Transient Receptor Potential Vanilloid Type 1 Receptors in Hypertensive Renal Damage
A Promising Therapeutic Target?

Tilmann Ditting, Roland Veelken, Karl F. Hilgers

In the development and progression of hypertensive organ damage, hemodynamic factors such as high pressure, turbulent flow, and shear stress are thought to cause endothelial dysfunction and vascular remodeling. Nephrosclerosis may eventually result from a complex cascade of inflammatory and fibrotic processes. Research on novel therapeutic targets has, therefore, focused on regulatory systems that play a significant role for the regulation of blood pressure and volume homeostasis, as well as for modulating inflammation or fibrosis. The autonomic innervation of the kidney may be such a regulatory system but has been difficult to study at the molecular level.

This issue of Hypertension contains a report by Wang et al1 that is an important step forward in that regard. The authors studied the transient receptor potential vanilloid type 1 (TRPV1) receptor, a member of the mammalian transient receptor potential channel superfamily. Transient receptor potential channels mediate the transmembrane flux of cations down their electrochemical gradients, thereby raising intracellular Ca2+ and Na+ concentrations and depolarizing the cell.2 The TRPV1 channel was identified by expression cloning using the hot pepper–derived vallinoid compound capsaicin as a ligand and is, therefore, referred to as the capsaicin or vallinoid receptor. TRPV1 channels are mainly expressed on a subset of primary afferent neurons, with unmyelinated (C-fibers) or thinly myelinated axons (Aδ-fibers). TRPV1 channels are not only sensitive to capsaicin but can be stimulated by thermal, acidic, chemical, or mechanical factors,3 as well as endogenous arachidonic acid derivates, such as anandamide.4

Wang et al1 demonstrated in a mouse model of deoxycorticosterone acetate (DOCA)-salt hypertension that deletion of TRPV1 receptors, using TRPV1-null mutant (TRPV1−/−) mice, exaggerates renal damage. DOCA-salt hypertension led to albuminuria, glomerulosclerosis, tubulointerstitial injury, and fibrosis, all of which were more severe in DOCA-salt–treated TRPV1−/− mice than in TRPV1+/+ mice. Remarkably, TRPV1−/− mice and wild-type controls developed the same degree of hypertension when treated with DOCA-salt. Although the underlying mechanisms by which TRPV1 deletion leads to exaggerated renal damage remain unclear, this important study opens an interesting discussion and warrants further fundamental research work.

The DOCA-salt model is a logical choice for this type of investigation. Inflammation and fibrosis in the kidney are extensive, and there is evidence for an altered function of cardiovascular and afferent nerves.5 An altered function of TRPV1-positive afferent fibers may contribute to the deleterious effects of the TRPV1 deficiency. Transmitter release from TRPV1-positive afferent fibers may occur from terminals in the central nervous system, from terminals distributed in paravertebral ganglia, and from peripheral terminals. Transmitter release at the former 2 sites is essential for the perception of somatic and visceral pain, whereas peripheral release may exert paracrine effects. Importantly, transmitter release from peripheral terminals is not restricted to the particular terminal that was stimulated but may spread to other afferent fibers as well.

Among a multitude of different transmitters that can be released at the nerve endings of capsaicin sensitive neurons, substance P (SP) and calcitonin-gene related peptide (CGRP) stand out. These neuropeptides are involved in the regulation of local perfusion, and there is increasing evidence that either the afferent signal conduction or the neurotransmitter release play a key role in inflammation. In the kidney, CGRP-positive afferent fibers are found in close vicinity to tyrosine-hydroxylase–positive sympathetic efferent nerve fibers, spatially related to macrophages and dendritic cells.6 In a normotensive model of nephritis (anti-Thy1.1), autonomic renal denervation alleviated inflammation and fibrosis.6 This finding is not easy to reconcile with a beneficial effect of TRPV1. On the other hand, the effects of the loss of efferent renal nerve activity may predominate in this situation.

Although the exact role of the afferent fibers and their local effects in kidney tissue remains to be defined, Xie et al7 have recently studied the putative cross-talk between TRPV1 receptors SP and CGRP in the renal pelvis. Activation of TRPV1 receptors in the renal pelvis by capsaicin induces an increase in ipsilateral afferent renal nerve activity and in contralateral renal excretory function. Activation of TRPV1 receptors by capsaicin caused release of SP, CGRP, and other neuropeptides (see Figure). Consecutive SP-induced neurokin-1 receptor activation in the afferent nerve terminals seems to be a prerequisite for the generation and propagation of afferent action potentials.

In contrast, CGRP-induced afferent nerve activity and contralateral renal function enhancement depend on TRPV1 activation, whereas TRPV1 stimulation caused by putative microenvironmental changes may function independent from
CGRP receptors. A similar reflex can be elicited by renal pelvis perfusion with hypertonic saline or increased renal pelvic pressure,\(^3\,8\) indicating that TRPV1 receptors might also contribute in an autocrine manner to the propagation of the afferent signal to the central nervous system where the signal may in turn affect sympathetic nervous system (SNS) activity.

The lack of a blood pressure difference between TRPV1\(^{−/−}\) and wild-type mice with DOCA-salt hypertension is well documented by state-of-the-art radiotelemetry recordings, but this observation is nevertheless surprising. Using a pharmacological approach, Wang and Wang\(^8\) could show previously that TRPV1 receptors might also act as mechanotransducers. However, whether these mechanisms in the renal pelvis really play a role for intrarenal tissue damage caused by hypertension remains open to discussion. Therefore, further investigation of intrarenal TRPV1-positive peptidergic nerves is needed.

In any case, similar levels of arterial blood pressure do not exclude a different hemodynamic load in the glomerulus, and there is evidence that TRPV1 may affect glomerular hemodynamics: Li and Wang\(^9\) demonstrated in an isolated kidney perfusion model that TRPV1 activation by capsaicin leads to increased glomerular filtration while decreasing perfusion pressure. This effect was seen only at higher perfusion pressures >150 mm Hg, when phenylephrine was added to the perfusate, whereas perfusion flow was kept constant but not in the “normotensive” pressure range. These findings indicate that TRPV1 activation might cause greater vasodilation in afferent rather than efferent glomerular arterioles, leading to an increased glomerular filtration rate despite decreased perfusion pressure. Furthermore these TRPV1-mediated effects seem to be of greater importance in the hypertensive state. Thus, despite the same systemic blood pressure in DOCA-salt–treated wild-type and TRPV1\(^{−/−}\) mice, the more severe tissue damage in TRPV1\(^{−/−}\) mice might at least in part be because of the lack of such a TRPV1-mediated and CGRP-dependent vasoregulatory mechanism.

Taken together, the study by Wang et al,\(^1\) published in this issue of Hypertension, and their recent work indicating a critical role of TRPV1 receptors in sensing microenvironmental changes, deserves our best attention, because these findings provide important steps to identify a novel complex paracrine pathway (see Figure) contributing to hypertensive renal organ damage.

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References