been isolated in mouse and rat models that can modulate TRPV1-mediated responses to environmental stimuli. A novel splice variant has recently been discovered in the rat renal papilla that could add another point of regulation to the TRPV1-mediated response to a salt load [85]. Our recent data also showed that TRPV1 mediates diuresis and natriuresis induced by hypertonic saline perfusion into the renal pelvis via increasing the activity of afferent renal nerve activity, indicating that TRPV1 may indeed serve as a sensor detecting microenvironmental changes in the renal pelvis to modulate renal function [113*]. The TRPV1-induced sodium and water excretion appears to be mediated by increases in glomerular filtration rate 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 [109, 114].

TRPV1 and Increased Salt Sensitivity

Salt sensitivity is present in over 50% of essential hypertensive patients, and is more prevalent among African Americans, obese and elderly patients, and patients with renal insufficiency or diabetes. Although the participation of several neurohormonal systems has been extensively studied, the mechanism responsible for increased salt sensitivity has yet to be defined. We have conducted a series studies presented below to elucidate whether a dysfunctional TRPV1 system may contribute to increased salt sensitivity.

Degeneration of TRPV1-positive sensory nerves rendered a rat salt-sensitive with impaired natriuretic and diuretic response along with an increase in blood pressure [10]. Losartan (a type 1 angiotensin II receptor blocker) prevented the development of salt-induced hypertension in this model [86], suggesting that the renin-angiotensin-aldosterone system (RAAS) may be hyperactive in this model and that TRPV1-positive sensory nerves may normally suppress RAAS activity [86,96,97]. Furthermore, it appeared that the sympathetic nervous system [87], the endothelin system [98,99], or oxidative stress generation [100,104] became more active upon sensory denervation plus high salt intake, suggesting that TRPV1 may play a counterbalancing role in inhibiting these prohypertensive systems.

Activation of TRPV1 by an exogenous agonist, capsaicin, led to an increase in plasma CGRP levels and a decrease in MAP, which were blocked by capsazepine [92,93]. TRPV1 mediated at least in part the depressor effect of anandamide, an endogenous agonist, in normotensive or spontaneously hypertensive rats [94,103]. High salt intake upregulated mesenteric and renal medullary TRPV1 expression, and pro-hypertensive effects of salt were unmasked when TRPV1 was blocked by capsazepine in rats fed a high salt diet [92,93]. Depressor responses to *N*-arachidonoyl-dopamine, an endogenous TRPV1 agonist, were enhanced during high salt intake [108]. In genetically predisposed Dahl salt sensitive rats, renal TRPV1 expression decreased in response to high salt intake while an increase in renal TRPV1 content was found in Dahl salt resistant rats fed a high salt diet [95]. As a result, blockade of TRPV1 rendered a Dahl salt resistant rat salt sensitive while Dahl salt sensitive rats were unresponsive, indicating that activation of TRPV1 during high salt intake may prevent salt-induced increases in blood pressure and that impairment in the TRPV1 system may contribute to increased salt sensitivity.

TRPV1 and Inflammation

The inflammatory process is present at various stages of hypertension that may eventually develop into end organ or tissue damage, and TRPV1 may play a key role in mediating the inflammatory process. Activation of TRPV1 stimulated release of inflammatory cytokines in a human bronchial epithelial cell line and corneal epithelium through MAPK signalling [133, 134]. On the other hand, the inflammatory mediators may modulate TRPV1 sensitivity through both PKC-dependent and independent pathways [42]. Inflammatory mediators including nerve growth factor (NGF), bradykinin, and the proinflammatory cytokine IL-1 β contribute to TRPV1-mediated inflammatory hyperalgesia via PKC-dependent pathways [45–47]. Furthermore, PLC-dependent potentiation of TRPV1 is based upon a PIP₂ binding site on the C-terminus of TRPV1 relieving TRPV1 from PIP₂-mediate inhibition [43].

Additional forms of regulation of TRPV1 includes enhanced gating of TRPV1 by prostaglandin E₂ via the cAMP-PKA signaling pathway [48], TRPV1 sensitization by a proinflammatory chemokine, CCL3 [135], increased expression of TRPV1 receptors as mediated by the inflammatory mediators ATP, bradykinin, and NGF [136], the regulation of the oxidation state of key cysteine residues on the extracellular side of TRPV1 by dithiothreitol [137], and the upregulation of TRPV1 mRNA expression by neurotrophic factors [17].

As a result of this complex web of regulatory mechanisms there is tremendous potential for future study into how these systems interact in many physiological and pathophysiological states. Further complication relating to effects of sensory neuropeptides released upon TRPV1 activation on inflammation may impose additional challenge. Our recently data show that TRPV1 plays a protective role against endotoxin-induced hypotension and mortality in rats via the release of SP and CGRP [110*].

TRPV1 and End Organ Damage

One of devastating consequences of hypertension is end organ damage, which includes renal failure, myocardial ischemia or hypertrophy, stroke, and vascular damage. Moreover, salt sensitive subpopulations are particularly susceptible to detrimental effects of salt on organ damage that may be independent of or in addition to elevated blood pressure. Recently data suggest that TRPV1 may play a role in protecting tissues or organs from damage.

Our data showed that vasodilation in response to perivascular nerve stimulation in mesenteric arteries of TRPV1-null mutant mice was impaired, indicating that TRPV1 plays a key role in modulating perivascular sensory nerve-mediated vasodilation [102]. *N*-oleoyldopamine, a novel endogenous capsaicin-like lipid, played a protective role in the heart against ischemia-reperfusion injury via activation of TRPV1 [116]. TRPV1 gene knockout impaired both

postischemic recovery and preconditioning protection against myocardial injury [101,107**], lending further support that TRPV1 plays a protective role against ischemic injury of the heart. Finally, TRPV1 gene deletion exaggerated renal tissue and functional damage in DOCA-salt hypertension, suggesting that TRPV1 confers protection of the kidney from hypertension- and salt-induced injury [117]

TRPV1 as Targets of Therapy for Cardiovascular Disease

Given the possible involvement of TRPV1 in the pathophysiological states discussed above that involve more than 65 million Americans and 1 billion subjects worldwide who suffer from hypertension and its associated end organ damage, agonism or antagonism of TRPV1 may have enormous therapeutic potential. While much progress has been made in defining the structure, activation, and functional role of TRPV1 in the pathophysiological state, the quest to find safe, effective therapeutics to act at TRPV1 is currently hindered by factors including incomplete understanding of endogenous ligands, complex nature of activation and signalling pathways, divergent central and peripheral effects, and its involvement in multiple pathological states/processes. Better understanding of these issues may shed light on insights of pathologies related to cardiovascular homeostasis and beyond, and may aid the development of therapy targeted on TRPV1 for these disorders.

Conclusion

Accumulating evidence indicates that TRPV1 plays a key role in cardiovascular health and disease by acting as a sensor and regulator of cardiovascular homeostasis and a protector against cardiovascular injury (Figure 1). Given the huge population who suffers from cardiovascular disease, the study of the TRPV1 system may improve our understanding of pathogenesis of several common cardiovascular disorders and may lead to development of therapy for hypertension, inflammation, and organ damage.

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Figure 1.

A putative scheme for the possible pathways discussed in this article. Activation of TRPV1 by chemical or physical stimuli causes the release of the neuropeptides, including CGRP and SP. TRPV1 as well as sensory neuropeptides may inhibit or counter-balance several pro-hypertensive systems to regulate cardiovascular and renal tissue function, resulting in renal and/or extra-renal vasodilatation, anti-hypertension, inhibition of inflammation, and protection of organs from damage. It is unknown whether all of the components in the TRPV1 system or the pro-hypertensive systems may convey/link these effects, and the scheme is a simplified version that intends to depict possible effects and cross-talk between the TRPV1 system and the pro-hypertensive systems. Solid lines represent activation/stimulation; broken lines represent suppression/inhibition. TRPV1, transient receptor potential vanilloid type 1 channels; SP, substance P; CGRP, calcitonin gene-related peptide; SNS, the sympathetic nervous system; RAAS, the renin-angiotensin aldosterone system; ETS, the endothelin system; ROS, reactive oxygen species; BF, blood flow; TPVR, total peripheral vascular resistance; GFR, the glomerular filtration rate; RBF, renal blood flow; RVR, renal vascular resistance;

UNa, urinary sodium excretion; UFR, urinary flow rate; BP, blood pressure; EOD, end organ damage.