# Role of ion channels in the mechanism of proteinuria (Review)

JIE LIU[1*], XUEWEI LI[2*], NING XU[1], HUIRONG HAN[3] and XIANGLING LI[1]

Departments of [1]Nephrology and [2]Rheumatology, Affiliated Hospital of Weifang Medical University;
[3]Department of Anesthesiology, Weifang Medical University, Weifang, Shandong 261000, P.R. China

**Abstract.** Proteinuria is a common clinical manifestation of kidney diseases, such as glomerulonephritis, nephrotic syndrome, immunoglobulin A nephropathy and diabetic nephropathy. Therefore, proteinuria is considered to be a risk factor for renal dysfunction. Furthermore, proteinuria is also significantly associated with the progression of kidney diseases and increased mortality. Its occurrence is closely associated with damage to the structure of the glomerular filtration membrane. An impaired glomerular filtration membrane can affect the selective filtration function of the kidneys; therefore, several macromolecular substances, such as proteins, may pass through the filtration membrane and promote the manifestation of proteinuria. It has been reported that ion channels play a significant role in the mechanisms underlying proteinuria. Ion channel mutations or other dysfunctions have been implicated in several diseases, therefore ion channels could be used as major therapeutic targets. The mechanisms underlying the action of ion channels and ion transporters in proteinuria have been overlooked in the literature, despite their importance in identifying novel targets for treating proteinuria and delaying the progression of kidney diseases. The current review article focused on the four key ion channel groups, namely $Na^+$, $Ca^{2+}$, $Cl^-$ and $K^+$ ion channels and the associated ion transporters.

## Contents

1. Introduction
2. Role of various ion channels in the mechanism of proteinuria
3. Conclusion

*Correspondence to:* Professor Xiangling Li, Department of Nephrology, Affiliated Hospital of Weifang Medical University, 2428 Yu He Road, Weifang, Shandong 261000, P.R. China
E-mail: lixiangling163@163.com

*Contributed equally

## 1. Introduction

Ion channels are pore-creating proteins that allow the flow of inorganic ions through the cell membrane, plasma membrane or intracellular organelles in a variety of tissues. They can also provide a rapid diffusion pathway depending on the electrochemical potential of the ions across the cell membrane. Therefore, they can regulate the intracellular and extracellular ion concentration involved in the establishment of membrane potential, thus enabling them to play a notable role in several physiological activities. Such basic physiological activities include muscle contraction, protrusion transmission, action potential transmission and cell secretion (1-6).

The three Nobel Prizes in physiology or medicine in 1963 and 1991 and in chemistry in 2003, revealed the necessary to research the structure and function of ion channels (1). Ion channels are characterized by two fundamental features, namely selectivity and gating (2). Therefore, depending on the sensitivity of the gate to different stimuli, the ion channels can be divided into voltage-, chemically- and mechanically gated subgroups. The majority of ion channels, such as $K^+$, $Na^+$, $Ca^{2+}$, HCN and transient receptor potential (TRP) channels, are similar in structure and form the subgroup of voltage-gated channels since they may arise from the same distant progenitor gene. Other ion channels such as $Cl^-$, aquaporins and junction proteins have different structures compared with voltage-gated channels (1,2). The function of ion channels is to respond to the opening and closing of gating cues and to determine the types of ions that can pass through. Additionally, ion channels consist of a ligand-binding and ion permeation mechanism. Currently, the mechanisms underlying ion permeation remains unclear (7,8). Since several diseases are caused by ion channel mutations or other dysfunctions, ion channels are considered major therapeutic targets (9,10).

Proteinuria is a condition characterized by the presence of protein in the urine at >150 mg/24 h or by positive result from qualitative urinalysis testing. Proteinuria can be divided into five categories: i) physiological proteinuria; ii) glomerulinuria; iii) tubulminuria; iv) overload proteinuria; and v) mixed proteinuria. The occurrence of proteinuria is closely associated with impaired glomerular filtration membrane, which can affect glomerular selective filtration function, thus allowing several macromolecular substances, including proteins, to pass through the filtration membrane, eventually promoting the development of proteinuria (11). The glomerular filtration membrane consists of glomerular capillary endothelial cells

(ECs), the glomerular basement membrane (GBM) and renal capsule visceral layer epithelial cells (podocytes) (12-14). The outermost layer of the glomerular basement membrane, the outermost podocyte foot processes and its inter slit diaphragm (SD; fissure membrane) are the main barriers of the glomerular filtration membrane, as such they are key points of weakness in the development of proteinuria (12-14). The SD is a thin film between the adjacent bipedal processes on the epithelial side of the GBM and is an isoaperture zipper-like electron dense structure that forms the final part of the molecular barrier and plays a significant role in preventing the efflux of the majority of proteins (15). When podocytes are damaged by several factors (such as genetic abnormalities or infection) the expression of SD-related proteins can decrease, leading to foot process fusion (a manifestation of podocyte damage, which can increase glomerular permeability to macromolecular substances) and GBM shedding, eventually resulting in proteinuria. SD-associated proteins include nephrotic protein (nephrin), podocyte cleft membrane protein (podocin), CD2-associated protein and TRP cation channel protein (TRPC) (16) and each protein plays a different role. Nephrin maintains the structural strength of SD and participates in the signal transmission of podocytes to regulate the remodeling of podocyte cytoskeleton; podocin can form protein complexes in the lipid microdomain of foot process membrane and regulates SD filtration permeability through signal transduction; CD2AP is important for maintaining the integrity of the structure and function of podocytes; and the role of TRPC is described in $Ca^{2+}$ channels (15,16). In addition, proteinuria is one of the suggestive indicators of kidney diseases and contributes to the diagnosis of these diseases. Currently, studies have supported the association between the onset of proteinuria and the activation or inhibition of ion channels (8,12). Therefore, further understanding of the mechanism underlying the action of ion channels and that of the related ion transporters in proteinuria could advance targeted therapy in patients with kidney disease-induced proteinuria.

## 2. Role of various ion channels in the mechanism of proteinuria

*Na+ ion channels.* These channels are transmembrane proteins that allow a small amount of $Na^+$ to flow into cells along its electrochemical gradient. *In vivo*, $Na^+$ channels can be divided into voltage-gated $Na^+$ channels (VGSCs) and epithelial $Na^+$ channels (ENaCs). VGSCs are transmembrane proteins present in different cell types throughout the body. These channels consist of voltage-related activation and time-related inactivation gates that work together to ensure that cells are depolarized within a controllable degree (17). VGSCs act on a specific intracellular domain and interact with various membranes, extracellular matrices (ECM) and cytoskeletal proteins to exert their function (17,18). ENaCs are heteromeric proteins, composed of α, β and γ subunits, that are mainly distributed in the epithelial cells of the far renal units and lung epithelial cells and are highly selective under suitable conditions. These channels serve a key role in organism growth and development, metabolism and energy conversion (19). Since the α and β subunits of VGSC are highly expressed only in cardiomyocytes, skeletal myocytes, neurons and some unexcitable

cells. Current research has not demonstrated the function of the VGSC in the kidney, meaning the mechanisms underlying their function bears little significance on the development of proteinuria (20). Therefore, the current review article focused on the role of ENaCs in proteinuria.

*ENaCs.* ENaCs are non-voltage-dependent channels and have minor impact on potential changes across the cell membrane but with higher selectivity for $Na^+$ over $K^+$ compared with other $Na^+$ channels. ENaCs are highly expressed in the distal renal tubules, the large intestinal epithelium, the exocrine glandular duct, the airway epithelium and the bladder epithelium and can be blocked by amiloride, a pharmaceutical inhibitor and its analogues. $Na^+$ crosses the polarized cell membrane along its electrochemical gradient through ENaCs, while $Na^+$ is pumped out of the cell by the $Na^+/K^+$-ATPase, thus maintaining water and $Na^+$ balance and blood pressure (Fig. 1) (21-23). Svenningsen *et al* (24) demonstrated that impaired glomerular filtration barrier can activate ENaCs. This modulation is affected by several regulatory factors such as proteases. Under physiological conditions, the activity of soluble protease is notably low in urine (25). However, this rises in proteinuria, which is also characterized by increased levels of plasma proteinases, thus the proteinases activating ENaCs in the collecting duct (24,26). Larionov *et al* (27) showed that the activation of ENaCs was protease-dependent. Additionally, the above study revealed that the expression of $Na^+/K^+$-ATPase in the collecting duct was also increased when the ENaC was activated. Proteinuria is the major clinical symptom of nephrotic syndrome and is characterized by the presence of serine proteases in the urine. Previous studies suggested that proteinuria is a major mechanism of $Na^+$ retention in patients with nephrotic syndrome and this mechanism has been associated with the activation of $Na^+$ channels (28,29). In nephrotic syndrome models, administration of amiloride or triamterene can reduce $Na^+$ retention in patients by inhibiting ENaCs in distal renal and collecting tubules to prevent $Na^+$ reabsorption. Therefore, amiloride or triamterene can also combat the activation of ENaCs by serine proteases leading to the urinary excretion of active serine proteases in nephrotic syndrome (30). Alternatively, treatment with serine protease inhibitors can attenuate the activation of $Na^+$ channels to reduce proteinuria. Passero *et al* (31) also indicated that proteases can enhance the activity of ENaCs showing this mechanism is in part involved in proteinuria. In addition, aldosterone, a steroid hormone that mediates $Na^+$ reabsorption in the renal distal nephron of the kidneys by upregulating the expression of the apical membrane ENaCs, has also been associated with podocyte injury and mesangial cell proliferation. Interventional experiments demonstrated that the addition of aldosterone antagonists to the standard therapy significantly alleviates proteinuria in patients with chronic kidney disease (32). The aforementioned findings indicate that the mechanism of proteinuria is associated with ENaCs and their inhibition can decrease proteinuria.

*$Ca^{2+}$ ion channels.* $Ca^{2+}$ channels are transmembrane signaling proteins that tightly regulate the process of $Ca^{2+}$ entering cells to initiate physiological processes such as the initiation of excitation, excitation-contraction coupling and gene transcription (33,34). $Ca^{2+}$ channels mainly include voltage-gated $Ca^{2+}$ channels (VGCCs), ligand-gated $Ca^{2+}$ channels, TRP
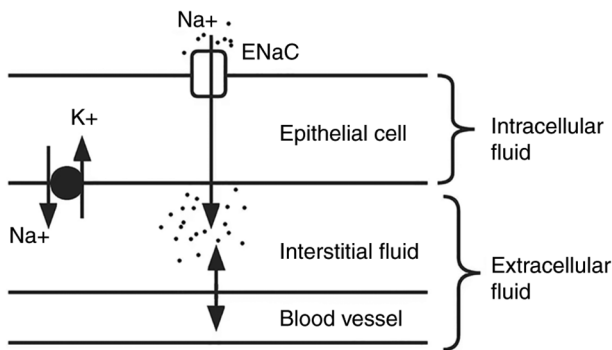
Figure 1. Localization and role of epithelial Na$^+$ channels in distal convoluted tubule and collection tubule epithelial cells. ENaC, epithelial Na$^+$ channels.

channels, Ca$^{2+}$ library-regulated Ca$^{2+}$ channels and arachidonic acid-regulated Ca$^{2+}$ channels (35). Given the importance of Ca$^{2+}$ homeostasis in cellular processes (such as maintaining the biopotential on both sides of the cell membrane and nerve conduction), Ca$^{2+}$ regulation is very strict and the kidneys, being one of the main excretory organs of the body, control the filtration and reabsorption of Ca$^{2+}$ to maintain this homeostasis in the body. It has been reported that ~99% of Ca$^{2+}$ is reabsorbed in the renal tubules of the kidney (36,37). Ca$^{2+}$ also affects kidney development, kidney cell function and the occurrence of several kidney diseases, including proteinuria (38,39). This section subsequently focuses on VGCCs and TRP channels.

*VGCCs*. VGCCs are macromolecular protein complexes embedded in the cell membrane and are highly selective hydrophilic channels that is permeable for Ca$^{2+}$. VGCCs are composed of 4-5 subunits encoded by multiple genes and play a significant role in regulating the transport of Ca$^{2+}$ in and out of the cell. Currently, at least 10 genes have been identified that encode VGCC α1 subunits (40,41). All different subtypes of VGCC play different roles in cell signaling. VGCCs are divided into the following six subtypes: i) L-type; ii) N-type; iii) P-type; iv) Q-type; v) R-type; and vi) T-type. The main function of L-type VGCC is excitation-contraction coupling and regulation of gene transcription, while N-type, P-type and Q-type VGCCs are all involved in the release of neurotransmitters. Additionally, R-type VGCCs are involved in pacing and repeated discharge, while T-type Ca$^{2+}$ channels can attenuate the action potential threshold and enhance prominent excitability (42-45). Hansen (46) suggested that VGCCs serve a key role in vascular smooth muscle cells (VSMCs), cardiomyocytes and renal blood vessels (Fig. 2). Additionally, the aforementioned study showed that cell treatment with Ca$^{2+}$ channel receptor blockers attenuate proteinuria. A previous study investigated the role L-type and T-type Ca$^{2+}$ channel blockers in 58 patients with hypertension (47). The results demonstrated that blood pressure and proteinuria are both reduced in patients treated with Ca$^{2+}$ channel blockers. N-type Ca$^{2+}$ channels are mainly expressed in the nervous system and it has been reported that L/N-type Ca$^{2+}$ channel blockers reduce proteinuria after blocking renal sympathetic nerves (48). Furthermore, previous studies have revealed that N-type Ca$^{2+}$ channels are also expressed in kidney endothelial cells and podocytes, and treatment of injured podocytes in these investigations with L/N-type Ca$^{2+}$ channel blockers

alleviated increased protein expression and pressure fiber dissolution (48-50). In addition, compared with L-type Ca$^{2+}$ channel blockers, L/N-type and L/T-type VGCCs blockers has been shown to significantly restore the expression of podocin and nephrin and attenuate proteinuria and podocyte injury (51-54). This effect could be due to the effects of N-type and T-type VGCCs on intrarenal pressure and renal hemodynamics. Another study showed that the expression levels of P/Q-type VGCCs is similar with those of L-type VGCCs in renal blood vessels and that these channels are involved in regulating renal vasoconstriction (55). The aforementioned results suggest that VGCC blocking can reduce proteinuria.

*TRP channels*. TRP channels, a class of cationic channel proteins, act as signal converters via altering membrane potential or the intracellular concentration of Ca$^{2+}$ (56,57). In 1989, Montell and Rubin (58) identified the TRP ion channels. TRP channels can be divided into the following six subfamilies: i) TRPA (ankyrin); ii) TRPC (canonical); iii) TRPM (melastatin); iv) TRPML (mucolipin); v) TRPP (polycystin); and vi) TRPV (vanilloid) (59-61). TRP channels can be activated through several pathways, such as intracellular or extracellular transmitters, chemical stimulation and osmotic pressure. Furthermore, the body can perceive the changes of the external environment through the instantaneous receptor potential channels in the surrounding environment, thus protecting the body (62-67). The current review article focused on the roles of TRPC and TRPV4 on proteinuria.

The members of the TRPC subfamily can act as both Ca$^{2+}$ pool regulatory channels and receptors to regulate other Ca$^{2+}$ channels. A total of seven different TRPC members have been identified in mammals that can be subdivided into the following four subgroups based on their protein sequence and function: i) TRPC1; ii) TRPC2; iii) TRPC4/5; and iv) TRPC3/6/7. Among them, TRPC2 is not expressed in humans (68). Previous studies demonstrated that only TRPC3, TRPC5 and TRPC6 were able to promote podocyte Ca$^{2+}$ entry (69-71). Currently, the role of TRPC family members in several kidney diseases has become increasingly important. Specifically, it has been reported that TRPC5 mediates the activation of ras-related C3 botulinum toxin substrate 1, a member of the Rho GTPase family and synaptic lipoprotein degradation involved in the cytoskeleton hub structure of podocytes (72). Additionally, TRPC6 can affect the movement of podocytes by regulating RhoA (Fig. 3) (73). Another study showed that TRPC6, an important ion channel in podocytes, can interact with other SD proteins, as well as with signal transduction molecules such as vascular endothelial growth factor to regulate the actin cytoskeleton rearrangement of podocytes, thus affecting pathological proteinuria (74). It has been also reported that TRPC6 is upregulated in renal diseases, commonly accompanied by proteinuria, including membranous nephropathy, focal glomerulopathy and minor pathological nephropathy (75-77). Since TRPC6 is considered to be one of the most significant podocyte cleft membrane proteins involved in proteinuria and it can be used as a therapeutic target to improve proteinuria and to delay the development of kidney diseases (78-80). Reiser *et al* (81) demonstrated that TRPC6 overexpression increased proteinuria in mice. After podocytes were transfected with a circular
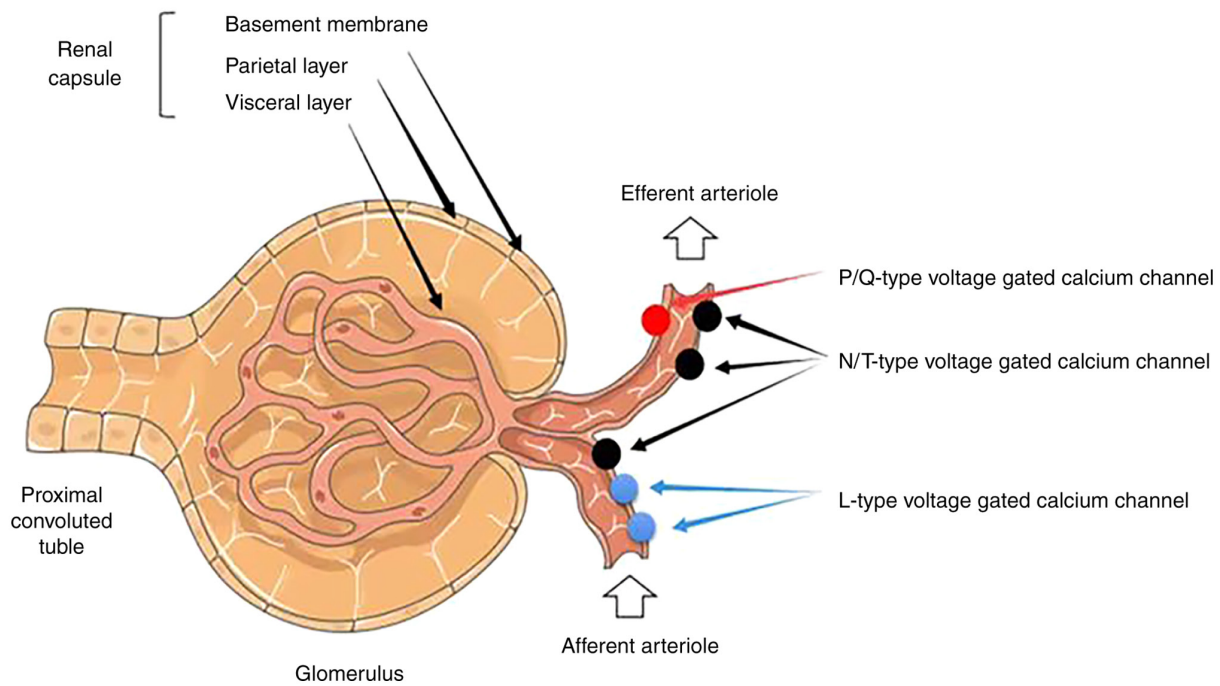
Figure 2. Distribution of P, Q, N, T and L- type voltage-gated $Ca^{2+}$ channels in renal blood vessels.
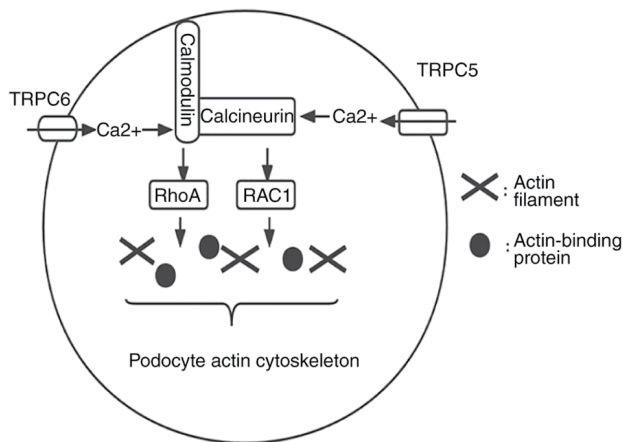


Figure 3. Intracellular $Ca^{2+}$ activates RhoA through TRPC6 and calmodulin and RAC1 through TRPC5 and calcineurin. TRPC, transient receptor potential cation channel; RAC1, ras-related C3 botulinum toxin substrate 1; RhoA, ras homolog family member A.

TRPC6 overexpression plasmid, $Ca^{2+}$ concentration and the enzymatic activity of RhoA increased in podocytes, resulting in podocyte cytoskeletal remodeling, podocyte contraction, a reduced number of podocytes and disordered F-actin distribution. The aforementioned effects were remediated after the administration of RhoA inhibitors. This indicated that TRPC6 overexpression, which increases intracellular $Ca^{2+}$ concentration and activates the $Ca^{2+}$-dependent RhoA signaling pathway, can result in podocyte damage and the onset of proteinuria (82). Proteinuria and podocyte shedding are also inhibited in systemic TRPC5 knockdown animal models. To evaluate the role of TRPC5 in different diseases, Zhou *et al* (83) showed that mice treated with the TRPC5-specific inhibitor AC1903 demonstrate reduced proteinuria and loss of podocytes.

Therefore, targeting TRPC5 can serve as a treatment approach for reducing proteinuria. Another study revealed that podocyte treatment with angiotensin II, which activates the ERK signaling pathway and promotes translocation of NF-kB, a transcription factor involved in TRPC upregulation, increases $Ca^{2+}$ influx, promotes podocyte apoptosis and enhances proteinuria (84). Alternatively, Wang *et al* (85) demonstrated in a puromycin-induced podocyte injury model that enhanced NADPH oxidase activity upregulated TRPC6 expression and increased $Ca^{2+}$ influx, thus promoting proteinuria. The above studies suggest that the normal function and structure of podocytes can be maintained by regulating the abnormal expression of TRPC6 and TRPC5 to reduce proteinuria (86,87).

The TRPV4 receptor is expressed in the cardiovascular system, including endothelial cells, cardiac fibroblasts, VSMCs and perivascular nerves, but also in the kidneys. This receptor can be activated by physical factors such as high temperature and mechanical stimulation as well as by chemical factors such as arachidonic acid (88-92). Gualdani *et al* (93) showed that fluid flow-induced mechanical force in proximal renal tubules activates TRPV4 and promotes the endocytosis of albumin in proximal renal tubular epithelial cells (Fig. 4), thus promoting albumin retention. Perineuria is also significantly increased in TRPV4-depleted tubular cells in mice when the glomerular filter permeability in the proximal tubules is enhanced. Taken together, the TRPV4-mediated defects in endocytosis may underlie proteinuria and therefore TRPV4 receptors can be considered as promising targets for controlling proteinuria (93).

*Cl⁻ ion channels.* Cl⁻ channels are expressed in cell membranes and organelles and are of great significance, including stabilization of membrane potential and fluid transport. These channels can be divided into five categories: i) voltage-dependent Cl⁻ channels (ClCs); ii) cystic fiber transmembrane conductance
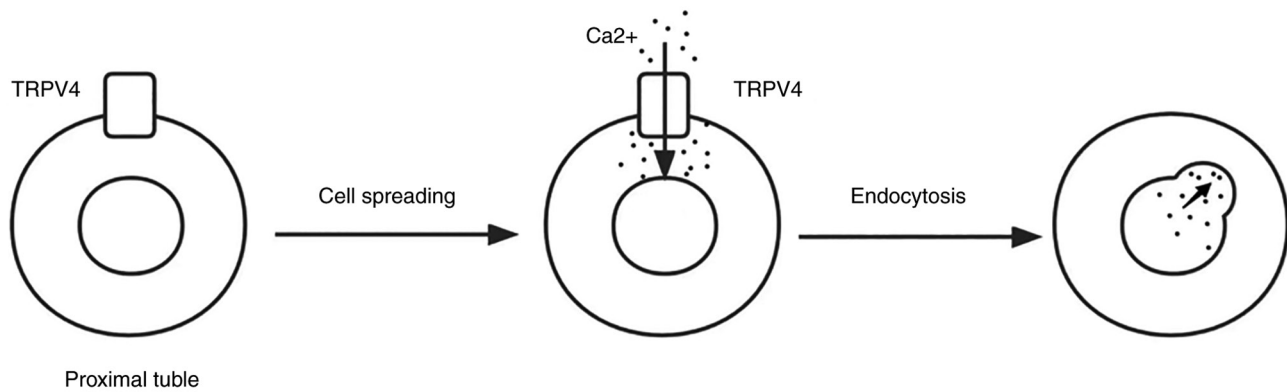
Figure 4. TRPV4 in the proximal tubule regulates protein endocytosis. TRPV4, transient receptor potential vanilloid type 4.

regulators; iii) $Ca^{2+}$-activated $Cl^-$ channels (CaCCs); iv) volume regulatory $Cl^-$ channels; and v) ligand-gated $Cl^-$ channels (94-98). Among them, voltage-dependent ClCs and CaCCs are involved in the occurrence of proteinuria. In mammals, voltage-dependent ClCs include nine members, with ClC-0, ClC-1, ClC-2, ClC-Ka and ClC-Kb commonly found in the cell membrane and ClC-3, ClC-4, ClC-5 and ClC-7 in organelle membranes (99,100). Among them, ClC-Ka, ClC-Kb and ClC-5 are expressed in the kidneys and serve a key role in the reabsorption of renal tubular $Cl^-$ (101,102). ClC-5 is mainly expressed in proximal renal and collecting tubules and regulates cytoplasmic membrane currents (103). ClC-5 serves a significant role in proximal tubular endocytosis and intracellular function (Fig. 5), connotation acidification, receptor regulation, intracellular maturation and enzyme activation (104). It has been reported that the damage caused by urinary protein in renal tubular epithelial cells leads to diminished proton pump expression in the intracellular connotation epitope membrane, thus affecting ClC-5 expression and $Cl^-$ transport. During proteinuria reuptake, damage to renal tubular epithelial cells can also be caused, and direct or indirect ClC-5 downregulation can affect protein absorption via the proximal renal tubules to increase proteinuria (104-106). A previous study showed that ClC-5 depletion in a knockdown mouse model reduced phosphorylation compared with wild-type mice, resulting in impaired invagination function and proteinuria (107). CaCCs are widely expressed in non-excitatory cells, such as endothelial cells, epithelial cells and VSMCs and play key roles in several processes. Transmembrane member 16A (TMEM16A) is involved in $Ca^{2+}$ activation of $Cl^-$ channels and is associated with the formation of CaCCs. TMEM16A is prominently expressed in renal tubular proximal epithelial cells, but also in podocytes and other renal tubular segments (108). Previous studies demonstrated that the ability of tubular proximal epithelial cells to reabsorb protein is reduced and excretion was enhanced in TMEM16A-depleted mice, subsequently promoting proteinuria (109).

*$K^+$ ion channels.* $K^+$ channels specifically allow $K^+$, but not other ions, especially $Na^+$, to pass through the plasma membrane. The molecular structure of $K^+$ channels consists of the T1 tetrameric functional domain of the amino-terminal cytosolic domain, six transmembrane-helical domains, the voltage sensing domain, the pore region and an intracellular carboxylated cytosolic domain (110-112). $K^+$ channels can be divided into $K^+$ channels with only pore-forming areas, voltage-gated $K^+$ channels, inward rectifier $K^+$ channels and ligand-gated $K^+$ channels (113). A novel ATP-sensitive $K^+$ channel was identified on the mitochondrial membrane, which belongs to the inward rectifying $K^+$ channels, where the channel activity is inhibited when intracellular ATP concentration increases (Fig. 6) (114-117). Among the aforementioned channels, voltage-gated $K^+$ channels, also known as voltage-dependent $K^+$ channels, can be further divided into delayed rectifier $K^+$ channels (Kr), type A transient $K^+$ channels (KA) and $Ca^{2+}$-activated $K^+$ channels (KCa) (118-123).

$K^+$ channels are distributed in the apical and basement membrane of the renal tubules at several segments of the kidney (124). It has been suggested that $K^+$ conductance plays an important role in VSMC and endothelial cell membrane potential in the kidneys. Therefore, changes in the activity of $K^+$ channels may cause changes in hemodynamic resistance, kidney blood flow and glomerular filtration pressure, thus affecting the excretion of substances into the urine (125). A previous study revealed that nicorandil, an activator of the ATP-dependent $K^+$ channel, exerts a protective effect on the renal vasculature. The nicorandil treatment of mice in an acute kidney injury and glomerulonephritis model significantly reduces proteinuria and kidney injury by inhibiting oxidative stress (126). Additionally, Snijder *et al* (127) used H2S intervention to explore its protective effect on angiotensin-induced hypertensive nephropathy mice. The results demonstrated that H2S activates ATP-sensitive $K^+$ channels to attenuate angiotensin-related podocyte injury and intrarenal pressure, thus alleviating proteinuria and kidney injury. Voltage-gated $K^+$ channels can be expressed in glomeruli as well as in portions of the renal tubules. In a study using an anti-glomerular basement membrane glomerulonephritis mouse model, treatment of mice with $K^+$ channel blockers significantly reduced urinary protein (128). In addition, Huang *et al* (129) subcutaneously injected streptozotocin-induced diabetic nephropathy mice with a KCa inhibitor to evaluate proteinuria, the expression of renal inflammation-related markers and ECM precipitation. The results showed that KCa inhibitors decrease the expression of inflammation-related markers and attenuate proteinuria by inhibiting TGF-β1 signaling to reduce kidney injury. Piwkowska *et al* (130) investigated whether BKCa is involved in insulin-mediated and protein kinase type GI (PKGI)
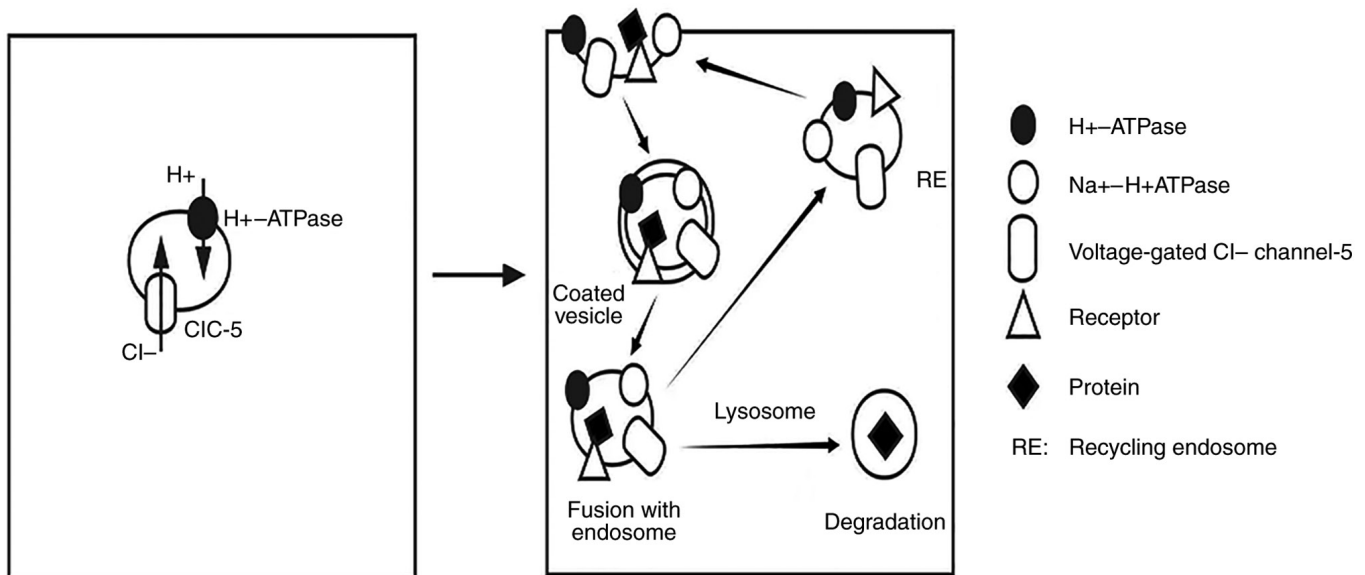
Figure 5. ClC-5, concentrated in the microvilli at the brush edge of the proximal tubule, co-locates with H+-ATPase, thereby mediating the uptake of protein complexes by proximal tubule cells. ClC, voltage-gated Cl- channel; RE, recycling endosome.
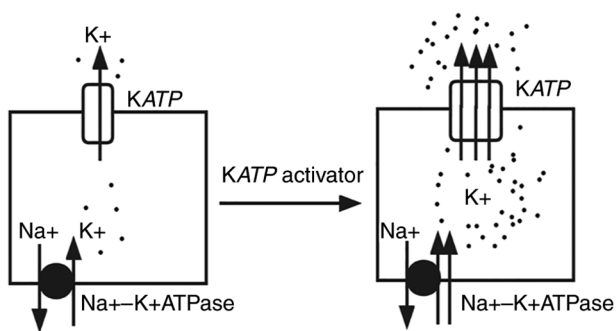


Figure 6. Activation of KATP, on the mitochondrial membrane of podocytes, activates the antioxidant system, inhibits the pro-oxidation system, reduces the production of reactive oxygen species and alleviates damage to podocytes. KATP, ATP-sensitive K+ channel.

protein-dependent glomerular filtration barrier permeability. This study showed that a BKCa blocker is able to attenuate the flow of insulin-induced albumin and PKGI-dependent trans-epithelial albumin through the podocyte monolayer by reducing the permeability of the cell filtration barrier, eventually alleviating the excretion of proteins in the urine. This finding could also provide a novel therapeutic target for reducing proteinuria.

*Ion transporters.* Transporters are the other types of membrane proteins that mediate the flow of ions through the cell membrane. These proteins are different from ion channels. Pumps, the main active transporters, use energy generated by ATP hydrolysis to transport ions against electrochemical gradients, independent of passive diffusion (131). In addition, pumps are involved in several activities, such as maintaining ion homeostasis by regulating the activity of pumps, and require one or more proteins to maintain, including $Na^+/K^+$-ATPases and $Na^+/H^+$ exchanger proteins (131,132). Orlov *et al* (133) showed that proteinuria is associated with

abnormalities in the ion transporter $Na^+/H^+$ exchange factor and $Na^+/K^+/2Cl^-$ co-transporter in a human model of primary hypertension. Hypertension and proteinuria are the main features of preeclampsia (134). Graves (134) demonstrated that the above effect is partially due to defects in $Na^+/K^+$-ATPases or $Na^+$ pumps. ClC-5 is the $Cl^-/H^+$ anti-transporter expressed in early proximal tubular endosomes (135). When the function of ClC-5 is impaired in endosomes, not only is the expression of $Na^+/H^+$ exchange factors on the apical surface of proximal tubules altered, but also reabsorption of low molecular weight proteins and proximal tubular cell dysfunction are observed, thus leading to albuminuria (135-137). A study on a nephrotic syndrome rat model revealed that amiloride-sensitive ENaCs are activated and the expression levels of $Na^+$ transporters are reduced in proximal renal tubules, which may be due to the compensatory function (138). Furthermore, Gadau *et al* (139) used an anti-Thy1 vasoproliferative glomerulonephritis rat model to evaluate the association between the changes in $Na^+$ and water homeostasis and those in the renal tubular epithelium with $Na^+$ retention. The results showed that the abundance of salt and water transporters ($Na^+/H^+$ exchanger-3, $Na^+/K^+/2Cl^-$ co-transporter and aquaprin-1) in the proximal tubular brush border membrane decreased, thus indicating that ion transporters are a relevant mechanism of channel activation in glomerular diseases. These findings suggest that there is an association between the above mechanism and the occurrence and development of proteinuria. In addition, de Seigneux *et al* (140) investigated the association between proteinuria and phosphoremia in a nephrotic proteinuria mouse model. The results showed that expression of $Na^+/Na^+$ phosphate apical symporter is abnormal in mice with proteinuria, while the albuminuria-induced alterations on phosphate tubular handling are not associated with the glomerular filtration rate. Another study by Shimizu *et al* (141) exploring the effects of N-acetylcysteine on kidney function and $Na^+$ and water transporters in mice, showed that $Na^+/K^+/2Cl^-$ co-transporter 2 and aquaporin 2 are both upregulated and proteinuria is alleviated

in mice in that received the treatment. The above studies support an association between proteinuria and ion transporters, thus indicating that ion transporters could also be considered as therapeutic targets for reducing proteinuria in patients.

## 3. Conclusion

Proteinuria is a significantly distinct determinant of kidney disease progression and mortality. Therefore, unravelling the mechanism of action of $Na^+$, $Ca^{2+}$, $Cl^-$ and $K^+$ channels and ion transporters in proteinuria could provide novel insights into the identification of novel targets for treating proteinuria and delaying kidney diseases.

## Acknowledgements

## Funding

## Availability of data and materials

Not applicable.

## Authors' contributions

JL, XuL and NX wrote the review, collected literature information and created figures. HH and XiL reviewed the manuscript and proposed final revisions. All authors read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

## References

1. Kondratskyi A, Kondratska K, Skryma R, Klionsky DJ and Prevarskaya N: Ion channels in the regulation of autophagy. Autophagy 14: 3-21, 2018.
2. Alexander SPH, Mathie A, Peters JA, Veale EL, Striessnig J, Kelly E, Armstrong JF, Faccenda E, Harding SD, Pawson AJ, et al: The concise guide to pharmacology 2019/20: Ion channels. Br J Pharmacol 176 (Suppl 1): S142-S228, 2019.
3. Roux B: Ion channels and ion selectivity. Essays Biochem 61: 201-209, 2017.
4. Cheng J, Wen J, Wang N, Wang C, Xu Q and Yang Y: Ion channels and vascular diseases. Arterioscler Thromb Vasc Biol 39: e146-e156, 2019.
5. Anderson KJ, Cormier RT and Scott PM: Role of ion channels in gastrointestinal cancer. World J Gastroenterol 25: 5732-5772, 2019.
6. Armijo JA, Shushtarian M, Valdizan EM, Cuadrado A, de las Cuevas I and Adín J: Ion channels and epilepsy. Curr Pharm Des 11: 1975-2003, 2005.
7. Moiseenkova-Bell V, Delemotte L and Minor DL Jr: Ion channels: Intersection of structure, function, and pharmacology. J Mol Biol 433: 167102, 2021.
8. Wang L and Yule DI: Differential regulation of ion channels function by proteolysis. Biochim Biophys Acta Mol Cell Res 1865: 1698-1706, 2018.
9. Catterall WA, Lenaeus MJ and Gamal El-Din TM: Structure and pharmacology of voltage-gated sodium and calcium channels. Annu Rev Pharmacol Toxicol 60: 133-154, 2020.
10. De Logu F and Geppetti P: Ion channel pharmacology for pain modulation. Handb Exp Pharmacol 260: 161-186, 2019.
11. Pallet N, Bastard JP, Claeyssens S, Fellahi S, Delanaye P, Piéroni L and Caussé E; groupe de travail SFBC, SFNDT, SNP: Proteinuria typing: How, why and for whom? Ann Biol Clin (Paris) 77: 13-25, 2019.
12. Barton M: Reversal of proteinuric renal disease and the emerging role of endothelin. Nat Clin Pract Nephrol 4: 490-501, 2008.
13. Nowak A and Serra AL: Assessment of proteinuria. Praxis (Bern 1994) 102: 797-802, 2013 (In German).
14. D'Amico G and Bazzi C: Pathophysiology of proteinuria. Kidney Int 63: 809-825, 2003.
15. Menzel S and Moeller MJ: Role of the podocyte in proteinuria. Pediatr Nephrol 26: 1775-1780, 2011.
16. Miner JH: Glomerular basement membrane composition and the filtration barrier. Pediatr Nephrol 26: 1413-1417, 2011.
17. Kallen RG, Cohen SA and Barchi RL: Structure, function and expression of voltage-dependent sodium channels. Mol Neurobiol 7: 383-428, 1993.
18. Lee CH and Ruben PC: Interaction between voltage-gated sodium channels and the neurotoxin, tetrodotoxin. Channels (Austin) 2: 407-412, 2008.
19. Hanukoglu I and Hanukoglu A: Epithelial sodium channel (ENaC) family: Phylogeny, structure-function, tissue distribution, and associated inherited diseases. Gene 579: 95-132, 2016.
20. Brunklaus A, Ellis R, Reavey E, Semsarian C and Zuberi SM: Genotype phenotype associations across the voltage-gated sodium channel family. J Med Genet 51: 650-658, 2014.
21. Soundararajan R, Pearce D, Hughey RP and Kleyman TR: Role of epithelial sodium channels and their regulators in hypertension. J Biol Chem 285: 30363-30369, 2010.
22. Büsst CJ: Blood pressure regulation via the epithelial sodium channel: From gene to kidney and beyond. Clin Exp Pharmacol Physiol 40: 495-503, 2013.
23. Zachar RM, Skjødt K, Marcussen N, Walter S, Toft A, Nielsen MR, Jensen BL and Svenningsen P: The epithelial sodium channel γ-subunit is processed proteolytically in human kidney. J Am Soc Nephrol 26: 95-106, 2015.
24. Svenningsen P, Friis UG, Bistrup C, Buhl KB, Jensen BL and Skøtt O: Physiological regulation of epithelial sodium channel by proteolysis. Curr Opin Nephrol Hypertens 20: 529-533, 2011.
25. Ware AW, Rasulov SR, Cheung TT, Lott JS and McDonald FJ: Membrane trafficking pathways regulating the epithelial $Na^+$ channel. Am J Physiol Renal Physiol 318: F1-F13, 2020.
26. Bockenhauer D: Over- or underfill: Not all nephrotic states are created equal. Pediatr Nephrol 28: 1153-1156, 2013.
27. Larionov A, Dahlke E, Kunke M, Zanon Rodriguez L, Schiessl IM, Magnin JL, Kern U, Alli AA, Mollet G, Schilling O, et al: Cathepsin B increases ENaC activity leading to hypertension early in nephrotic syndrome. J Cell Mol Med 23: 6543-6553, 2019.
28. Fila M, Sassi A, Brideau G, Cheval L, Morla L, Houillier P, Walter C, Gennaoui M, Collignon L, Keck M, et al: A variant of ASIC2 mediates sodium retention in nephrotic syndrome. JCI Insight 6: e148588, 2021.
29. Svenningsen P, Skøtt O and Jensen BL: Proteinuric diseases with sodium retention: Is plasmin the link? Clin Exp Pharmacol Physiol 39: 117-124, 2012.
30. Hinrichs GR, Jensen BL and Svenningsen P: Mechanisms of sodium retention in nephrotic syndrome. Curr Opin Nephrol Hypertens 29: 207-212, 2020.
31. Passero CJ, Hughey RP and Kleyman TR: New role for plasmin in sodium homeostasis. Curr Opin Nephrol Hypertens 19: 13-19, 2010.

32. Briet M and Schiffrin EL: Aldosterone: Effects on the kidney and cardiovascular system. Nat Rev Nephrol 6: 261-273, 2010.
33. Shapovalov G, Skryma R and Prevarskaya N: Calcium channels and prostate cancer. Recent Pat Anticancer Drug Discov 8: 18-26, 2013.
34. Prevarskaya N, Ouadid-Ahidouch H, Skryma R and Shuba Y: Remodelling of Ca2+ transport in cancer: How it contributes to cancer hallmarks? Philos Trans R Soc Lond B Biol Sci 369: 20130097, 2014.
35. Mignen O, Thompson JL and Shuttleworth TJ: Ca2+ selectivity and fatty acid specificity of the noncapacitative, arachidonate-regulated Ca2+ (ARC) channels. J Biol Chem 278: 10174-10181, 2003.
36. Lewis RS: Store-operated calcium channels: From function to structure and back again. Cold Spring Harb Perspect Biol 12: a035055, 2020.
37. Zhou Y and Greka A: Calcium-permeable ion channels in the kidney. Am J Physiol Renal Physiol 310: F1157-F1167, 2016.
38. Patergnani S, Danese A, Bouhamida E, Aguiari G, Previati M, Pinton P and Giorgi C: Various aspects of calcium signaling in the regulation of apoptosis, autophagy, cell proliferation, and cancer. Int J Mol Sci 21: 8323, 2020.
39. Lou J, Yang X, Shan W, Jin Z, Ding J, Hu Y, Liao Q, Du Q, Xie R and Xu J: Effects of calcium-permeable ion channels on various digestive diseases in the regulation of autophagy (review). Mol Med Rep 24: 680, 2021.
40. Perez-Reyes E: Molecular physiology of low-voltage-activated t-type calcium channels. Physiol Rev 83: 117-161, 2003.
41. Zamponi GW, Striessnig J, Koschak A and Dolphin AC: The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. Pharmacol Rev 67: 821-870, 2015.
42. Catterall WA: Voltage-gated calcium channels. Cold Spring Harb Perspect Biol 3: a003947, 2011.
43. Sairaman A, Cardoso FC, Bispat A, Lewis RJ, Duggan PJ and Tuck KL: Synthesis and evaluation of aminobenzothiazoles as blockers of N- and T-type calcium channels. Bioorg Med Chem 26: 3046-3059, 2018.
44. Tsunemi T, Saegusa H, Ishikawa K, Nagayama S, Murakoshi T, Mizusawa H and Tanabe T: Novel Cav2.1 splice variants isolated from Purkinje cells do not generate P-type Ca2+ current. J Biol Chem 277: 7214-7221, 2002.
45. Yamaguchi S, Okamura Y, Nagao T and Adachi-Akahane S: Serine residue in the IIIS5-S6 linker of the L-type Ca2+ channel alpha 1C subunit is the critical determinant of the action of dihydropyridine Ca2+ channel agonists. J Biol Chem 275: 41504-41511, 2000.
46. Hansen PB: Functional and pharmacological consequences of the distribution of voltage-gated calcium channels in the renal blood vessels. Acta Physiol (Oxf) 207: 690-699, 2013.
47. Ohta M, Sugawara S, Sato N, Kuriyama C, Hoshino C and Kikuchi A: Effects of benidipine, a long-acting T-type calcium channel blocker, on home blood pressure and renal function in patients with essential hypertension: A retrospective, 'real-world' comparison with amlodipine. Clin Drug Investig 29: 739-746, 2009.
48. Mishima K, Maeshima A, Miya M, Sakurai N, Ikeuchi H, Hiromura K and Nojima Y: Involvement of N-type Ca(2+) channels in the fibrotic process of the kidney in rats. Am J Physiol Renal Physiol 304: F665-F673, 2013.
49. Tamargo J and Ruilope LM: Investigational calcium channel blockers for the treatment of hypertension. Expert Opin Investig Drugs 25: 1295-1309, 2016.
50. Khanna R, Yu J, Yang X, Moutal A, Chefdeville A, Gokhale V, Shuja Z, Chew LA, Bellampalli SS, Luo S, et al: Targeting the CaVα-CaVβ interaction yields an antagonist of the N-type CaV2.2 channel with broad antinociceptive efficacy. Pain 160: 1644-1661, 2019.
51. Ando K: L-/N-type calcium channel blockers and proteinuria. Curr Hypertens Rev 9: 210-218, 2013.
52. Lei B, Nakano D, Fujisawa Y, Liu Y, Hitomi H, Kobori H, Mori H, Masaki T, Asanuma K, Tomino Y and Nishiyama A: N-type calcium channel inhibition with cilnidipine elicits glomerular podocyte protection independent of sympathetic nerve inhibition. J Pharmacol Sci 119: 359-367, 2012.
53. Fan YY, Kohno M, Nakano D, Ohsaki H, Kobori H, Suwarni D, Ohashi N, Hitomi H, Asanuma K, Noma T, et al: Cilnidipine suppresses podocyte injury and proteinuria in metabolic syndrome rats: Possible involvement of N-type calcium channel in podocyte. J Hypertens 28: 1034-1043, 2010.
54. Tamargo J: New calcium channel blockers for the treatment of hypertension. Hipertens Riesgo Vasc 34 (Suppl 2): S5-S8, 2017 (In Spanish).
55. Hansen PB, Poulsen CB, Walter S, Marcussen N, Cribbs LL, Skøtt O and Jensen BL: Functional importance of L- and P/Q-type voltage-gated calcium channels in human renal vasculature. Hypertension 58: 464-470, 2011.
56. Nilius B and Owsianik G: The transient receptor potential family of ion channels. Genome Biol 12: 218, 2011.
57. Ramsey IS, Delling M and Clapham DE: An introduction to TRP channels. Annu Rev Physiol 68: 619-647, 2006.
58. Montell C and Rubin GM: Molecular characterization of the Drosophila trp locus: A putative integral membrane protein required for phototransduction. Neuron 2: 1313-1323, 1989.
59. Gees M, Owsianik G, Nilius B and Voets T: TRP channels. Compr Physiol 2: 563-608, 2012.
60. Caterina MJ and Pang Z: TRP channels in skin biology and pathophysiology. Pharmaceuticals (Basel) 9: 77, 2016.
61. Li H: TRP channel classification. Adv Exp Med Biol 976: 1-8, 2017.
62. Zhao Y, McVeigh BM and Moiseenkova-Bell VY: Structural pharmacology of TRP channels. J Mol Biol 433: 166914, 2021.
63. Nilius B: TRP channels in disease. Biochim Biophys Acta 1772: 805-812, 2007.
64. Moran MM: TRP channels as potential drug targets. Annu Rev Pharmacol Toxicol 58: 309-330, 2018.
65. Koivisto AP, Belvisi MG, Gaudet R and Szallasi A: Advances in TRP channel drug discovery: From target validation to clinical studies. Nat Rev Drug Discov 21: 41-59, 2022.
66. Feng YL, Chen H, Chen DQ, Vaziri ND, Su W, Ma SX, Shang YQ, Mao JR, Yu XY, Zhang L, et al: Activated NF-κB/Nrf2 and Wnt/β-catenin pathways are associated with lipid metabolism in CKD patients with microalbuminuria and macroalbuminuria. Biochim Biophys Acta Mol Basis Dis 1865: 2317-2332, 2019.
67. Voets T, Vriens J and Vennekens R: Targeting TRP channels-valuable alternatives to combat pain, lower urinary tract disorders, and type 2 diabetes. Trends Pharmacol Sci 40: 669-683, 2019.
68. Wang Q, Tian X, Wang Y, Wang Y, Li J, Zhao T and Li P: Role of transient receptor potential canonical channel 6 (TRPC6) in diabetic kidney disease by regulating podocyte actin cytoskeleton rearrangement. J Diabetes Res 2020: 6897390, 2020.
69. Bacsa B, Tiapko O, Stockner T and Groschner K: Mechanisms and significance of Ca2+ entry through TRPC channels. Curr Opin Physiol 17: 25-33, 2020.
70. Möller CC, Flesche J and Reiser J: Sensitizing the slit diaphragm with TRPC6 ion channels. J Am Soc Nephrol 20: 950-953, 2009.
71. Möller CC, Wei C, Altintas MM, Li J, Greka A, Ohse T, Pippin JW, Rastaldi MP, Wawersik S, Schiavi S, et al: Induction of TRPC6 channel in acquired forms of proteinuric kidney disease. J Am Soc Nephrol 18: 29-36, 2007.
72. Schaldecker T, Kim S, Tarabanis C, Tian D, Hakroush S, Castonguay P, Ahn W, Wallentin H, Heid H, Hopkins CR, et al: Inhibition of the TRPC5 ion channel protects the kidney filter. J Clin Invest 123: 5298-5309, 2013.
73. Tian D, Jacobo SM, Billing D, Rozkalne A, Gage SD, Anagnostou T, Pavenstädt H, Hsu HH, Schlondorff J, Ramos A and Greka A: Antagonistic regulation of actin dynamics and cell motility by TRPC5 and TRPC6 channels. Sci Signal 3: ra77, 2010.
74. Shalygin A, Shuyskiy LS, Bohovyk R, Palygin O, Staruschenko A and Kaznacheyeva E: Cytoskeleton rearrangements modulate TRPC6 channel activity in podocytes. Int J Mol Sci 22: 4396, 2021.
75. Schlondorff J: TRPC6 and kidney disease: Sclerosing more than just glomeruli? Kidney Int 91: 773-775, 2017.
76. Schlöndorff JS and Pollak MR: TRPC6 in glomerular health and disease: What we know and what we believe. Semin Cell Dev Biol 17: 667-674, 2006.
77. Kim EY, Yazdizadeh Shotorbani P and Dryer SE: Trpc6 inactivation confers protection in a model of severe nephrosis in rats. J Mol Med (Berl) 96: 631-644, 2018.
78. Hall G, Wang L and Spurney RF: TRPC channels in proteinuric kidney diseases. Cells 9: 44, 2019.
79. van der Wijst J and Bindels RJM: Renal physiology: TRPC5 inhibition to treat progressive kidney disease. Nat Rev Nephrol 14: 145-146, 2018.
80. Walsh L, Reilly JF, Cornwall C, Gaich GA, Gipson DS, Heerspink HJL, Johnson L, Trachtman H, Tuttle KR, Farag YMK, et al: Safety and efficacy of GFB-887, a TRPC5 channel inhibitor, in patients with focal segmental glomerulosclerosis, treatment-resistant minimal change disease, or diabetic nephropathy: TRACTION-2 trial design. Kidney Int Rep 6: 2575-2584, 2021.

81. Reiser J, Polu KR, Möller CC, Kenlan P, Altintas MM, Wei C, Faul C, Herbert S, Villegas I, Avila-Casado C, *et al*: TRPC6 is a glomerular slit diaphragm-associated channel required for normal renal function. Nat Genet 37: 739-744, 2005.
82. Wiggins RC: The spectrum of podocytopathies: A unifying view of glomerular diseases. Kidney Int 71: 1205-1214, 2007.
83. Zhou Y, Castonguay P, Sidhom EH, Clark AR, Dvela-Levitt M, Kim S, Sieber J, Wieder N, Jung JY, Andreeva S, *et al*: A small-molecule inhibitor of TRPC5 ion channels suppresses progressive kidney disease in animal models. Science 358: 1332-1336, 2017.
84. Zhang H, Ding J, Fan Q and Liu S: TRPC6 up-regulation in Ang II-induced podocyte apoptosis might result from ERK activation and NF-kappaB translocation. Exp Biol Med (Maywood) 234: 1029-1036, 2009.
85. Wang Z, Wei X, Zhang Y, Ma X, Li B, Zhang S, Du P, Zhang X and Yi F: NADPH oxidase-derived ROS contributes to upregulation of TRPC6 expression in puromycin aminonucleoside-induced podocyte injury. Cell Physiol Biochem 24: 619-626, 2009.
86. Kistler AD, Singh G, Altintas MM, Yu H, Fernandez IC, Gu C, Wilson C, Srivastava SK, Dietrich A, Walz K, *et al*: Transient receptor potential channel 6 (TRPC6) protects podocytes during complement-mediated glomerular disease. J Biol Chem 288: 36598-36609, 2013.
87. Zhou Y, Kim C, Pablo JLB, Zhang F, Jung JY, Xiao L, Bazua-Valenti S, Emani M, Hopkins CR, Weins A and Greka A: TRPC5 channel inhibition protects podocytes in puromycin-aminonucleoside induced nephrosis models. Front Med (Lausanne) 8: 721865, 2021.
88. Randhawa PK and Jaggi AS: TRPV4 channels: Physiological and pathological role in cardiovascular system. Basic Res Cardiol 110: 54, 2015.
89. Everaerts W, Nilius B and Owsianik G: The vanilloid transient receptor potential channel TRPV4: From structure to disease. Prog Biophys Mol Biol 103: 2-17, 2010.
90. Kassmann M, Harteneck C, Zhu Z, Nürnberg B, Tepel M and Gollasch M: Transient receptor potential vanilloid 1 (TRPV1), TRPV4, and the kidney. Acta Physiol (Oxf) 207: 546-564, 2013.
91. Mannaa M, Markó L, Balogh A, Vigolo E, N'diaye G, Kaßmann M, Michalick L, Weichelt U, Schmidt-Ott KM, Liedtke WB, *et al*: Transient receptor potential vanilloid 4 channel deficiency aggravates tubular damage after acute renal ischaemia reperfusion. Sci Rep 8: 4878, 2018.
92. Karasawa T, Wang Q, Fu Y, Cohen DM and Steyger PS: TRPV4 enhances the cellular uptake of aminoglycoside antibiotics. J Cell Sci 121: 2871-2879, 2008.
93. Gualdani R, Seghers F, Yerna X, Schakman O, Tajeddine N, Achouri Y, Tissir F, Devuyst O and Gailly P: Mechanical activation of TRPV4 channels controls albumin reabsorption by proximal tubule cells. Sci Signal 13: eabc6967, 2020.
94. Duran C, Thompson CH, Xiao Q and Hartzell HC: Chloride channels: Often enigmatic, rarely predictable. Annu Rev Physiol 72: 95-121, 2010.
95. Xia J, Wang H, Li S, Wu Q, Sun L, Huang H and Zeng M: Ion channels or aquaporins as novel molecular targets in gastric cancer. Mol Cancer 16: 54, 2017.
96. Gururaja Rao S, Ponnalagu D, Patel NJ and Singh H: Three decades of chloride intracellular channel proteins: From organelle to organ physiology. Curr Protoc Pharmacol 80: 11.21.1-11.21.17, 2018.
97. Berend K, van Hulsteijn LH and Gans RO: Chloride: The queen of electrolytes? Eur J Intern Med 23: 203-211, 2012.
98. Jentsch TJ, Stein V, Weinreich F and Zdebik AA: Molecular structure and physiological function of chloride channels. Physiol Rev 82: 503-568, 2002.
99. Suzuki M, Morita T and Iwamoto T: Diversity of Cl(-) channels. Cell Mol Life Sci 63: 12-24, 2006.
100. Scheel O, Zdebik AA, Lourdel S and Jentsch TJ: Voltage-dependent electrogenic chloride/proton exchange by endosomal CLC proteins. Nature 436: 424-427, 2005.
101. Uchida S: In vivo role of CLC chloride channels in the kidney. Am J Physiol Renal Physiol 279: F802-F808, 2000.
102. Schriever AM, Friedrich T, Pusch M and Jentsch TJ: CLC chloride channels in Caenorhabditis elegans. J Biol Chem 274: 34238-34244, 1999.
103. Jentsch TJ and Pusch M: CLC chloride channels and transporters: Structure, function, physiology, and disease. Physiol Rev 98: 1493-1590, 2018.
104. Hryciw DH, Ekberg J, Pollock CA and Poronnik P: ClC-5: A chloride channel with multiple roles in renal tubular albumin uptake. Int J Biochem Cell Biol 38: 1036-1042, 2006.
105. Novarino G, Weinert S, Rickheit G and Jentsch TJ: Endosomal chloride-proton exchange rather than chloride conductance is crucial for renal endocytosis. Science 328: 1398-1401, 2010.
106. Devuyst O and Luciani A: Chloride transporters and receptor-mediated endocytosis in the renal proximal tubule. J Physiol 593: 4151-4164, 2015.
107. Günther W, Piwon N and Jentsch TJ: The ClC-5 chloride channel knock-out mouse-an animal model for Dent's disease. Pflugers Arch 445: 456-462, 2003.
108. Faria D, Rock JR, Romao AM, Schweda F, Bandulik S, Witzgall R, Schlatter E, Heitzmann D, Pavenstädt H, Herrmann E, *et al*: The calcium-activated chloride channel Anoctamin 1 contributes to the regulation of renal function. Kidney Int 85: 1369-1381, 2014.
109. Yang YD, Cho H, Koo JY, Tak MH, Cho Y, Shim WS, Park SP, Lee J, Lee B, Kim BM, *et al*: TMEM16A confers receptor-activated calcium-dependent chloride conductance. Nature 455: 1210-1215, 2008.
110. González C, Baez-Nieto D, Valencia I, Oyarzún I, Rojas P, Naranjo D and Latorre R: K(+) channels: Function-structural overview. Compr Physiol 2: 2087-2149, 2012.
111. Sigworth FJ: Potassium channel mechanics. Neuron 32: 555-556, 2001.
112. Gulbis JM and Doyle DA: Potassium channel structures: Do they conform? Curr Opin Struct Biol 14: 440-446, 2004.
113. Kuang Q, Purhonen P and Hebert H: Structure of potassium channels. Cell Mol Life Sci 72: 3677-3693, 2015.
114. Noma A: ATP-regulated K+ channels in cardiac muscle. Nature 305: 147-148, 1983.
115. Ashcroft FM and Rorsman P: K(ATP) channels and islet hormone secretion: New insights and controversies. Nat Rev Endocrinol 9: 660-669, 2013.
116. Rorsman P, Ramracheya R, Rorsman NJ and Zhang Q: ATP-regulated potassium channels and voltage-gated calcium channels in pancreatic alpha and beta cells: Similar functions but reciprocal effects on secretion. Diabetologia 57: 1749-1761, 2014.
117. Tinker A, Aziz Q, Li Y and Specterman M: ATP-sensitive potassium channels and their physiological and pathophysiological roles. Compr Physiol 8: 1463-1511, 2018.
118. Cole WC, Chen TT and Clément-Chomienne O: Myogenic regulation of arterial diameter: Role of potassium channels with a focus on delayed rectifier potassium current. Can J Physiol Pharmacol 83: 755-765, 2005.
119. Jackson MB, Konnerth A and Augustine GJ: Action potential broadening and frequency-dependent facilitation of calcium signals in pituitary nerve terminals. Proc Natl Acad Sci USA 88: 380-384, 1991.
120. Guéguinou M, Chantôme A, Fromont G, Bougnoux P, Vandier C and Potier-Cartereau M: KCa and Ca(2+) channels: The complex thought. Biochim Biophys Acta 1843: 2322-2333, 2014.
121. Sforna L, Megaro A, Pessia M, Franciolini F and Catacuzzeno L: Structure, gating and basic functions of the Ca2+-activated K channel of intermediate conductance. Curr Neuropharmacol 16: 608-617, 2018.
122. Walewska A, Kulawiak B, Szewczyk A and Koprowski P: Mechanosensitivity of mitochondrial large-conductance calcium-activated potassium channels. Biochim Biophys Acta Bioenerg 1859: 797-805, 2018.
123. Fezai M, Ahmed M, Hosseinzadeh Z and Lang F: Up-regulation of the large-conductance Ca2+-activated K+ channel by glycogen synthase kinase GSK3β. Cell Physiol Biochem 39: 1031-1039, 2016.
124. Giebisch G: Potassium channels and the kidney. Nephrologie 21: 223-228, 2000 (In French).
125. Sorensen CM, Braunstein TH, Holstein-Rathlou NH and Salomonsson M: Role of vascular potassium channels in the regulation of renal hemodynamics. Am J Physiol Renal Physiol 302: F505-F518, 2012.
126. Tamura Y, Tanabe K, Kitagawa W, Uchida S, Schreiner GF, Johnson RJ and Nakagawa T: Nicorandil, a K(atp) channel opener, alleviates chronic renal injury by targeting podocytes and macrophages. Am J Physiol Renal Physiol 303: F339-F349, 2012.
127. Snijder PM, Frenay AR, Koning AM, Bachtler M, Pasch A, Kwakernaak AJ, van den Berg E, Bos EM, Hillebrands JL, Navis G, *et al*: Sodium thiosulfate attenuates angiotensin II-induced hypertension, proteinuria and renal damage. Nitric Oxide 42: 87-98, 2014.

128. Hyodo T, Oda T, Kikuchi Y, Higashi K, Kushiyama T, Yamamoto K, Yamada M, Suzuki S, Hokari R, Kinoshita M, *et al*: Voltage-gated potassium channel Kv1.3 blocker as a potential treatment for rat anti-glomerular basement membrane glomerulonephritis. Am J Physiol Renal Physiol 299: F1258-F1269, 2010.

129. Huang C, Zhang L, Shi Y, Yi H, Zhao Y, Chen J, Pollock CA and Chen XM: The KCa3.1 blocker TRAM34 reverses renal damage in a mouse model of established diabetic nephropathy. PLoS One 13: e0192800, 2018.

130. Piwkowska A, Rogacka D, Audzeyenka I, Kasztan M, Angielski S and Jankowski M: Insulin increases glomerular filtration barrier permeability through PKGIα-dependent mobilization of BKCa channels in cultured rat podocytes. Biochim Biophys Acta 1852: 1599-1609, 2015.

131. Neverisky DL and Abbott GW: Ion channel-transporter interactions. Crit Rev Biochem Mol Biol 51: 257-267, 2015.

132. Veiras LC, McFarlin BE, Ralph DL, Buncha V, Prescott J, Shirvani BS, McDonough JC, Ha D, Giani J, Gurley SB, *et al*: Electrolyte and transporter responses to angiotensin II induced hypertension in female and male rats and mice. Acta Physiol (Oxf) 229: e13448, 2020.

133. Orlov SN, Adragna NC, Adarichev VA and Hamet P: Genetic and biochemical determinants of abnormal monovalent ion transport in primary hypertension. Am J Physiol 276: C511-C536, 1999.

134. Graves SW: Sodium regulation, sodium pump function and sodium pump inhibitors in uncomplicated pregnancy and preeclampsia. Front Biosci 12: 2438-2446, 2007.

135. Devuyst O, Jouret F, Auzanneau C and Courtoy PJ: Chloride channels and endocytosis: New insights from Dent's disease and ClC-5 knockout mice. Nephron Physiol 99: p69-p73, 2005.

136. Shipman KE and Weisz OA: Making a dent in dent disease. Function (Oxf) 1: zqaa017, 2020.

137. Anglani F, Gianesello L, Beara-Lasic L and Lieske J: Dent disease: A window into calcium and phosphate transport. J Cell Mol Med 23: 7132-7142, 2019.

138. Svenningsen P, Friis UG, Versland JB, Buhl KB, Møller Frederiksen B, Andersen H, Zachar RM, Bistrup C, Skøtt O, Jørgensen JS, *et al*: Mechanisms of renal NaCl retention in proteinuric disease. Acta Physiol (Oxf) 207: 536-545, 2013.

139. Gadau J, Peters H, Kastner C, Kühn H, Nieminen-Kelhä M, Khadzhynov D, Krämer S, Castrop H, Bachmann S and Theilig F: Mechanisms of tubular volume retention in immune-mediated glomerulonephritis. Kidney Int 75: 699-710, 2009.

140. de Seigneux S, Wilhelm-Bals A and Courbebaisse M: On the relationship between proteinuria and plasma phosphate. Swiss Med Wkly 147: w14509, 2017.

141. Shimizu MH, Volpini RA, de Bragança AC, Campos R, Canale D, Sanches TR, Andrade L and Seguro AC: N-acetylcysteine attenuates renal alterations induced by senescence in the rat. Exp Gerontol 48: 298-303, 2013.