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TRPs in the Kidney- Location, Location, Location

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A recent study by Chen et al., featured in this issue of *Acta Physiologica*, may provide the molecular basis for new treatment avenues for acute kidney injury (AKI) by targeting of specific members of the vanilloid (V) transient receptor potential (TRP) subfamily of cation channels (Chen et al., 2014). Maintenance of ideal tissue hemodynamics is vital for organ homeostasis and relies in part on the finely tuned ability of small arteries and arterioles to constrict or dilate in response to changes in perfusion pressure. Pathological states can impair this intrinsic ability, leading to increases in vascular resistance and ischemic injuries. A reduction in blood flow to the kidneys, usually caused by acute hypovolemia, sepsis, surgery and major trauma, can lead to AKI, a disease characterized by rapid loss of kidney function and reduction in glomerular filtration rate (GFR), mainly due to reduction in renal blood flow. AKI is a disease with a high mortality rate, ranging from 40-75%. Impairment of endothelium-dependent dilation of the renal microcirculation, mainly through generation of nitric oxide (NO), is involved in the development of AKI and its progression to chronic kidney disease (Basile and Yoder, 2014). Currently, treatment of AKI consists of pharmacological interventions to mitigate the underlying cause and maintain blood electrolytes values within normal ranges, and dialysis. The findings of Chen and colleagues described in this issue could lead to the development of therapeutics that specifically restore blood flow to the renal pre-glomerular microvasculature during AKI.

Heterogeneous tissue distribution of the members of the TRP channel superfamily is well appreciated, but the study by Chen et al. shows that there is differential activity, likely due to preferential expression, of a single TRP channel, TRPV1, within the renal vascular tree. The authors show that activation of Ca²⁺-permeable TRPV1 channels with capsaicin, a substance derived from hot peppers, dilated vessels in the renal preglomerular microvasculature, characterized by a blunted vascular resistance in isolated perfused kidneys. This effect was inhibited by capsazepine, a selective TRPV1 inhibitor, and was absent from *TRPV1*^{-/-} mice. Interestingly, large conductance renal arteries only dilated to high concentrations of capsaicin, an effect that was still observed in *TRPV1*^{-/-} mice, suggesting TRPV1-independent dilatory mechanisms (Chen et al., 2014). In addition, isolated arterioles from the medullary vasa recta were unresponsive to capsaicin stimulation, strengthening the argument that involvement of TRPV1 in endothelium-dependent dilation is indeed restricted

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CONFLICT OF INTEREST

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to the pre-glomerular renal microcirculation. These novel data compellingly highlight functional heterogeneity of TRP channel activity within the renal vascular tree. Such differential responses may allow the development of tailored therapies aimed at reducing vascular resistance in the renal pre-glomerular microvasculature that will improve renal blood flow and function during AKI.

A second intriguing finding of this study is that TRPV4 channels are functional in all segments of the renal circulation, and that TRPV4 vasodilatory activity seems to be coupled to the generation of NO by the enzyme NO synthase (NOS). These data add another dimension to our current understanding of TRPV4 channels in the regulation of vascular tone. Most studies report the importance of TRPV4 in dilations mediated by endothelium-derived hyperpolarization independent of NO production (Sonkusare et al., 2012, Earley et al., 2009). However, TRPV4 has recently been shown to be important for the rescue of NO production in endothelial cells after hypoxic pre-conditioning both *in vitro* and *in vivo* (Rath et al., 2012), showing its vital role in the organ protective responses facing ischemic injuries. Thus, TRPV4-mediated NO generation could emerge as a prominent drug target for the treatment of AKI.

The present study raises stimulating questions that warrant further investigation. It remains to be determined what genetic factors regulate the selective expression of TRPV1 in the renal pre-glomerular microcirculation, and if this occurs during development or post-development. In addition, it would be interesting to determine if TRPV4 and NOS are located in close proximity, such as that the inflow of Ca^{2+} caused by TRPV4 activity in the form of TRPV4 sparklets (Sullivan et al., 2012, Sonkusare et al., 2012) generate Ca^{2+} microdomains with locally elevated Ca^{2+} concentration that directly activate NOS. It is also possible TRPV4-mediated Ca^{2+} influx causes a global increase in intracellular Ca^{2+} by Ca^{2+} -induced Ca^{2+} release from intracellular stores. It should be noted that TRPV4 is present in membrane caveolae rich in the protein caveolin-1, which is a stereotactic inhibitor of the endothelial NOS (Trane et al., 2014). Unraveling the interplay between TRPV4 and NOS would provide further insight in the intracellular organization of membrane subdomains. Such data would complement recent studies that provide evidence that TRPV4 channels in smooth muscle cells are present in signaling complexes organized by A-kinase anchor protein 150 (AKAP150) allowing activation downstream of G-protein coupled receptors (Mercado et al., 2014). In contrast, the endogenous regulation of TRPV1 channels in the vasculature remains unknown.

In summary, the report by Chen et al. elegantly shows through functional studies using isolated arteries and perfusion of whole kidneys differential functional consequences of TRPV1 and TRPV4 activity in different segments of the renal circulation. Pharmacological activation of TRPV1 may emerge as a promising candidate for treatment of AKI to selectively target the pre-glomerular microcirculation, possibly restoring renal blood flow, GFR and, with them, renal function.

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