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TRP Channels in Kidney Disease**Yu-Juei Hsu^{1,2}, Joost G. J. Hoenderop¹ and René J. M. Bindels¹**

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Abstract

Mammalian TRP channel proteins form six-transmembrane cation-permeable channels that may be grouped into six subfamilies on the basis of amino acid sequence homology (TRPC, TRPV, TRPM, TRPA, TRPP, and TRPML). Recent studies of TRP channels indicate that they are involved in numerous fundamental cell functions and are considered to play an important role in the pathophysiology of many diseases. Many TRPs are expressed in kidney along different parts of the nephron and growing evidence suggest that these channels are involved in hereditary, as well as acquired kidney disorders. TRPC6, TRPM6, and TRPP2 have been implicated in hereditary focal segmental glomerulosclerosis (FSGS),

hypomagnesemia with secondary hypocalcemia (HSH), and polycystic kidney disease (PKD), respectively. In addition, the highly Ca^{2+} -selective channel, TRPV5, contributes to several acquired mineral (dys)regulation, such as diabetes mellitus (DM), acid-base disorders, diuretics, immunosuppressant agents, and vitamin D analogues-associated Ca^{2+} imbalance whereas TRPV4 may function as an osmoreceptor in kidney and participate in the regulation of sodium and water balance. This review presents an overview of the current knowledge concerning the distribution of TRP channels in kidney and their possible roles in renal physiology and kidney diseases.

Introduction

The transient receptor potential (TRP) protein superfamily is a diverse group of voltage-independent cation-permeable channels expressed in most mammalian cells. Mammalian TRP channels have been organized into six protein subfamilies based on sequence identity [1-3]. These have been designated C (Canonical, TRPC1–TRPC7), V (Vanilloid, TRPV1–TRPV6), M (Melastatin, TRPM1–TRPM8), A (Ankyrin, TRPA1), P (Polycystin, TRPP1–TRPP3), and ML (Mucolipin, TRPML1–TRPML3). TRP channels have been shown to be expressed in many different tissues and may participate in a wide range of processes such as sensory signaling and regulation of systemic osmolality, blood circulation, gut motility, airway and bladder hypersensitivity and cell differentiation [4]. Due to the great functional potentials of TRP channels, it is deduced that abnormality of TRP channels might be involved in the pathogenesis of various systemic diseases.

The nephron is the functional unit of the kidney and consists of a Malpighian corpuscle, with a vascular glomerulus within a matrix formed by mesangial cells and an epithelial Bowman's capsule. The capsule joins a series of tubules starting with the proximal tubule (PT) and followed by the loop of Henle, the distal convoluted tubule (DCT) and ending in the collecting ducts (CD) [5]. Recently, several subfamilies of TRP channels including TRPC, TRPV, TRPM and TRPP have been disclosed in different parts of nephron (Figure 1). A recent study in rat found that TRPC1 immunofluorescence is detected in glomeruli and co-localized with aquaporin-1 in PT and descending thin limb (DTL), whereas TRPC3 and TRPC6 are predominantly confined to glomeruli and co-expressed with aquaporin-2 in principle cells of the CD [6]. Among the structure of glomeruli, TRPC1 is exclusively expressed in mesangial cell and TRPC3 and TRPC6 are found in podocytes [6]. Thus, TRPC1, TRPC3 and TRPC6 might be involved in phospholipase C (PLC)-dependent signaling in specific regions of the nephron [7].

The distal part of the nephron is a major site responsible for active Ca^{2+} and Mg^{2+} reabsorption in kidney [8, 9]. TRPV5, a highly Ca^{2+} -selective channel in the TRP family, is the first TRP channel identified in kidney [10]. TRPV5 is abundantly expressed in DCT and the connecting tubule (CNT) and has been recognized as the gatekeeper of active Ca^{2+} reabsorption in kidney [11]. Its function is further characterized by TRPV5 knockout ($\text{TRPV5}^{-/-}$) mice, which exhibit profound hypercalciuria, intestinal Ca^{2+} hyperabsorption and reduced bone thickness [12]. TRPV6, a homologous highly Ca^{2+} -selective channel was originally identified from rat

duodenum [13], but is also expressed in DCT, CNT and cortical and medullary CD [14]. Although TRPV6 has been implicated as the gatekeeper of intestinal Ca^{2+} absorption, its role in kidney remains largely unknown [14]. TRPM6, a highly Mg^{2+} -permeable channel, is localized along the apical membrane of DCT, has been postulated to be the key channel controlling the transcellular Mg^{2+} reabsorption in kidney [8]. These findings suggested TRPV5 and TRPM6 function as the crucial players in the process of renal reabsorption of divalents [8].

TRPV4 is an osmotically responsive cation channel, which is abundantly expressed in the ascending thin limb (ATL), thick ascending limb (TAL), DTL and CNT [15]. Interestingly, TRPV4 is expressed in only those nephron segments that are constitutively water impermeable. However, it is absent from nephron segments exhibiting water permeability and enhanced aquaporin-2 expression [15]. The unique distribution and characteristics of TRPV4 suggest that it might participate in the renal regulation of water and sodium balance, though the role of TRPV4 in kidney is still elusive. TRPP1 and TRPP2 belong to polycystin TRP subfamily, which exist throughout the animal kingdom [1]. TRPP2 has been found at plasma membrane (PM) and endoplasmic reticulum (ER) [16] and it assembles with TRPP1 to form a multiprotein complex [17], which functions as transducer of Ca^{2+} -dependent signaling [18]. TRPP2 has been implicated in several biological processes including cell proliferation, sperm development and function, mating behavior and asymmetric gene expression [16]. Importantly, recent studies suggest that both proteins are localized in primary cilia of renal epithelial cells and might act as mechanosensors [19, 20].

As shown above, growing evidence is supporting the emerging roles of TRP channels in kidney physiology. Thus, TRP channels are implicated in the pathogenesis of numerous kidney diseases. This review provides an overview of the current knowledge and recent advances concerning the physiological functions of TRP channels in kidney and explores the correlations between TRP channels and kidney diseases.

TRPC6 and focal segmental glomerulosclerosis

Ultrafiltration of plasma by renal glomeruli is the main function of the kidney. The glomerular filter comprises a fenestrated capillary endothelium, the glomerular basement membrane and podocyte foot processes [5]. Podocytes are specialized glomerular epithelial cells that encompass the glomerular capillaries and the complex

interdigital proteins between podocyte foot processes form the slit diaphragm [5]. Podocyte foot processes and glomerular slit diaphragm construct the glomerular filter and damage of podocytes or defects of the slit diaphragm could lead to proteinuria [5]. Nephrin and podocin are central protein components of podocyte foot processes and slit diaphragm, respectively. Both proteins are part of the slit diaphragm signaling platform and mutations of these two proteins have been found to be involved in the pathogenic mechanisms of proteinuric glomerular diseases. Mutations in gene encoding nephrin (NPHS1) cause the rare autosomal recessive disorder congenital nephrotic syndrome of the Finnish type (CNF) whereas mutations in the podocin gene (NPHS2) lead to autosomal recessive steroid resistant nephrotic syndrome [21, 22]. TRPC6 is enriched in the podocyte foot processes and recent work by Winn *et al.* and Reiser *et al.* reported the identification of six mutations in TRPC6 associated with autosomal dominant focal segmental glomerulosclerosis (FSGS). All these mutations are positioned within either the cytoplasmic amino- or carboxy-terminal domains of the TRPC6 protein resulting in missense mutations or a premature stop of the protein [23, 24]. Among these six TRPC6 mutants, three of them (P112Q, R895C, E897K) are gain-of-function mutations, which result in increased Ca^{2+} current amplitudes. Since only three of the six TRPC6 mutants showed increased channel activity it is currently not known whether the excessive receptor-induced cation influx is the disease-causing mechanism. TRPC6 co-localizes with podocin and nephrin and immunoprecipitation studies showed physical interaction between TRPC6 and these proteins, indicating that the channel is integrated into the signaling complex at the slit diaphragm [23]. In addition, Möller *et al.* demonstrated that TRPC6 is functionally connected to the actin cytoskeleton in the podocyte and transient overexpression of the channel in mice leads to proteinuria [25]. Taken together, these data suggest that TRPC6 mutations might cause proteinuria and play a key role in the pathogenesis of FSGS.

TRPP2 and polycystic kidney disease

The TRPP family is divided structurally and functionally into two groups, the polycystin 1 (PKD1, also called TRPP1)-like and polycystin (PKD2, also called TRPP2)-like proteins [17, 18]. In human, the TRPP2-like subgroup, consisting of PKD2/TRPP2, PKD2L1/TRPP3, PKD2L2/TRPP3, have a predicted topology of six putative transmembrane (TM) domains. The PKD1-like subgroup contains five homologous proteins, including PKD1/TRPP1, PKDREJ, PKD1L1, PKD1L2, PKD1L3, all with putative 11 TM domains. Although PKD1-like proteins are structurally distinct from PKD2-like proteins, PKD1-like proteins are still included in

TRPP family because they assemble with PKD2-like proteins to form functional complexes [26]. In kidney, PKD1 has been identified in the plasma membrane of tubular epithelial cells, particularly in DT and CD [27], whereas PKD2 localizes in the plasma membrane and ER, with highest levels in TAL and DCT [28]. Polycystic kidney disease (PKD), a common genetic cause which leads to chronic renal failure, is characterized by the accumulation of fluid-filled cysts in the kidney, liver, pancreas and choroid plexus [29]. Autosomal dominant PKD (ADPKD), the most frequent form of PKD, has been disclosed to arise from mutations in the PKD1 and PKD2 gene. Mutations of PKD1, which is located on chromosome 16p13.3, are responsible for 85% of the PKD cases, whereas mutations in PKD2, which located on chromosome 4q21-23, are responsible for 15% of the PKD cases [30-32]. Although the mechanisms responsible for the cyst formation remain incompletely understood, recent studies showed that PKD1 can activate G proteins and multiple enzymatic signaling cascades [33]. Subsequently, activation of G α subunit and release G $\beta\gamma$ subunits affects the activity of adenylyl cyclase, MAP kinase and other downstream effectors which regulate the processes that are possibly involved in cyst formation, such as fluid secretion and epithelial cell proliferation, polarity and differentiation. On the other hand, the interaction of PKD2 with the coiled-coil domain of PKD1 inhibits G protein signaling [34]. In addition to the studies directed towards polycystins, investigations of PKD pathogenesis have focused on numerous genetic mouse models and the *orpk* and *cpk* mice are the most extensively studied [35]. The *orpk* and *cpk* gene, encode polaris and cystin proteins, respectively. Both proteins are localized in cilia of renal epithelial cells and defects in these two proteins cause abnormalities of cilia structure and function. The *orpk* and *cpk* mutant mice develop renal cysts and biliary dysgenesis in a pattern that mimics autosomal recessive PKD (ARPKD) [36, 37]. Recently, Pazour *et al.* and Yoder *et al.* found that PKD1 and PKD2 co-localize with polaris and cystin in cilia of renal epithelial cells [38, 39] and the PKD1-PKD2 complex has been proposed as a component of a cilia as mechanosensor of epithelial cells [40-42]. Furthermore, the expression of PKD2 is increased in *orpk* mutant mice, which have stunted renal cilia and develop PKD [38]. Taken together, these data suggested that PKD1 and PKD2 might interact with polaris and cystin involved in the pathogenesis of PKD secondary to ciliary dysfunction. In addition, Zhou and colleagues reported that PKD2 regulates the cell cycle through direct interaction with Id2, a member of the helix-loop-helix (HLH) protein family that is known to regulate cell proliferation and differentiation. Id2 expression suppresses the induction of a cyclin-dependent kinase inhibitor, p21, by either PKD1 or PKD2. They proposed that Id2 has a crucial role in cell-cycle

regulation that is mediated by PKD1 and PKD2 [43]. Future studies are needed to elucidate how PKD1 and PKD2 alternations influence ciliary function and result in cyst formation.

TRPV4 and regulation of renal medullary tonicity

The TRPV4 protein, initially described as OTRPC4 [44], VR-OAC [45], TRP12 [46], and VRL-2 [47], is an osmotically-responsive cation channel. In mammals, TRPV4 is activated by hypotonic stimuli, resulting in an increase in intracellular Ca^{2+} concentration [48]. In addition, this channel is found in the circumventricular nuclei of the central nervous system (CNS) [45] and TRPV4 knockout mice ($\text{TRPV4}^{-/-}$) exhibit dysregulation of vasopressin secretion [49, 50]. It has, therefore, been suggested that TRPV4 functions as an osmoreceptor in the CNS. Interestingly, recent studies demonstrated that TRPV4 is highly expressed in mammalian kidney where it is restricted to water-impermeant nephron segments, including ATL, TAL and DCT [15]. The sodium-potassium-chloride cotransporter (NKCC2), couples the inward movement 1 Na^+ , 1 K^+ , 2 Cl^- ion in an electroneutral process, is mainly responsible for the transcellular reabsorption of NaCl in the TAL, which ultimately contributes to the hyperosmotic medulla of the kidney [5]. The co-localization of NKCC2 and TRPV4 in TAL suggests that they might be functionally coupled and involved in the molecular mechanism of renal adaptation to systemic osmotic change. Recently also a role for aquaporin 5 (AQP5) was postulated in activation of TRPV4 to control cell volume. Ambudkar and colleagues examined the mechanism of regulatory volume decrease in salivary gland cells and reported a novel association between TRPV4 and AQP5, which is required for regulating water permeability and cell volume [51]. All together, it is tempting to speculate that TRPV4 functions as an osmoreceptor in kidney and participates in the regulation of sodium and water balance by interacting with NKCC2.

TRPM6 and hypomagnesemia with secondary hypocalcemia

Mg^{2+} is the second most abundant intracellular cation and plays an essential role as co-factor in many enzymatic reactions. Regulation of the total body Mg^{2+} balance principally resides within the kidney that tightly matches the intestinal absorption of Mg^{2+} . Approximately 20% of Mg^{2+} is reabsorbed by the PT. However, the bulk amount of Mg^{2+} (50 - 70%) is reabsorbed by the TAL, which mediates Mg^{2+} reabsorption via paracellular transport. The DCT reabsorbs 5-10% of the filtered Mg^{2+} and the reabsorption rate in this segment defines the final urinary Mg^{2+} concentration, because virtually no reabsorption takes places beyond this segment [52]. Recently, a

positional candidate screening approach in consanguineous families with hypomagnesemia with secondary hypocalcemia (HSH) revealed a critical region identified on chromosome 9q21.13 [53]. Individuals suffering from HSH display neurologic symptoms including seizures and tetany during infancy [54]. The physiological studies of HSH patients have shown that there are defects in both intestinal Mg^{2+} absorption and renal Mg^{2+} reabsorption [55, 56]. Subsequent analysis of the critical region pointed to a gene, *TRPM6*, which was mutated in patients with HSH [54, 55]. Bindels and co-workers demonstrated that TRPM6 is specifically localized along the apical membrane of the renal DCT and the brush-border membrane of the small intestine, epithelia particularly associated with active Mg^{2+} (re)absorption [57]. Furthermore, heterologous expression in human embryonic kidney (HEK) 293 cells of TRPM6, but not TRPM6 mutants identified in patients with HSH, induces a Mg^{2+} -permeable cation channel that is tightly regulated by the intracellular Mg^{2+} concentration [57]. These findings indicated that TRPM6 comprises all or part of the apical Mg^{2+} channel of Mg^{2+} absorbing epithelia where it plays a key role in the pathogenomic mechanisms of HSH.

TRPM6 and Gitelman's syndrome

Gitelman's syndrome (GS) is an autosomal recessive renal tubular disorder characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria [58]. At the molecular level, GS is caused by inactivating mutations in the *SLC12A3* gene encoding the thiazide-sensitive Na^+Cl^- cotransporter (NCC) in the luminal membrane of DCT [59]. Thus, the electrolyte disturbances in GS resemble those observed with long-term administration of thiazide diuretics. However, hypomagnesemia, as a side effect of chronic thiazide administration and a defining feature of GS, remained unexplained. As TRPM6 and NCC predominantly co-localize in DCT [57], a direct inhibitory effect of decreased NaCl influx on active Mg^{2+} reabsorption could in principal be involved. Previous work by Schultheis *et al.* generated NCC knockout ($NCC^{-/-}$) mice, which exhibit both hypocalciuria and hypomagnesemia, representing an animal model mimicking GS [60]. Interestingly, during chronic thiazide administration and in $NCC^{-/-}$ mice, the TRPM6 abundance in DCT was significantly reduced [61]. Thus, TRPM6 down-regulation may represent a general mechanism involved in the pathogenesis of hypomagnesemia in GS and chronic thiazide administration.

TRPV5 and renal Ca^{2+} disorders

The calcium ion (Ca^{2+}) is essential for the normal function of all living cells. In

mammals, the Ca^{2+} balance is tightly controlled through constant regulation of three physiological processes: intestinal absorption, renal reabsorption and exchange of Ca^{2+} from the bone mass [9]. In kidney, Ca^{2+} can re-enter the circulation by paracellular (passive) as well as transcellular (active) Ca^{2+} reabsorption that is the main target for the calciotropic hormones [9]. Active Ca^{2+} reabsorption comprises a sequence of processes restricted to the DCT and the CNT [62]. At the cellular level, transcellular reabsorption is mediated by Ca^{2+} entry across the apical membrane through the specialized epithelial Ca^{2+} channel, intracellular buffering of Ca^{2+} and facilitated diffusion of Ca^{2+} bound to Ca^{2+} -binding proteins (calbindins) and finally Ca^{2+} extrusion across the basolateral membrane by a $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX1) and a plasma membrane Ca^{2+} -ATPase (PMCA1b) [9]. In 1999, Hoenderop *et al.* first identified the renal epithelial Ca^{2+} channel (ECaC) [10] and subsequently the generation TRPV5^{-/-} mice by the same group [12] made substantial progress in our understanding of the molecular mechanism of active renal Ca^{2+} reabsorption. The renal epithelial Ca^{2+} channel has been renamed as TRPV5 due to its sequence and predicted structure which are comparable to TRP superfamily. TRPV5, a highly Ca^{2+} selective TRP channel, has been shown to be the gatekeeper of active renal Ca^{2+} reabsorption and its expression can be regulated by parathyroid hormone (PTH), 1,25 dihydroxyvitamin D₃ (1,25(OH)₂D₃), estrogen, and dietary Ca^{2+} content [63-65]. TRPV5^{-/-} mice display profound renal Ca^{2+} wasting due to impaired active reabsorption in DCT and CNT, accompanied by elevated plasma 1,25(OH)₂D₃ levels, compensatory intestinal Ca^{2+} hyperabsorption and reduced bone thickness [12]. Recently, the investigations of the phenotypes of several different gene ablation mice, including calbindin-D_{28K} knockout, TRPV5 and calbindin-D_{28K} double knockout, and TRPV5 and 1- α -hydroxylase (1 α -OHase) double knockout mice further substantiated that TRPV5 constitutes the rate-limiting step of active Ca^{2+} reabsorption in kidney [66, 67]. Numerous clinical disorders and side effects of commonly prescribed medication for renal disorders directly result from dysregulation of the body Ca^{2+} balance and several studies recently implicated TRPV5 in the pathogenesis of Ca^{2+} -associated kidney diseases and the mechanisms of adverse effects of some renal medication.

TRPV5 and diuretics

Thiazide diuretics are among the most commonly prescribed drugs employed in the treatment of arterial hypertension. These diuretics enhance renal Na^+ excretion through inhibition of NCC present in the apical membrane of DCT cells [68]. Chronic thiazide administration induces hypocalciuria, which is a unique phenotype of GS

[69]. The hypocalciuric effect was suggested to result from direct stimulation of transcellular Ca^{2+} transport and, in particular, apical Ca^{2+} entry through TRPV5 [11, 70]. Alternatively, hypocalciuria was proposed to result from enhancement of passive paracellular Ca^{2+} reabsorption in proximal tubules secondary to extracellular volume (ECV) contraction, distinct from any direct effect on transcellular Ca^{2+} transport [71, 72]. Previously, we reported that thiazide-induced hypocalciuria occurs in spite of reduced renal expression of Ca^{2+} transport proteins in rat [73]. In addition, we showed that ECV contraction mimics the hypocalciuria, and volume repletion completely reverses thiazide-induced hypocalciuria in these rats [73]. Micropuncture experiments disclosed that reabsorption of Na^+ and, importantly, Ca^{2+} in the PT is increased during chronic hydrochlorothiazide (HCTZ) treatment, whereas Ca^{2+} reabsorption in DCT/CNT appeared unaffected [61]. Furthermore, chronic HCTZ administration still induced hypocalciuria in TRPV5^{-/-} mice, in which active Ca^{2+} reabsorption is abolished. HCTZ did not affect renal expression of the proteins involved in active Ca^{2+} transport, including TRPV5 mRNA and protein expression in wild-type mice [61]. Lee *et al.* confirmed that thiazide treatment in mice does not affect renal TRPV5 expression, except when thiazide treatment is combined with salt repletion [74]. However, salt repletion alone induced TRPV5 mRNA expression to a similar extent, suggesting that this effect is not thiazide-specific [74]. Loffing *et al.* recently demonstrated that renal TRPV5 expression is unaffected in NCC knockout mice, an animal model for GS [60, 75]. In accordance, micropuncture experiments in these mice showed that active Ca^{2+} reabsorption is unaltered in DCT/CNT and indicated increased fractional absorption of both Na^+ and Ca^{2+} upstream of DCT [75]. Together these studies conclusively demonstrated that thiazide does not directly affect TRPV5 expression and transcellular Ca^{2+} reabsorption, but increased passive Ca^{2+} reabsorption in the proximal tubule explains the Ca^{2+} -sparing during thiazide treatment and GS.

TRPV5 and immunosuppressant agents

Immunosuppressant drugs, like the calcineurin inhibitors FK506 (tacrolimus) and cyclosporine A, along with glucocorticoids such as dexamethasone and prednisolone, are prescribed in glomerulonephritis and widely used for renal transplantation. These drugs are associated with an increased bone turnover, a negative Ca^{2+} balance and hypercalciuria [76, 77]. Recently, we showed that FK506 treatment in mice reduces renal TRPV5 mRNA and protein expression associated with renal Ca^{2+} wasting, suggesting that down-regulation of Ca^{2+} channel abundance provides the molecular mechanism for FK506-induced hypercalciuria [78]. The

immunosuppressive action of FK506 depends on the inhibition of the Ca^{2+} -dependent phosphatase calcineurin in T lymphocytes [79, 80]. Another calcineurin inhibitor, cyclosporine A, increased urinary Ca^{2+} excretion and decreased calbindin- $\text{D}_{28\text{K}}$ protein levels [81, 82]. This suggested that calcineurin inhibition may play a role in the impairment of Ca^{2+} reabsorption. In addition, tacrolimus binds to intracellular immunophilins called FK506-binding proteins (FKBPs), which were implicated as ion channel regulators [83]. Recent studies by Gkika *et al.* identified FKBP52 as an auxiliary protein of TRPV5, inhibiting channel activity. FKBP52 specifically interacted with TRPV5, and both proteins co-localize in DCT. On the other hand, gene silencing of FKBP52 or administration of the FKBP52 blocker FK-506 alters Ca^{2+} influx through TRPV5 [84]. Therefore, binding of FK506 to FKBPs could affect TRPV5 expression explaining the hypercalciuric effect of FK506. In contrast to FK506, the glucocorticoid agent dexamethasone increased renal TRPV5 expression, suggesting that stimulation of corticoid receptors positively affects TRPV5 transcription, counteracting the negative Ca^{2+} balance during treatment with these compounds [78].

TRPV5 and Vitamin D analogues

Secondary hyperparathyroidism (SHPT), a common disorder in patients with chronic renal failure, develops in response to low serum levels of Ca^{2+} and active vitamin D metabolites. SHPT requires treatment to minimize the effect of elevated PTH on bone and other tissues [85]. Vitamin D compounds have been widely used in the treatment of this disorder and several different vitamin D analogues are available for clinical practice [86]. The 1α -hydroxyvitamin D_2 ($1\alpha(\text{OH})\text{D}_2$) is a vitamin D prodrug, less calcemic than $1,25(\text{OH})_2\text{D}_3$ in animal studies, which must be metabolized to become active [85], resulting in altered pharmacokinetics relative to active vitamin D compounds. $1\alpha,24$ -dihydroxyvitamin D_2 ($1,24(\text{OH})_2\text{D}_2$) is an active metabolite of $1\alpha(\text{OH})\text{D}_2$ with greatly reduced calcemic activity relative to $1,25(\text{OH})_2\text{D}_3$ [87, 88]. The 1α -OHase knockout mice were used to study the activity of vitamin D compounds, namely $1,25(\text{OH})_2\text{D}_3$, $1\alpha(\text{OH})\text{D}_2$, and $1,24(\text{OH})_2\text{D}_2$, on serum Ca^{2+} levels and the expression of Ca^{2+} transport genes. All three compounds were able to increase serum Ca^{2+} levels, although at different time-scales, reflecting their individual pharmacokinetics, thereby increasing serum $1,25(\text{OH})_2\text{D}_3$ levels. Interestingly, TRPV5 and TRPV6 mRNA levels in duodenum increased in parallel with serum levels of Ca^{2+} . Effects of vitamin D compounds on Ca^{2+} regulatory genes in kidney were more diverse, of which $1,24(\text{OH})_2\text{D}_2$ did not up-regulate TRPV5 [89]. However, use of compounds such as $1,25(\text{OH})_2\text{D}_3$ has frequently been accompanied by the undesired side effects of hypercalcemia and hyperphosphatemia through intestinal

hyperabsorption, which increase the risk of soft tissue and vascular calcification [90]. To avoid these side effects, new vitamin D analogues have been developed with the aim of suppressing PTH secretion with minimal calcemic action [91, 92]. Recently, Nijenhuis *et al.* reported a novel vitamin analogue ZK191784 displaying tissue-specific effects when administered *in vivo* or *in vitro* [92]. ZK 191784 enhanced renal TRPV5 expression and exerted an agonist effect on Ca^{2+} handling in kidney. However, ZK191784 did not stimulate intestinal Ca^{2+} absorption. This compound acts as an intestine-specific $1,25(\text{OH})_2\text{D}_3$ antagonist by down-regulation of TRPV6 expression in duodenum. The tissue-specific $1,25(\text{OH})_2\text{D}_3$ effect of this new-generation of vitamin D analogues might be of great benefit in treatment of SHPT.

TRPV5 and uremic calcification

Chronic renal failure (CRF) is characterized by hyperphosphatemia, hypocalcemia and SHPT [93]. Dysregulation of phosphate (P_i), Ca^{2+} and PTH lead to catastrophic complications in patients with CRF. Maintenance of Ca^{2+} and P_i balance is important to prevent progression of renal failure, development of SHPT, generation of uremic bone diseases and cardiovascular sequelae [94, 95]. Until now, it remains a challenge to manage $\text{P}_i/\text{Ca}^{2+}$ abnormalities in uremic patients. Recently, a newly discovered gene, *klotho*, predominantly expressed in kidney has been found to be involved in the development of human aging [96]. The *klotho* mutant mice show reduced life span, decreased activity, infertility, osteoporosis, atrophy of skin, abnormal $\text{Ca}^{2+}/1,25(\text{OH})_2\text{D}_3$ metabolism, hyperphosphatemia and vascular calcification [96]. Interestingly, some characteristics of CRF patients resemble the phenotypes of *klotho* mice and diminished *klotho* production has been found in uremic patients [97]. Furthermore, Chang *et al.* found that *klotho* possesses glucuronidase activity and co-localizes with TRPV5 in DCT [98]. *Klotho* can hydrolyze extracellular sugar residues on TRPV5, which contributes to entrapment of TRPV5 in the plasma membrane and thereby increases Ca^{2+} translocation [98]. Another study by Segawa *et al.* demonstrated that hyperphosphatemia in *klotho*^{-/-} mice is due to dysregulation of expression and trafficking of the renal type Na/P_i IIa/IIc transporters rather than due to intestinal Na/P_i IIb uptake [99]. Taken together, *klotho* regulates TRPV5 and Na/P_i transporters, two major channels responsible for Ca^{2+} and P_i handling in kidney, respectively. Thus, it is tempting to speculate that *klotho* is involved in the pathogenesis of Ca^{2+} and P_i abnormalities in CRF by influence upon TRPV5 and Na/P_i expression.

TRPV5, TRPM6 and diabetes mellitus

Renal Ca^{2+} and Mg^{2+} wasting are two common complications of uncontrolled diabetes mellitus (DM) [100]. After glomerular filtration, Ca^{2+} and Mg^{2+} are reabsorbed largely in the proximal tubule and subsequently in TAL and DCT [8]. Although only a small part of these divalents are reabsorbed in DCT, recent studies demonstrated that TRPV5 and TRPM6 finely tune in this latter segment the final urinary Ca^{2+} and Mg^{2+} concentrations, respectively [8, 9]. Increasing evidence supported the gatekeeper roles of these two TRP channels in renal active Ca^{2+} and Mg^{2+} handling in DCT. However, the underlying mechanisms contributing to diabetes-associated hypercalciuria and hypermagnesiuria remain unclear. Increased filtration load of these divalent cations, and tubular reabsorption defects in TAL or DCT have been proposed to be responsible for renal Ca^{2+} and Mg^{2+} loss [101, 102]. Recently, Lee *et al.* measured TRPV5 and TRPM6 expressions in streptozotocin (STZ)-induced diabetic rats [103]. In their study, diabetic rats displayed a significant increase in their fractional excretion of Ca^{2+} and Mg^{2+} , accompanied by an increased mRNA abundance, rather than anticipated down-regulation, of TRPV5 and TRPM6 in kidney. In addition, insulin administration completely corrected the hyperglycemia-associated hypercalciuria and hypermagnesiuria and abolished the up-regulation of TRPV5 and TRPM6. These findings suggest that the increased TRPV5 and TRPM6 abundance in STZ-induced diabetic rats is due to a compensatory adaptation to an increased load of Ca^{2+} and Mg^{2+} secondary to hyperglycemia.

TRPV5, TRPM6 and acid-base status

Acid-base homeostasis is known to affect renal handling of the divalents Ca^{2+} and Mg^{2+} [9, 104]. Chronic metabolic acidosis, which can occur as a result of clinical disorders such as renal failure, distal renal tubular acidosis, or chronic diarrhea, is associated with increased renal Ca^{2+} and Mg^{2+} excretion [9, 52]. Conversely, chronic metabolic alkalosis in, for example, the milk-alkali syndrome, volume contraction, or treatment of nephrolithiasis by bicarbonate supplementation is known to decrease urine Ca^{2+} and Mg^{2+} excretion [9, 52]. Recently, the molecular mechanisms that explain the altered renal divalent excretion during these disturbances of acid-base balance have been addressed by Bindels and co-workers [105]. Chronic metabolic acidosis was induced by NH_4Cl loading or administration of the carbonic anhydrase inhibitor acetazolamide for 6 days. This enhanced the calciuresis that was accompanied by decreased renal TRPV5 mRNA and protein abundance compared to control mice. In contrast, metabolic acidosis did not affect Ca^{2+} excretion in TRPV5^{-/-} mice, in which active Ca^{2+} reabsorption is effectively abolished. This demonstrates that down-regulation of renal Ca^{2+} transport proteins is responsible for

the observed hypercalciuria. Conversely, chronic metabolic alkalosis that was induced by NaHCO_3 administration for 6 days increased the expression of TRPV5 accompanied by diminished urine Ca^{2+} excretion. However, this Ca^{2+} -sparing action persisted in TRPV5^{-/-} mice, suggesting that additional mechanisms apart from upregulation of active Ca^{2+} reabsorption contribute to the hypocalciuria. Furthermore, chronic metabolic acidosis decreased renal TRPM6 expression, increased Mg^{2+} excretion, and decreased serum Mg^{2+} concentration, whereas chronic metabolic alkalosis resulted in the opposite effects. These data suggest that regulation of Ca^{2+} and Mg^{2+} transport proteins contributes importantly to the effects of acid-base status on renal divalent handling.

Conclusion and perspectives

Different parts of the kidney expressed TRP channels, some of which have been implicated in human diseases (Table 1). The glomeruli contain TRPC1, TRPC3 and TRPC6, while the tubules express TRPC1, TRPC3, TRPC6, TRPV4-6, TRPM6, and TRPP2. The distinct distribution of these cation channels along the nephron underlies their importance in the regulation of many renal physiological processes. TRPC6 conducts Ca^{2+} influx in the podocyte and is likely involved in slit diaphragm signaling. TRPP1 and TRPP2 are expressed in cilia and might function as mechanical sensors. TRPV4, an osmotically responsive cation channel, is activated by hypotonic stimuli. TRPV5 and TRPM6 are highly permeable to Ca^{2+} and Mg^{2+} , respectively and constitute the gatekeepers of active renal Ca^{2+} and Mg^{2+} reabsorption. Until now, growing evidence suggests that TRP channels are implicated in several disease processes including FSGS, ADPKD, HSH, GS, DM, CRF and dys-regulation of Na^+ , Ca^{2+} or Mg^{2+} balance and disturbances of the acid-base status. Furthermore, common prescribed renal medication, such as diuretics, immunosuppressant agents and vitamin D analogues, may lead to TRP channels-associated mineral (dys)regulation. Future studies are warranted to unravel the underlying molecular mechanisms by which TRP channels contribute to kidney physiology and the potential of TRP channels in therapeutic settings. The transgenic technology is currently applied to further understand how TRP channels may cause human disease.

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Figure legend**Figure 1.**

Distribution of TRP channels along the nephron. Abbreviations: G, glomerulus; PT, proximal tubulus; DTL, descending thin limb; ATL, ascending thin limb; TAL, thick ascending limb, DCT, distal convoluted tubule; CNT, connecting tubule; CD, collecting duct.

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Table 1. TRP channels related to kidney diseases and medication

Isoform	Gene location (human)	Distribution in kidney	Proposed function in kidney	Associated kidney diseases	Identified mutations
TRPC6	11q21-22	Podocyte, principle cells of CD	Regulate slit diaphragm function and permeability to protein	FSGS	P112Q, N143S, S270T, R895C, E897K, K874stop (ref. 23, 24)
TRPP1	16p13.3	Cilia of renal epithelial cells	Interaction with TRPP2 as mechanosensor	ADPKD	56 mutations (ref. 32)
TRPP2	4q21-23	Cilia of renal epithelial cells	Interaction with TRPP1 as mechanosensor	ADPKD	45 mutations (ref. 32)
TRPV4 TRPM6	12q24.1 9q22	ATL, TAL, DTL, CNT DCT	Regulate renal medullary tonicity Renal Mg ²⁺ reabsorption	Na ⁺ and water balance HSH	NA 1769C→G, 2667+1G→A 2207delG [3537-1G→A]+[422C→T] [1280delA]+[3779-91del] (ref. 53-55)
TRPV5	7q35	DCT, CNT	Renal Ca ²⁺ reabsorption	GS Adverse effects of diuretics Adverse effects of immunosuppressant agents Vitamin D analogs associated Ca ²⁺ disorders Uremic calcification DM associated Ca ²⁺ and Mg ²⁺ disorders Acid-base associated Ca ²⁺ and Mg ²⁺ disorders	NA NA NA NA NA NA NA

Abbreviations: CD, collecting duct; ATL, ascending thin limb; TAL, thick ascending limb, DTL, descending thin limb; CNT, connecting tubule; DCT, distal convoluted tubule; FSGS, focal segmental glomerulosclerosis; ADPKD, autosomal dominant polycystic kidney disease; HSH, hypomagnesemia with secondary hypocalcemia; GS, Gitelman's syndrome; DM, diabetes mellitus; del, deletion; NA, not available.

Figure 1

