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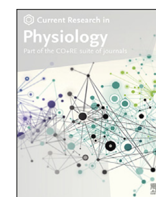
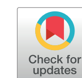


Review Article

Renal vascular TRP channels



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A R T I C L E I N F O

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A B S T R A C T

Members of the transient receptor potential (TRP) channels that are expressed in the kidney have gained prominence in recent years following discoveries of their role in maintaining the integrity of the filtration barrier, regulating tubular reabsorption of Ca^{2+} and Mg^{2+}, and sensing osmotic stimuli. Furthermore, evidence has linked mutations in TRP channels to kidney disease pathophysiological mechanisms, including focal segmental glomerulosclerosis, disturbances in Mg^{2+} homeostasis, and polycystic kidney disease. Several subtypes of TRP channels are expressed in the renal vasculature, from preglomerular arteries and arterioles to the descending vasa recta. Although investigations on the physiological and pathological significance of renal vascular TRP channels are sparse, studies on isolated vessels and cells have suggested their involvement in renal vasoregulation. Renal blood flow (RBF) is an essential determinant of kidney function, including glomerular filtration, water and solute reabsorption, and waste product excretion. Functional alterations in ion channels that are expressed in the endothelium and smooth muscle of renal vessels can modulate renal vascular resistance, arterial pressure, and RBF. Hence, renal vascular TRP channels are potential therapeutic targets for the treatment of kidney disease. This review summarizes the current knowledge of TRP channel expression in renal vasculature and their role in controlling kidney function in health and disease.

1. Introduction

The mammalian transient receptor potential (TRP) channels constitute a diverse superfamily of six-transmembrane, cation-selective ion channels with six major families, namely, TRPA (Ankyrin), TRPC (Canonical), TRPM (Melastatin), TRPV (Vanilloid), TRPP (Polycystin), and TRPML (Mucolipin). TRP channels are widely expressed in mammalian tissues and are activated by a myriad of physiological stimuli, including temperature, mechanical stress, intracellular and extracellular ligands, and redox signaling molecules (Clapham, 2003; Montell, 2005; Pedersen et al., 2005).

Like their nearly ubiquitous presence throughout the body, the TRP channels are widely distributed in mammalian kidneys in glomerular, tubular, and vascular cells (Carlstrom et al., 2015; Chubanov et al., 2017; Tomilin et al., 2016). Glomerular mesangial cells (GMCs) express TRPC channels and modulate cell surface area, proliferation, and survival (Adebiyi, 2014; Graham et al., 2007; Kong et al., 2015; Meng et al., 2014; Soni and Adebiyi, 2016, 2017; Sours et al., 2006; Wang et al., 2004). TRPP1 co-assemble with TRPC1 and TRPC4 and the resultant channel complexes mediate angiotensin II (AngII)-induced Ca^{2+} influx in human GMCs (Du et al., 2008). TRPC5- and TRPC6-mediated Ca^{2+} signal transduction mechanisms regulate podocytes' structure and function (Dryer and Reiser, 2010; Greka and Mundel, 2011, 2012; Staruschenko et al., 2019; Wieder and Greka, 2016). Gain-of-function mutations in TRPC6 result in hereditary glomerulopathy, including focal segmental glomerulosclerosis (Reiser et al., 2005; Winn et al., 2005). Recent studies have also proposed that TRPC5 channels contribute to podocyte derangement in animal models of progressive kidney disease (Schaldecker et al., 2013; Zhou et al., 2017).

TRP channels have been identified in different segments of the nephron. TRPC3 is abundantly expressed in the collecting ducts, colocalizes with aquaporin-2, and trafficked to the apical membrane in response to antidiuretic hormone (Goel et al., 2007, 2010). TRPC3 is a putative candidate for Ca^{2+} reabsorption and osmoregulation in the collecting ducts (Khayyat et al., 2020). Immunofluorescence indicated that TRPM2 is expressed in mouse proximal tubular epithelial cells (Gao et al., 2014). Pharmacological inhibition and genetic ablation of TRPM2 in mice ameliorated NADPH oxidase-dependent acute kidney injury (AKI) (Gao et al., 2014). TRPM3 is expressed in tubular epithelial cells and may contribute to Ca^{2+} homeostasis (Lee et al., 2003). TRPM6/7 control magnesium absorption in the distal convoluted tubule (Schlingmann and Gudermann, 2005). TRPP1 (polycystin-2), co-assembles with

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polycystin-1 (PC1) to form functional cation channels (Hanaoka et al., 2000; Koulen et al., 2002; Mochizuki et al., 1996). PC1 and TRPP1 are required for kidney development (Chauvet et al., 2002; van Adelsberg, 1999). Mutations of PKD1 and PKD2, the genes that encode PC1 and TRPP1, respectively, result in the progressive formation of numerous cysts in the kidney, common in autosomal dominant polycystic kidney disease (ADPKD) (Wilson, 2004). TRPP1 was detected in rat distal convoluted tubules, cortical collecting ducts, proximal tubules, and thick ascending limbs (Zhao et al., 2002). TRPP1 expression levels were increased in all segments of post-ischemic rat nephrons, suggesting that it may contribute to the mechanisms that underpin ischemic AKI (Zhao et al., 2002). Although TRPV1 has been implicated mainly in renal sensory responses, the channels are also expressed in the distal tubule apical membrane and collecting ducts (Feng et al., 2008). TRPV1 colocalizes with α-epithelial sodium channels (αENaC) in mouse cortical collecting ducts (Li et al., 2014). Capsaicin-induced activation of TRPV1 diminished αENaC-mediated sodium reabsorption (Li et al., 2014), but whether this effect alters blood volume and pressure is unclear. TRPV4 channels are abundant in the thin and thick ascending limb of the Loop of Henle and the distal convoluted and connecting tubules of adult mice and rats (Cohen, 2007; Tian et al., 2004). TRPV4-mediated osmoregulation in the kidney has been proposed (Cohen, 2007; Tian et al., 2004). Both TRPV5 and TRPV6 channels are expressed in the epithelial cells of the distal convoluted and connecting tubules (Hoenderop et al., 2001; Nijenhuis et al., 2003), where they control Ca^{2+} reabsorption (Bianco et al., 2007; Hoenderop et al., 2003; Nie et al., 2016; Peng et al., 2018).

Focused reviews on vascular TRP channel function are available (Di and Malik, 2010; Dietrich and Gudermann, 2011; Dietrich et al., 2010; Earley and Brayden, 2015; Jardín et al., 2013; Zholos and Curtis, 2013). However, despite extensive work in the cerebral, pulmonary, and mesenteric blood vessels, only a handful of studies have investigated TRP channels in the renal vascular bed. To the best of our knowledge, no review has yet been published on the role of TRP channels, specifically in the renal vasculature. Since renal vascular resistance controls critical physiological functions, including blood pressure, renal autoregulation, filtration, and electrolyte homeostasis, it is important to understand renal vascular TRP channels' distinctive roles. Therefore, this review aims to discuss the current knowledge of the expression and function of renal vascular TRP channels in health and disease.

2. Renal vascular TRPC channels

Expression of TRPC channels in renal vasculature. The TRPC family of the TRP channels is formed by seven mammalian members (TRPC1-7). RT-PCR indicated that TRPC1, TRPC3, TRPC4, TRPC5, and TRPC6 are expressed in rat preglomerular vessels (Facemire et al., 2004). However, only TRPC3, TRPC4, TRPC6, and TRPC7 mRNAs were found in SMCs isolated from canine renal arteries (Walker et al., 2001). TRPC3 mRNA expression level is ~ 3-fold more than TRPC1, TRPC5, and TRPC6 in rat renal microvessels (Facemire et al., 2004). Unlike TRPC1, TRPC5, and TRPC6, TRPC3 is ~ 7-fold more abundant in renal microvessels compared with the aorta (Facemire et al., 2004). SMC TRPC1 has been immunostained in rat afferent and efferent arterioles, although the study did not distinguish the level of TRPC1 expression between the arterioles (Takenaka et al., 2002). TRPC3 channels are expressed in the plasma membrane of neonatal pig afferent arteriolar SMCs (Soni et al., 2017a). TRPC3 protein expression levels in whole kidneys and afferent arterioles were higher in 20-days-old than newborn pigs, suggesting postnatal changes in the expression of the channels (Soni et al., 2017a). Whereas TRPC4 protein was detected in the rat descending vasa recta (DVR), TRPC5 was notably absent (Lee-Kwon et al., 2005). The expression of TRPC5 protein in renal medulla suggests its presence in medullary structures other than the DVR (Lee-Kwon et al., 2005).

The function of TRPC channels in renal vasculature. Endothelin-1 activated TRPC channels in primary SMCs that were cultured from rat renal microvessels (Palygin et al., 2016). L-type Ca^{2+} channel blocker nifedipine prevented AngII-induced Ca^{2+} entry in rat afferent arterioles, while a non-selective TPRC channel blocker SKF 96365 reduced AngII-induced Ca^{2+} influx in efferent arterioles (Loutzenhiser and Loutzenhiser, 2000). AngII-mediated constriction of rat afferent arterioles was also prevented by nifedipine (Takenaka et al., 2002). By contrast, AngII-induced constriction of the efferent arterioles was unaffected by nifedipine but inhibited by SKF 96365 (Takenaka et al., 2002). In another study, SKF 96365 and gadolinium (a non-selective TRPC channel blocker) reduced noradrenaline-induced increase in intracellular Ca^{2+} concentration in rat afferent arteriolar SMCs (Salomonsson et al., 2010). Taken together, these findings suggest that differential functions for TRPC channels in afferent and efferent arterioles may exist. However, since SKF 96365 and gadolinium are non-selective TRPC channel blockers, additional studies are necessary to characterize the role of TRPC channels in AngII-induced renal arteriolar reactivity.

Selective adenosine A_1-receptor (A_1R) activator 2-chloro-N6 cyclopentyladenosine (CCPA) stimulated receptor-operated calcium entry (ROCE) in neonatal pig afferent arterioles via TRPC3 channels (Soni et al., 2017a). Evidence indicated that induction of ROCE by CCPA is dependent on kidney maturation, as shown by a more significant increase in intracellular Ca^{2+} in 20 days-old piglets than in newborns, paralleling the increased protein expression of TRPC3 in the kidneys and afferent arterioles of the older pigs (Soni et al., 2017a). Postnatal kidney maturation did not alter A_1R expression (Soni et al., 2017a). Thus, the observed changes in ROCE are likely due to increased TRPC3 expression (Soni et al., 2017a). These findings are significant because A_1Rs control renal function, including the tubuloglomerular feedback (TGF) mechanism. Hence, adenosine-induced increase in renal vascular resistance during the TGF process may involve maturation-dependent Ca^{2+} influx via SMC TRPC3 channels.

The descending vasa recta (DVR) originating from the efferent arterioles of juxtamedullary glomeruli controls renal medullary perfusion (Pallone and Silldorff, 2001; Pallone et al., 1998; Zhang et al., 2002). DVR is primarily made up of pericytes and endothelial cells. Ca^{2+} influx into pericytes, the SMC-like contractile cells, regulates DVR reactivity, and hence, renal medullary blood flow (Pallone and Silldorff, 2001; Pallone et al., 1998; Zhang et al., 2002). The expression of TRPC4 in DVR pericytes and endothelial cells suggests the channel may be involved in Ca^{2+}-dependent signal transduction mechanisms in DVR that control medullary microcirculation (Lee-Kwon et al., 2005).

Despite the abundance of TRPC6 in renal microvasculature (Facemire et al., 2004; Salomonsson et al., 2010; Walker et al., 2001), its physiological role in the microvessels remains elusive. A study reported that flufenamic acid, a TRPC6 activator triggered a sustained increase in intracellular Ca^{2+} concentration in afferent arterioles, which was insensitive to L-type Ca^{2+} channel blockers, diltiazem, and nifedipine (Fellner and Arendshorst, 2008). Since flufenamic acid can modulate various ion channels (Guinamard et al., 2013), the contribution of TRPC6 to renal vasoregulation remains to be determined.

3. Renal vascular TRPM and TRPP channels

To date, there are no known published studies on renal vascular TRPM channels. However, unpublished data from Dr. Earley's group suggest that TRPM4 is expressed in renal interlobar artery SMCs and that TRPM4 channel inhibitor 9-phenanthrol attenuates myogenic constriction in isolated interlobar arteries (Earley, 2013). Whether TRPM4 inhibition alters myogenic tone in resistance size vessels or renal autoregulation is unknown.

TRPP1 was detected in human fetal and adult renal vessels (Chauvet et al., 2002). Unpublished data from our laboratory indicate that PC1 and TRPP1 mRNAs and proteins are expressed in neonatal pig renal vasculature, ranging from large vessels interlobar and arcuate arteries to small resistance vessels interlobular arteries and afferent arterioles (Fig. 1). Both PC1 and TRPP1 are also expressed in SMCs isolated from preglomerular renal microvessels of the pigs (Fig. 1A and B). Antibodies

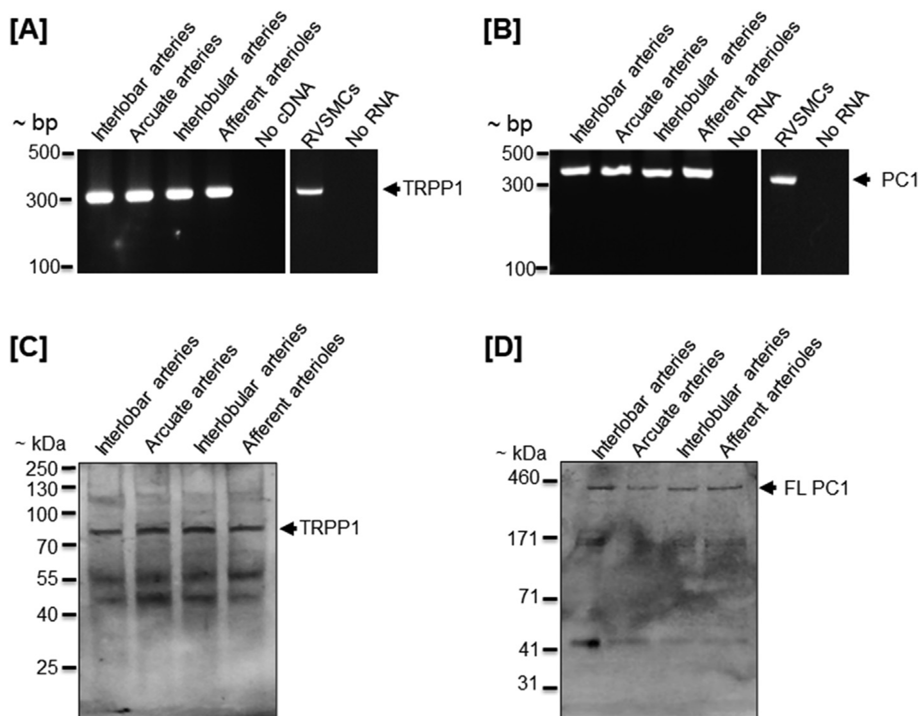

Fig. 1. ***Expression of TRPP1 and PC1 in intact renal vessels and vascular smooth muscle cells (RVSMCs) of neonatal pigs.*** A and B: agarose gels demonstrating amplification of TRPP1 (bp: 314) and PC1 (bp: 352) in renal vessels and RVSMCs. Western immunoblotting with: C: a goat anti-TRPP1 antibody (EB09540; Everest Biotech, Ramona CA) and D: a mouse monoclonal anti-PC1 antibody (C1749; full length: FL; Sigma-Aldrich, St. Louis, MO) showing expression of full-length TRPP1 and PC1 proteins. Whereas TRPP1 bands ran slightly lower (~90 kDa) than its expected molecular weight (106 kDa), PC1 bands correspond to the approximate size (460 kDa). RVSMCs were individually selected using a patch pipette, as previously described (Soni et al., 2017b). NuPAGE Tris-Acetate (3–8%) gels and HiMark protein standard (Invitrogen, Carlsbad CA) were used to separate the large molecular weight full-length PC1 protein.

directed against TRPP1 and the cytoplasmic COOH terminus of PC1 (PC1ctt) immunostained the proteins in the plasma membrane of neonatal pig renal vascular SMCs. (Fig. 2A). We also found that PC1ctt colocalizes and interacts with TRPP1 at the plasma membrane of the cells as determined by immunofluorescence and proximity ligation assay (Fig. 2B and C). These data indicate that endogenous TRPP1 interacts with PC1ctt in the plasma membrane of porcine renal vascular SMCs, the physiological implication of which is unclear. However, previous studies in other vascular beds indicated that PC1 and TRPP1 might regulate vascular myogenic response (Narayanan et al., 2013; Sharif-Naeini et al., 2009). Deleting PC1 in mouse SMCs caused a reduction in stretch-activated ion channel (SAC) current magnitude and mesenteric myogenic constriction (Sharif-Naeini et al., 2009). siRNA-mediated knockdown of TRPP1 (polycystin-2) did not alter myogenic tone in

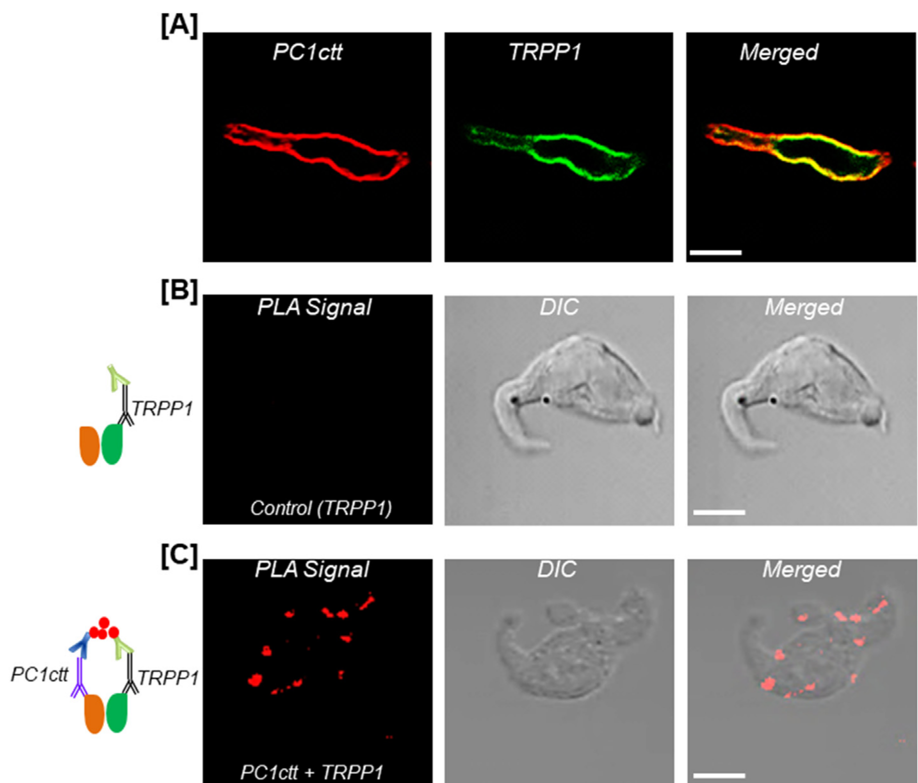

Fig. 2. ***Endogenous TRPP1 and the cytoplasmic COOH terminus of PC1 (PC1ctt) colocalize and interact in the plasma membrane of renal vascular smooth muscle cells (RVSMCs) of neonatal pigs.*** A: Immunofluorescence staining of a RVSMC, demonstrating that both TRPP1 and PC1ctt are expressed in the plasma membrane and colocalize. B and C: In situ proximity ligation assay (PLA) detected an interaction between PC1ctt and TRPP1 in RVMSCs. Whereas PLA signals (red fluorescence) were absent in negative control cells labeled only with anti-TRPP1, the signals were detected in cells labeled with anti-PC1ctt and anti-TRPP1 antibodies. PLA was performed using the Duolink in situ PLA kit (Olink Bioscience, Uppsala, Sweden), as we have previously described (Adebiyi, 2014). Images were acquired with a Zeiss LSM Pascal laser-scanning confocal microscope. The rabbit anti-PC1ctt antibody was a kind gift from Dr. Oxana Beskrovnaya (Chauvet et al., 2004) (Genzyme Corporation). Bar = 10 μm.

mesenteric arteries but restored SAC activity and tone in mesenteric arteries that lacked PC1 (Sharif-Naeini et al., 2009).

Findings from other studies suggested that TRPP1 is required for myogenic constriction of rat cerebral arteries and mouse hindlimb arteries (Bulley et al., 2018; Narayanan et al., 2013). If future studies reveal a similar role for TRPP channels in the renal vasculature, this could potentially impact our understanding of the autoregulation of RBF and GFR. Furthermore, pathological alterations in renal vascular TRPP1 or PC1, or both could contribute to complications and homeostatic imbalance seen in ADPKD.

4. Renal vascular TRPV channels

Expression of TRPV channels in renal vasculature. TRPV1 mRNA, along with TRPV4, has been detected in the main renal artery (Chen et al., 2015). Moreover, the expression of TRPV1 was 10 times lower, and TRPV4 was 10 times higher in renal parenchymal tissue than renal arteries (Chen et al., 2015). In a 2008 study, Willette et al. (2008) reported positive immunostaining for TRPV4 in rat renal arcuate artery endothelium, but not smooth muscle. Moreover, Western immunoblotting and PCR indicated that TRPV4 is expressed in intact renal vessels isolated from neonatal pigs (Soni et al., 2017b). TRPV4 protein expression levels in whole kidneys and renal microvasculature are higher in adult pigs, suggesting age-dependent expression of the channels (Soni et al., 2017b). Neonatal pig TRPV1, 2, and 3 may be restricted to renal vascular endothelial cells as PCR demonstrated that intact renal interlobular arteries express TRPV1, 2, 3, and 4 channels, but only TRPV4 was found in SMCs isolated from them (Soni et al., 2017b). TRPV4 channels are functionally expressed in both SMCs and endothelial cells across several vascular beds (Filosa et al., 2013). However, we have demonstrated that TRPV4 is predominantly expressed in neonatal pig renal vascular SMCs compared with endothelial cells (Soni et al., 2017b). The prevalent location of TRPV4 in blood vessels may likely determine its physiological function.

Function of TRPV channels in renal vasculature. Renal vascular TRPV1 appears to be bestowed with widely varying functions depending on the location of the channels. Nanomolar concentrations of TRPV1 agonist capsaicin caused endothelium-dependent dilation of phenylephrine-precontracted mesenteric arteries of adult mice, an effect reversed by TRPV1 antagonist capsazepine (Chen et al., 2015). However, micromolar concentrations of capsaicin are required to produce relaxation of the main renal arteries isolated from the mice (Chen et al., 2015). Capsaicin-induced relaxation of the main renal arteries was unaltered by endothelial denudation or TRPV1 deletion, suggesting that endothelium- and TRPV1-independent mechanisms underlie capsaicin-induced relaxation of large renal arteries (Chen et al., 2015).

In contrast to the large arteries, TRPV1 activation by capsaicin produced vasodilation of resistance vessels of perfused mouse kidneys precontracted with phenylephrine (Chen et al., 2015). In line with this observation, capsaicin-induced renal vasorelaxation was reversed by capsazepine and absent in TRPV1 knockout mice (Chen et al., 2015). Furthermore, inhibition of endothelial nitric oxide synthesis with L-NAME attenuated TRPV1-dependent renal vasodilation in perfused kidneys suggesting a possible role for nitric oxide (Chen et al., 2015). In contrast to renal arteries, capsaicin did not alter the diameter of adult rat DVRs pre-constricted with noradrenaline (Chen et al., 2015). Hence, TRPV1 channels appear to possess vasoregulatory effects only in pre-constricted preglomerular vessels of the kidney. This aspect of TRPV1 could be related to the increase in GFR seen with TRPV1 activation (Li and Wang, 2008), and might be of interest for future studies on hypertension and ischemia-reperfusion injury (Chen et al., 2015).

The study mentioned above also investigated the role of TRPV4 activation on renal conduit and resistance vessels (Chen et al., 2015). Unlike TRPV1, TRPV4 activation by GSK1016790A produced endothelium-dependent vasodilation of both phenylephrine-precontracted mesenteric and main renal arteries at nanomolar concentrations, which was reduced by AB159908, a TRPV4 channel blocker (Chen et al., 2015). TRPV4 activation also caused renal vasodilation in experiments using isolated perfused kidneys, and the effect was inhibited by AB159908 and absent in TRPV4 knockout mice (Chen et al., 2015). Contrary to the observations with TRPV1, activation of TRPV4 caused vasodilation of norepinephrine-precontracted rat DVR (Chen et al., 2015). These observations showed that the role of TRPV4 channels in renal vasculature might be broader than that of TRPV1, encompassing both preglomerular and post-glomerular vessels. However, the effects of activation or blockade of TRPV1 or TRPV4 channels on renal microvessels that had developed spontaneous physiological tone was not investigated in this study.

Data from our recent work support a mechanosensitive role for vascular SMC TRPV4 channels in neonatal renal myogenic autoregulation (Soni et al., 2017b). We showed that pharmacological inhibition of TRPV4 channels did not alter nimodipine-sensitive, 75 mM K^+-induced increase in intracellular Ca^{2+} concentration, and vasoconstriction in neonatal pig renal preglomerular microvessels. However, TRPV4 inhibition significantly diminished 1) pressure-induced membrane depolarization and spontaneous tone, 2) phospholipase A_2-independent increase in intracellular Ca^{2+} concentration and renal vasoconstriction induced by hypoosmotic stretch, and 3) pressure-induced increase in intracellular Ca^{2+} concentration and myogenic vasoconstriction. In anesthetized and mechanically ventilated neonatal pigs, intrarenal artery infusion of nicardipine, an L-type Ca^{2+}-channel blocker, reduced the mean arterial pressure (MAP) and abolished renal autoregulation triggered by a step increase in arterial pressure (Soni et al., 2017b). However, selective TRPV4 channel blockers HC 067047 and RN 1734 inhibited renal autoregulation without altering the MAP (Soni et al., 2017b). Thus, TRPV4-dependent renal myogenic mechanism in isolated microvessels is reproducible in vivo.

TRPV4-mediated cerebral and mesenteric vasodilation, aortic and pulmonary vasoconstriction, and endothelial store- and receptor-operated Ca^{2+} entry have been reported (Adapala et al., 2011; Earley et al., 2005; Goldenberg et al., 2015; Lorenzo et al., 2008; Ma et al., 2011; Saifeddine et al., 2015; Sonkusare et al., 2012, 2014; Xia et al., 2013). In a recent study, we showed that both GSK1016790A and 4α-PDD (selective TRPV4 channel agonists) constricted renal microvessels of neonatal pigs (Soni et al., 2019). Intrarenal artery infusion of a TRPV4 inhibitor into the kidney of neonatal pigs did not alter AngII-induced increase in MAP. However, it caused: 1) a reduction in AngII-induced receptor--operated Ca^{2+} entry in afferent arterioles and AngII-induced renal vasoconstriction, 2) a decrease in AngII-induced kidney hypoperfusion, and 3) a reduction in AngII-induced increase in renal vascular resistance (Soni et al., 2019). Hence, it is plausible to suggest that TRPV4 mediates multimodal Ca^{2+} signaling and physiological functions in the vasculature, depending on cell type, vascular bed, or animal species.

Ischemia-reperfusion (IR) injury to the kidneys of neonatal pigs resulted in an increase in TRPV4 protein expression in preglomerular resistance vessels and agonist-induced TRPV4 cation currents in renal vascular SMCs (Soni et al., 2019). Pharmacological inhibition of TRPV4 attenuated IR-induced increase in renal vascular resistance, IR-induced decrease in GFR, and IR-induced increase in the predictive biomarkers of AKI (Soni et al., 2019). Urinary AngII was increased in neonatal pigs subjected to renal IR (Soni et al., 2019). Since AngII-induced neonatal renal vascular reactivity is partly dependent on TRPV4 channels, AngII receptor-operated Ca^{2+} entry via SMC TRPV4 channels may contribute to kidney insufficiency in neonatal pig AKI (Soni et al., 2019). In addition to AngII, increased biosynthesis of other endogenous vasoactive mediators that activate TRPV4 channels may contribute to ischemic AKI.

5. Discussion

Various cardiovascular and kidney diseases are inextricably linked to alterations in renal microcirculation. The kidneys receive about 20% of the total cardiac output and play a vital role in removing toxic nitrogenous waste products and maintaining the balance of extracellular fluid volume and electrolyte compositions. Blood vessels of the kidney contribute to

Table 1
Expression and function of renal vascular TRP channels.

Publication	Animal species	Vasculature	Channel subtype	Methods used to study the expression	Salient finding(s)
Walker, R. L. et al. (2001)	Dog	Main renal arteries	TRPC3, 4, 6, & 7	RT-PCR and qRT-PCR	Canine renal arteries express TRPC3, 4, 6, and one splice variant of TRPC7.
Loutzenhiser and Loutzenhiser (2000)	Rat	Afferent & efferent arterioles	TRPC	Pharmacological interventions	AngII induces increase in $[Ca^{2+}]_i$ in both the afferent and efferent arterioles, where Ca^{2+} entry in the afferent arterioles is mediated by L-type Ca^{2+} channels, and in efferent arterioles is mediated by store-operated Ca^{2+} entry sensitive to TRPC blockade.
Takenaka, T. et al. (2002)	Rat	Afferent & efferent arterioles	TRP-1 (TRPC1)	Immunohistochemistry	Significant differences in functional characteristics exist between afferent and efferent arterioles. AngII mediated vasoconstriction of the afferent arterioles is VDCC-dependent, whereas that of efferent arterioles is TPRC-mediated.
Facemire, C. S. et al. (2004)	Rat	Preglomerular resistance vessels	TRPC1, 3, 4, 5, & 6.	RT-PCR, Western blotting	mRNAs for all TRPC subtypes except TRPC2 & 7 are expressed. TRPC3 mRNA is highly expressed in the resistance vessels in comparison to the aorta. Protein expression levels show an abundance of TRPC6.
Lee-Kwon, W. et al. (2005)	Rat	Vasa recta, peritubular capillaries,	TRPC4	RT-PCR, Western blotting, confocal microscopy	A potential association exists between TRPC4 channels and a PDZ domain adaptor protein, NHERF-2, expressed in the DVR. TRPC4 but not TRPC5 is co-expressed with NHERF-2 in the pericytes and endothelial cells of DVR.
Fellner, S. K. & W. J. Arendshorst (2008)	Rat	Afferent arterioles	TRPC6	Pharmacological interventions	AngII-mediated $[Ca^{2+}]$i increase in afferent arterioles is attenuated by TRPC blockade and exaggerated by TRPC6 activation.
Salomonsson, M. et al. (2010)	Rat	Afferent arterioles	TRPC1/3/6	Pharmacological interventions	Non-specific TRPC channel blockers SKF 96365 and Gd^{3+} attenuate norepinephrine-induced increase in $[Ca^{2+}]_i$ in preglomerular resistance vessels.
Soni, H. et al. (2017)	Pig	Afferent arterioles	TRPC3	RT-PCR, Western blot, and confocal microscopy	TRPC3 expression in the afferent arteriole increases with the maturation of the kidney in the postnatal period. A_1R-dependent increase in $[Ca^{2+}]_i$ is brought about by receptor-operated mechanisms and is dependent on the level of TRPC3 channel expression.
Unpublished data cited in Earley, S. (2013)	Rat	Interlobar arteries	TRPM4	RT-PCR Immunocytochemistry	TRPM4 is expressed in renal interlobar artery SMCs. TRPM4 channel inhibitor 9-phenanthrol inhibits myogenic constriction of isolated interlobar arteries.
Unpublished data presented in this review	Pig	Interlobar, arcuate, and interlobular arteries and afferent arterioles	TRPP1	RT-PCR, Western blotting, immunofluorescence	TRPP1 mRNA and protein are expressed by large and small resistance vessels of the porcine kidney. TRPP1 colocalizes and interacts with the cytoplasmic carboxy terminal of PC1.
Chen, L. et al. (2015)	Mice	Renal artery Preglomerular and afferent arterioles, vasa recta	TRPV1 and TRPV4	RT-PCR	TRPV1 activation causes NO-mediated vasorelaxation of phenylephrine-precontracted renal preglomerular resistance vessels but does not affect conduit arteries or vasa recta. Contrary to TRPV1, TRPV4 activation causes NO-mediated vasorelaxation in both conduit and resistance vessels.
Willette, R. N. et al. (2008)	Rat	Arcuate artery	TRPV4	Immunohistochemistry	Renal arcuate artery endothelium is positive for TRPV4 immunostaining, whereas arterial smooth muscle and glomeruli are negative.
Soni, H. et al. (2017)	Pig	Interlobular arteries	TRPV4	RT-PCR, qRT-PCR, Western blotting	TRPV4 channels mediate myogenic response in renal resistance arteries by activating downstream VDCCs via a phospholipase A_2-independent mechanism.
Soni, H. et al. (2019)	Pig	Interlobular arteries, afferent arterioles	TRPV4	Western blotting	TRPV4 channel expression is upregulated in renal IR injury, and TRPV4 is involved in renal IR injury by contributing to AngII evoked ROCE in SMCs.

these functions by controlling regional kidney perfusion (Carlstrom et al., 2015; Thomson and Blantz, 2008). Evidence from the studies discussed here (summarized in Table 1) demonstrates the presence of TRP channels in vascular segments that play crucial functions in regulating renal microcirculation. The afferent arterioles, which form the effector end of the myogenic and TGF autoregulation mechanisms, express TRPC and TRPV channels. Although TRPC3 contributes to adenosine receptor-mediated vasoconstriction of afferent arterioles in neonatal pigs (Soni et al., 2017a), additional animal studies are required to provide information on the unresolved role of renal vascular ion channels in TGF mechanisms. The cellular signal transduction pathway that underpins myogenic autoregulation includes stretch-induced activation of mechanosensitive ion channels in SMC plasmalemma and succeeding depolarization of the membrane, the opening of L-type Ca^{2+} channels, and extracellular Ca^{2+} influx (Davis and Hill, 1999; Schubert and Mulvany, 1999). TRPV4 appears to be a candidate for renal vascular SMC mechanosensitive ion channels, but this has only been proven in infant pigs.

Apart from their role in preglomerular resistance vessels, TRP channels might also serve essential functions in the renal medulla. TRPC4 may regulate Ca^{2+} entry into pericytes and endothelial cells that make up the DVR (Lee-Kwon et al., 2005), potentially controlling renal medullary vascular resistance. Blood flow through the vasa recta determines the medullary interstitial milieu, where juxtamedullary nephrons establish the medullary osmotic gradient via the countercurrent multiplier and the vasa recta maintain the gradient through the countercurrent exchange mechanism. Therefore, TRP channel regulation of vasa recta blood flow could, in turn, modulate urine concentration mechanisms.

6. Outlook

Among the six families of mammalian TRP channels, only renal vascular TRPC and TRPV have been modestly investigated. Evidence of their physiological function using whole animal models is minimal. Vasoregulation by these channels suggests that they may contribute not

only to renal vascular bed perfusion but the processes of reabsorption, secretion, urine concentration, and maintenance of blood volume. The emerging evidence of TRP channel signaling in renal vasculature suggests that these proteins might become potential new therapeutic targets for kidney disease associated with changes in renal vascular reactivity. Because of renal vasculature's unique anatomical characteristics and highly specialized physiological roles, no other vascular bed can serve as its model in the truest sense. Therefore, future studies must continue to investigate vascular TRP channel functions in their native locations rather than attempting to extrapolate their roles in other vascular beds with starkly different structural and physiological characteristics. Given the non-selectivity of many pharmacological modulators of TRP channels, more studies using genetic animal models are necessary to fill the knowledge gaps in the current understanding of the physiological and pathophysiological significance of renal vascular TRP channels.

CRediT authorship contribution statement

Praghalathan Kanthakumar: Writing, Revision and final approval. **Adebowale Adebiyi:** Conceptualization, writing, Revision and final approval.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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