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REVIEW ARTICLE

The key mediator of diabetic kidney disease: Potassium channel dysfunction

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Abstract Diabetic kidney disease is a leading cause of end-stage renal disease, making it a global public health concern. The molecular mechanisms underlying diabetic kidney disease have not been elucidated due to its complex pathogenesis. Thus, exploring these mechanisms from new perspectives is the current focus of research concerning diabetic kidney disease. Ion channels are important proteins that maintain the physiological functions of cells and organs. Among ion channels, potassium channels stand out, because they are the most common and important channels on eukaryotic cell surfaces and function as the basis for cell excitability. Certain potassium channel abnormalities have been found to be closely related to diabetic kidney disease progression and genetic susceptibility, such as K_{ATP}, K_{Ca}, K_{ir}, and K_V. In this review, we summarized the roles of different types of potassium channels in the occurrence and development of diabetic kidney disease to discuss whether the development of DKD is due to potassium channel dysfunction and present new ideas for the treatment of DKD.

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Introduction

As one of the most serious and common microvascular complications of diabetes, diabetic kidney disease (DKD) has become the leading cause of end-stage renal disease (ESRD). Since 2012, in the United Kingdom, Japan, South Korea, and the United States, the percentage of patients with DKD undergoing renal replacement therapy has occupied the first rank among patients with ESRD. In China, the prevalence of chronic kidney disease (CKD) is approximately 10.8% among approximately 119 million adults.[1] Among urban Chinese patients, the incidence of CKD caused by diabetic kidney injury exceeded that of CKD caused by glomerulonephritis in 2016, making diabetic kidney injury the leading cause of CKD.[2,3] The underlying mechanism of DKD is complex and involves renal hemodynamics, inflammation, secretion of cytokines, podocyte damage, endothelial cell injury, mesangial cell hypotrophy, and tubulointerstitial fibrosis (Fig. 1). Thus, analyzing the mechanisms in place from new perspectives will help clarify how to delay the progression of DKD into ESRD and exploring new therapeutic targets for this global public health problem.[4]

Ion channels are important structural components of the cell membrane and play a key role in maintaining the physiology of the cells, especially in excitable tissues. Disorders caused by the abnormal or dysfunctional expression of ion channel proteins are called channelopathies, and their importance is increasingly being recognized.[5] Functioning of ion channels (*e.g.*, calcium, potassium, chloride, and sodium channels) is very important in the kidney.[6] For instance, ion channels play a key regulatory role in ion reuptake and magnesium homeostasis that occur during nephron excretion to control water reabsorption in the collecting duct and maintain glomerular permeability.[5,7] They play an important role in cellular resting potential maintenance, metabolism and osmotic pressure regulation, acid-base balance, and other physiological activities.[8] More than twenty types of potassium channels are present in the kidney that influence its function in different ways[7,9] through multiple physiological processes and regulatory mechanisms. Potassium channels are also involved in the occurrence and development of various kidney diseases and conditions, such as the salt-wasting phenomenon in Bartter syndrome, EAST (epilepsy, ataxia, sensorineural deafness, and tubulopathy) syndrome, SeSAME (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance) syndrome, autosomal dominant hypomagnesemia, polycystic kidney disease, Dent's

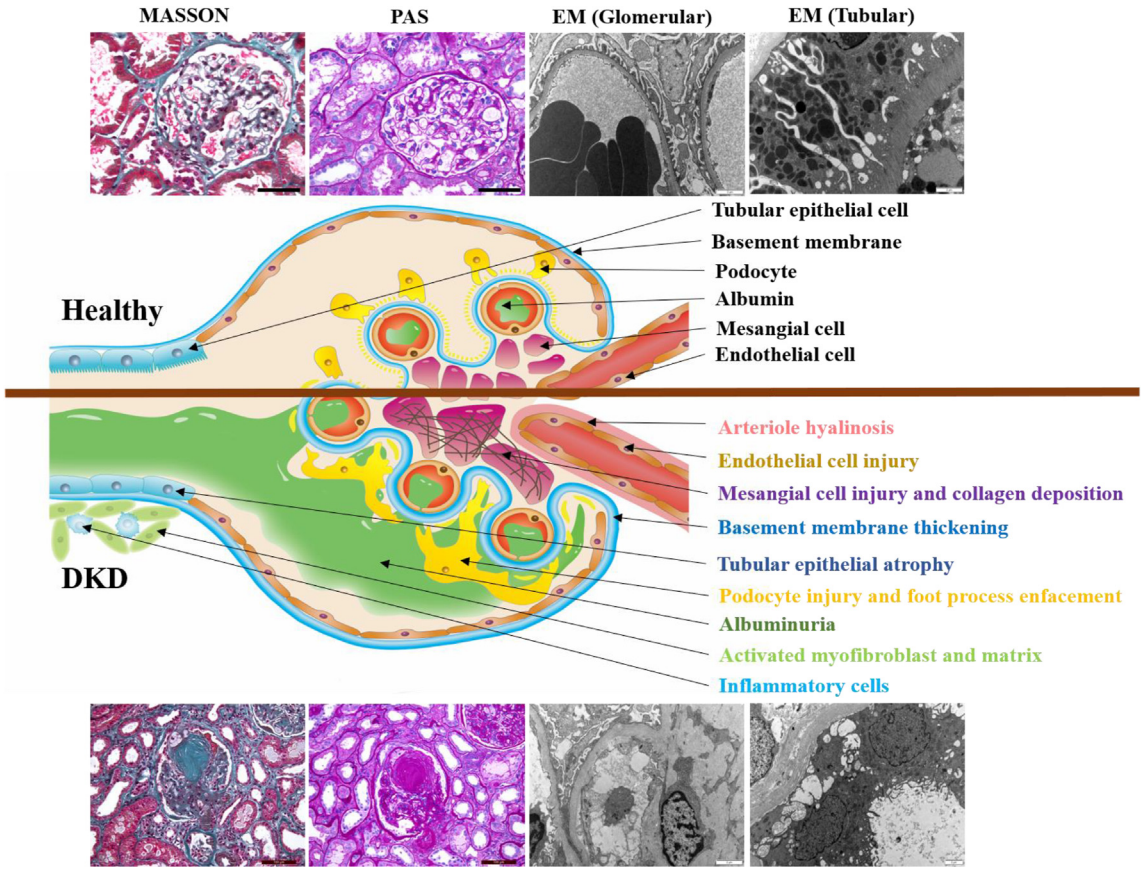

Figure 1 Presentation of the main pathophysiological characteristics of DKD and the special staining results of pathological sections. PASM + MASSON: Periodic acid silver methenamine staining and Masson staining. PAS: Periodic acid-Schiff staining. EM: Transmission electron microscope. The bar scale was set to 100 μM for PAS and MASSON and 2 μM for EM. On the top portion of the figure, the PASM + MASSON and PAS images of healthy kidney biopsies are shown. The lower part of the figure depicts recognizable fibrosis, sclerosis, matrix accumulation, mesangial cell proliferation, collagen deposition, and renal tubular damage after the glomeruli of DKD patients were stained with PASM + MASSON and PAS.

disease, focal segmental glomerular sclerosis, and DKD.[5–8,10–12]

The kidneys are responsible for systemic potassium homeostasis, which is essential for blood glucose control because insulin secretion is the result of potassium-induced depolarization of pancreatic β cells.[13] A low-potassium diet and hypokalemia impair insulin secretion and glucose tolerance, whereas a high-potassium diet reduces the risk of cardiovascular disease in healthy individuals.[14] Thiazide diuretics used to treat hypertension usually induce potassium depletion and increase the risk of developing diabetes.[15,16] In addition, abnormal K^+ levels in the blood often cause serious cardiovascular and kidney damage during diabetes onset. A high-potassium diet was also reported to improve kidney-related outcomes in nearly 30,000 patients with diabetes and other vascular diseases.[17] Interestingly, only potassium, but not sodium, could predict kidney-related outcomes.[17] In a study from Japan, the testing of more than 600 Japanese patients with type 2 diabetes mellitus (T2DM) revealed that high urinary excretion of K^+ indicative of a higher potassium intake was associated with better heart and kidney prognoses[18]; urinary excretion of Na^+ did not have such association. Although multiple factors influenced K^+ homeostasis, potassium channels acted as the crucial sensors of K^+ concentration in different tissues, including the kidney, pancreas, intestine, skeletal muscle, and adrenals.[19] Collectively, these findings indicate that an imbalance in potassium homeostasis and renal potassium channel dysfunction may be involved in the development of diabetic renal dysfunction.

There are some recent reports on the key role of potassium channels in the occurrence, development, and genetic susceptibility to DKD. Several studies have shown that certain potassium channel blockers or agonists can alleviate diabetic kidney injury, providing useful experimental evidence for the development of new treatments for DKD. Based on their structure and function, potassium channels are classified as voltage-gated potassium channels (K_v), inward-rectifier potassium channels (K_{ir}), calcium-activated potassium channels (K_{Ca}), and tandem pore domain potassium channels.[20] Each category is subdivided into several subcategories based on the activation style and ion channel conductance (Fig. 2), which play key roles in different cells and physiological processes[21–23] (Table 1). This review has summarized multiple pieces of evidence on the roles of potassium channels in the pathophysiology and hereditary characteristics of DKD and the effects of different types of potassium channel agonists or inhibitors to discuss whether the development of DKD is due to potassium channel dysfunction and present new ideas for the treatment of DKD.

Potassium channels and renal hemodynamic changes

Glomerular hemodynamic changes at the onset of diabetes often lead to sustained increases in glomerular filtration

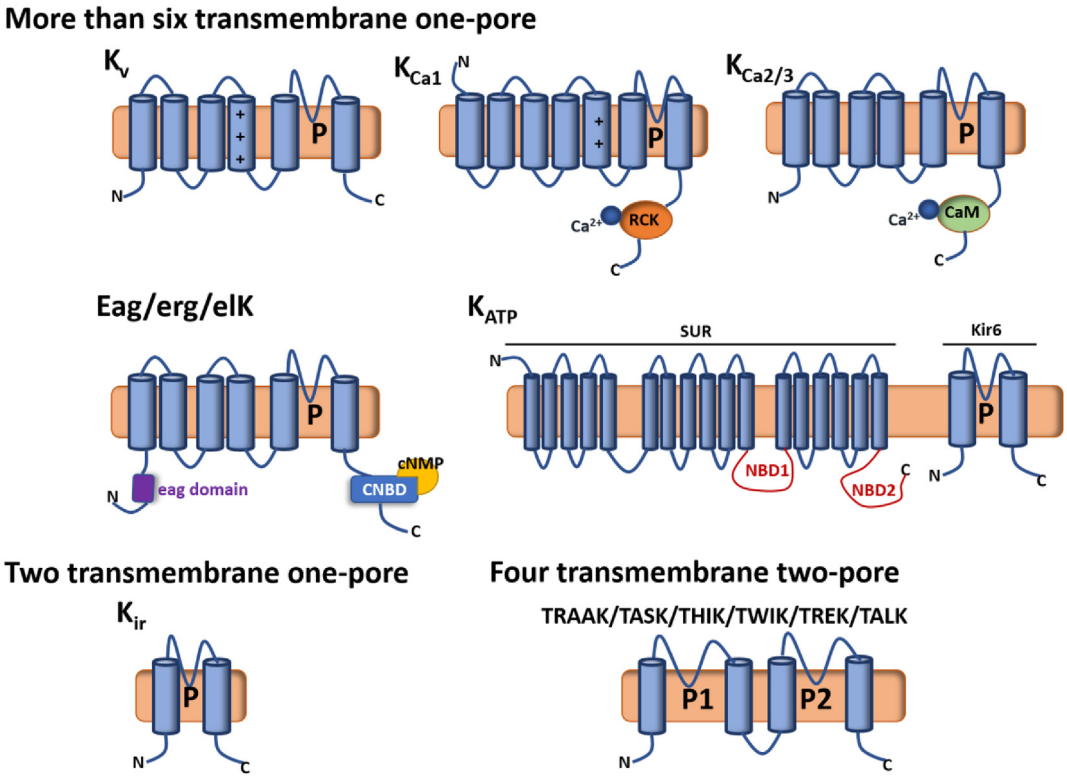

Figure 2 Main types of K^+ channel families. The topology diagrams of K^+ channel subunits show the locations of transmembrane domains, functional domains, and termini. Plus signs denote charged basic residues within the voltage sensor region of K_v and K_{Ca1} channels. RCK denotes a Ca^{2+}-binding regulator of conductance of K^+ channels. CaM denotes calmodulin bound to a CaM-binding site. CNBD denotes a cyclic nucleotide monophosphate (cNMP) binding site. NBD, nucleotide-binding domain; P, pore.

Table 1 The main classification and subtypes of potassium channels.

Name	Type	Subtype
Inward-rectifier K^+ channels	K_{ATP}	Kir6/sulfonylurea receptor
	Kir	Kir1-7
Voltage-gated K^+ channels	Kv	Kv1-9
	eag	Eag/erg/elk
Ca^{2+}-activated K^+ channels	K_{Ca}	BK_{Ca}/SK_{Ca}
Tandem pore domain K^+ channels		TASK/THIK/TWIK/TREK/TALK/TRAAK

rate, commonly referred to as hyperfiltration. The presence of hyperfiltration is considered a critical early driver of the development and progression of DKD, which is regarded as a prime therapeutic target in DKD.[24] The mechanisms underlying hyperfiltration are not fully understood. Proposed mechanisms include tubular sodium and glucose reabsorption, increased intra-renal nitric oxide signaling, and intraglomerular mechanical stress from glomerular hypertension.[24,25] However, the pathways regulating hyperfiltration in kidneys are not yet established. Recent studies showed K^+ channels may be associated with hyperfiltration.

The ATP-sensitive K^+ (K_{ATP}) channel, a K_{ir} channel, was originally identified in cardiac cells and is inhibited by intracellular ATP. K_{ATP} channels participate in the regulation of electrical activity, and cellular functions, such as cardiac preconditioning, vasodilation, and neuroprotection, and participate in glucose homeostasis through regulation of insulin secretion. K_{ATP} channels can also modulate blood flow to organs by regulating the contraction and relaxation of smooth muscles of blood vessels and play an important role in the expansion of renal afferent arterioles.[26] Experiments have shown that pharmacological blockade of the K_{ATP} channel causes significant contraction of the afferent arterioles in streptozotocin-induced diabetic rats, whereas in normal rats the effect on the afferent arterioles was low. This result indicated that K_{ATP} channel opening helps to expand the arterioles and promote glomeruli hyperperfusion during diabetes mellitus (DM).[27]

Besides the K_{ATP} channel, other potassium channels such as K_v (possibly $K_{ir2.1}$) and large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels are also involved in the contraction of renal afferent arterioles.[28] In DM, the effects of the small-conductance Ca^{2+}-activated K^+ (SK_{Ca}) channel and the extrarenal medullary K^+ (ROMK; $K_{ir1.1}$) channels on the expansion of renal afferent arterioles are significantly increased, resulting in an expanded hyperperfusion state for the renal arterioles. K_{ATP}, K_{ir}, or ROMK channel blockers can reverse the dilatation of afferent arterioles in streptozotocin-induced T1DM rat models.[27] These results indicate that the continuous activation of K^+ channels is essential for maintaining the expansion of arterioles in DM rats during ultrafiltration (3—4 weeks after the onset of DM). This activation could be an important factor leading to early glomerular hyperperfusion in DKD. One possible mechanism could be that these K^+ channels promote membrane potential hyperpolarization of vascular smooth muscle cells and reduce Ca^{2+} influx through voltage-gated channels, leading to a reduction in intracellular Ca^{2+}, thus promoting the expansion of afferent arterioles during DM.[29]

However, dysfunction of some potassium channels such as $K_{ir6.1}$ encoded by Kcnj8 could also lead to insufficient blood perfusion in organs during DM. Kcnj8-knockout mice have been found to exhibit serious diabetic complications,[30] and the abnormality of the $K_{ir6.1}$ potassium channel in blood vessels mitigates activity-dependent vasodilation,[30] which leads to insufficient blood perfusion in organs, hypoxia in tissues, and multiple organ failure. Moreover, Kcnj8-knockout mice showed higher expression of inflammatory cytokines, more severe renal cell apoptosis, and worse tissue destruction compared with wild-type mice.[26] This may explain why patients experience ischemic kidney damage caused by renal dysfunction during the progression of DKD.

These results indicate that K^+ channels play key roles in DKD-related hemodynamic changes in the kidney.

Potassium channel and glomerular intrinsic cellular damage in DKD

Persistent proteinuria is a common clinical symptom in the early stages of DKD and is closely related to functional damage of the glomerular filtration barrier.[31] According to previous reports, three main types of glomerular intrinsic cell injury are involved in the proteinuria of DKD, namely injuries of podocytes, glomerular endothelial cells, and mesangial cells. Mesangial cells are contractile cells that constitute the mesangium and structurally support the formation of glomerular clusters.[32] Podocytes are tightly packed cells that support glomerular capillaries through a complex network of foot processes. Glomerular endothelial cells cover the luminal surface of glomerular capillaries and are in direct contact with the blood. Glomerular endothelial cells, podocytes, and the glomerular basement membrane together form a glomerular filtration barrier that prevents albumin leakage. In this section, we review the relationship between potassium channel dysfunction and intrinsic cell injury in the glomeruli and discuss potassium channel-related mechanisms of proteinuria in DKD.

Potassium channels and mesangial cell damage

It is well-known that hyperglycemia causes inflammation and fibrosis, which eventually lead to glomerular sclerosis. This phenomenon is mainly due to the excessive formation of extracellular matrix and the expansion of glomerular mesangial cells, which block glomerular capillaries and gradually destroy the integrity of the glomerulus. The increased extracellular matrix content is the result of the increased expression of matrix metalloproteinases, type IV

collagen, fibronectin, and proteoglycans in mesangial cells.[33] Matrix metalloproteinase-9 expression in the urine of patients with diabetes is positively correlated with urinary albumin.[34] Both matrix metalloproteinase-2 and -9 expression levels in the serum were found to be significantly higher than those in the normal control group.[35] Thus, it is believed that glomerular mesangial cell dysfunction is an important pathological event of diabetic kidney injury. This damage leads to persistent fibrosis and scarring of the glomeruli, which are signs of glomerulosclerosis in patients with DKD.

Current research on potassium channels and mesangial cell damage in DKD is mainly focused on BK_{Ca} and K_{ATP} channels.[6] BK_{Ca} is a large-conductance calcium-activated potassium channel, and its abnormal activity causes changes in the cellular ultrastructure membrane potential.[36] Glomerular mesangial cells can contract similarly to vascular smooth muscle cells. Their tension is determined by the binding of intracellular Ca^{2+} to myosin and actin.[37] Upon activation of BK_{Ca} in mesangial cells, Ca^{2+} outflow from the endoplasmic reticulum and the negative feedback of membrane hyperpolarization potential activation inhibits the voltage-gated calcium channel, resulting in relaxation or contraction of the mesangial cells, thus affecting the glomerular filtration rate.[38] Studies have shown that high insulin or glucose levels can increase the activity or expression of BK_{Ca} channels through different signaling pathways and affect glomerular function.[6] *In vitro* and *in vivo* experiments have shown that a high insulin concentration or insulin-like growth factor I analog could promote the expression of BK_{Ca} channel proteins and BK_{Ca} K^+ flow in cultured human mesangial cells and hyperinsulinemic early-stage T2DM mice, respectively. However, this phenomenon can be partly abolished by inhibitors of mitogen-activated protein kinase (PD-098059 and U-0126).[39] Experiments with rat HBZY-1 mesangial cells have revealed that inhibition of BK_{Ca} channel expression could inhibit cell proliferation, migration, and apoptosis and reduce the secretion of type IV collagen and fibronectin induced by high glucose treatment, whereas BK_{Ca} channel excitation resulted in the occurrence of opposing effects.[36] These results indicate that the activity or expression levels of BK_{Ca} channels are important for mesangial cell health and inhibition of BK_{Ca} channels alleviates mesangial cell damage under high-insulin or high-glucose treatment.

The proliferation of mesangial cells and the release of matrix metalloproteinase-2, fibronectin, and type IV collagen are also influenced by K_{ATP} channels. Cultured or primary-isolated rat mesangial cells treated with high glucose (30—40 mM) for 24 h showed increased proliferation and expression of matrix metalloproteinase-2 and fibronectin, accompanied by a significant decrease in K_{ATP} mRNA expression, including that of $K_{ir6.1}$, $K_{ir6.2}$, and sulfonylurea receptor 1/2A/2B.[35,40] The use of diazoxide, a selective opener of K_{ATP}, could inhibit cell proliferation and suppress the release of matrix metalloproteinase-2, fibronectin, and type IV collagen,[41,42] which was corrected once 5-hydroxydecanoate (5HD), a selective inhibitor of K_{ATP}, was used. These data indicate that high glucose stimulates the proliferation of glomerular mesangial cells and the release of the cell matrix by inhibiting the activity of K_{ATP} channels. Thus, the occurrence of DKD is related to the activity of K_{ATP} channels.

Potassium channels and podocyte injury

As mentioned previously, persistent proteinuria in DKD is primarily caused by impaired filtration barriers.[43,44] Podocytes, the most critical components of the glomerular filtration barrier, are responsible for maintaining the charge and molecular barriers of the glomerular basement membrane and the shape and integrity of the glomerular capillary ring together with glomerular endothelial cells.[43,44] Podocytes are terminally differentiated cells that cover and attach to the outer glomerular basement membrane through the foot processes. Pathological adaptations of podocytes are induced by the diabetic environment, including cytoskeletal rearrangement, de-differentiation, apoptosis, and autophagy, which are manifested in the broadening, retraction, and flattening of podocytes, and reduced motility and increased formation of tightly-connected cells. All these issues eventually lead to excessive enlargement of the glomerulus, and podocytes fall off.[45] In addition, various reactions, such as inflammation and oxidative stress, can cause podocyte dysfunction or loss.[43,44] Furthermore, podocytes are direct targets of insulin, and insulin can promote a rapid increase in glucose uptake by podocytes. However, this effect depends on the podocyte-specific marker nephrin which is a transmembrane cell adhesion molecule and an essential component of the glomerular slit diaphragm. The cytoplasmic domains of nephrin are a platform for the formation of multiple signaling pathway complexes and play a key role in signal transduction[46] of podocytes. Thus, decreased nephrin expression induces podocyte injury and proteinuria.

The BK_{Ca} channel is expressed not only in mesangial cells, but also in glomerular podocytes, thick ascending branches of the medullary loop, distal convoluted tubules, cortical collecting ducts, and the outer medulla.[47] Current research on potassium channels related to podocyte damage in DKD mainly focuses on BK_{Ca} channels. The BK_{Ca} channel binds to a variety of glomerular slit diaphragm proteins, including nephrin, transient receptor potential canonical 6 channels, and several actin-binding proteins in podocytes. In particular, the expression of nephrin on the surface of podocytes is necessary for the stable expression of the BK_{Ca} protein, which highlights the importance of BK channels. In cultured podocytes, insulin increases the cell surface expression of BK_{Ca} channels and stimulates their activity. High insulin levels have been reported to increase the activity of BK_{Ca} channels through type I protein kinase G and increase the permeability of the glomerular filtration barrier. Type I protein kinase G is an important molecule that mediates insulin signaling in podocytes. In primary-cultured rat podocytes, the BK_{Ca} channel inhibitor iberiotoxin (ibTX) was found to reduce type I protein kinase G-dependent transepithelial albumin flux and increased glomerular permeability to albumin in insulin-free glomeruli; similar results were obtained with BK_{Ca} siRNA.[48] However, high glucose (36.1 mM) treatment for 24 h was found to significantly reduce the expression of nephrin, thus affecting the expression of BK_{Ca} channels and partially eliminating the stimulatory effect of insulin on the current density of BK_{Ca} channels.[49]

BK_{Ca} channels can interact with Ca^{2+}-mediated classical transient receptor potential canonical 6 channels in

podocytes, leading to Ca^{2+} influx through these channels. This phenomenon may lead to the activation of BK_{Ca} channels and prevent membrane depolarization, thus maintaining the driving force of Ca^{2+} influx through these channels. Increased Ca^{2+} influx causes irreversible damage to podocytes.[50] These results show that the potassium channel BK_{Ca} plays an important role in podocyte damage and proteinuria in DKD.

Potassium channels and glomerular endothelial cell damage

Glomerular endothelial cells are another key structure of the filtration barrier that covers the surface of the glomerular capillary lumen and is in direct contact with blood. Glomerular endothelial cells are highly fenestrated, where the sizes of their fenestrae are about 17 times larger than the diameter of the albumin molecule. This structure is a foundation for the glomerulus to deal with the high water permeability or hydraulic conductivity required to process large amounts of water. If endothelial cells are directly exposed to hyperglycemic conditions, they are more susceptible to hyperglycemia-induced damage, which includes changes in the cell phenotype and abnormal intracellular signal conduction, leading to endothelial cell dysfunction.[51] The abnormal functioning of glomerular endothelial cells is deemed an important pathogenesis of glomerulosclerosis, including DKD. Endothelial cell dysfunction is characterized by the reduced bioavailability of nitric oxide, decreased endothelial-mediated vasodilation, hemodynamic disorders, impaired fibrinolytic capacity, and growth factor renewal and overproduction. Compared with podocyte injury, endothelial cell abnormalities are closely related to increased urinary albumin excretion.[31] It has been suggested that glomerular changes in DKD are more affected by endothelial cell injury compared with podocyte damage.[31]

One study suggested that K_{Ca} channels are highly linked to diabetes-related endothelial dysfunction in small renal arteries. This study investigated acetylcholine-induced vasodilation of renal arcuate arteries in obese Zucker rats with different durations of diabetes. Inhibition of endothelial K_{Ca} channels significantly reduced acetylcholine-induced vasodilation in rats of the control group, but not in 20-week-old obese Zucker rats.[52] This shows that the K_{Ca} channel is involved in acetylcholine-induced vasodilation; however, prolonged diabetes caused a decline in the expression and activity of the K_{Ca} channel, meaning that its role in the regulation of vasoconstriction and vasorelaxation was weakened. Another study found that blocking K_{ATP} or K_{ir} channels with 30 μmol/L glibenclamide or barium chloride did not affect acetylcholine-induced vasodilation in rats,[53] which sheds light on the leading role of K_{Ca} channels in the regulation of vasodilation.

Potassium channels and tubular cell damage and tubular interstitial fibrosis

Almost all kidney diseases eventually result in chronic renal failure, *i.e.*, tubular interstitial fibrosis.[54] In recent years, DKD has been found to be implicated in inducing renal tubular epithelial cell injury and interstitial lesions before causing glomerular lesions, thus playing an important role in the progression of renal functional impairment.[54] Under diabetic conditions, activation of the inflammation and fibrosis signaling pathways of renal tubular epithelial cells occurs due to various stimuli, such as hyperglycemia, advanced glycation end products, and reactive oxygen species. When stimulated, these renal tubular cells synthesize a variety of inflammatory molecules, such as monocyte chemotactic protein-1, interleukin-6, and chemokine (C—C motif) ligand 20, and chemokines including transforming growth factor (TGF)-β1, which further leads to tubulointerstitial damage and ultimately fibrosis and renal failure.[55,56] Additionally, activated renal tubular epithelial cells can undergo significant phenotypic changes by epithelial—mesenchymal transition, thus promoting interstitial fibrosis.[57] Hence, inhibiting the activation of renal tubular cell inflammation and trans-differentiation signaling pathways under diabetic conditions is an important measure to slow the process of renal fibrosis in DKD.

Current research on potassium channels and DKD renal tubular damage and interstitial fibrosis mainly focuses on the $K_{Ca3.1}$ channel.[58] $K_{Ca3.1}$ (also called IK1, SK4, or KCNN4) is a medium-conductance K^+ channel activated by calcium ions, presenting in fibroblasts, vascular smooth muscle cells, endothelial cells, macrophages, and T lymphocytes, all being related to fibrosis.[59] $K_{Ca3.1}$ in the kidneys of DKD rat models and DKD patients has been found to be significantly up-regulated.[6] $K_{Ca3.1}$ channel activity is required in fibroblast activation.[60] Blockade of $K_{Ca3.1}$ attenuates diabetic renal interstitial fibrogenesis through inhibiting activation of fibroblasts and phosphorylation of Smad2/3 and ERK1/2.[60] The mRNA and protein levels of the inflammatory factor chemokine (C—C motif) ligand 20 in the kidneys of $K_{Ca3.1}^{-/-}$ diabetic mice were significantly reduced when compared with the kidneys of wild-type diabetic mice. Blocking the $K_{Ca3.1}$ channel in the kidney tissue of diabetic mice lacking endothelial nitric oxide synthase ($eNOS^{-/-}$) also led to a decrease of phosphorylated NF-κB, thus reducing inflammation.[61] These results reveal the pro-inflammatory effects of $K_{Ca3.1}$ channel in DKD. Furthermore, $K_{Ca3.1}$ inhibition was found to suppress the expression of TGF-β1 in human proximal renal tubular cells (HK2) through the Smad2/3 pathway and reduced the expression of monocyte chemotactic protein-1 and type III/IV collagens,[62] thus improving renal fibrosis in diabetic mice.

Autophagy deficiency and mitochondrial dysfunction are important pathological mechanisms of DKD. In addition to being involved in inflammation and fibrosis, $K_{Ca3.1}$ plays a role in DKD by mediating autophagy defects in renal tubular cells and mitochondrial quality control deficiency.[63,64] Experiments using $K_{Ca3.1}^{+/+}$ and $K_{Ca3.1}^{-/-}$ mice, in which diabetes was induced by injecting a low dose of streptozotocin, revealed that accompanied by increased rates of mitochondrial fission and fusion, the expression of microtubule-associated protein 1A/1B-light chain 3 (LC3) and nitrotyrosine and the phosphorylation of mTOR in the kidneys of $K_{Ca3.1}^{+/+}$ diabetic mice were significantly higher than those in the kidneys of non-diabetic $K_{Ca3.1}^{+/+}$ mice.[65] Conversely, in the kidneys of diabetic $K_{Ca3.1}^{-/-}$ mice, these factors were significantly weakened. In *in vitro* experiments, HK2 cells were transfected with a $K_{Ca3.1}$ siRNA vector and were exposed to TGF-β1 for 48 h. It was found

that the increased formation of autophagic vesicles, LC3 expression, and PI3K phosphorylation induced by TGF-β1 were reversed in $K_{Ca3.1}$ siRNA-transfected HK2 cells.[60] Increased mitochondrial fission and inhibited fusion were also noted. In another study, interfering with the expression of $K_{Ca3.1}$ resulted in significantly reduced expression and phosphorylation of AKT and mTOR in the kidney tissues of diabetic mice and cultured HK2 cells accompanied by a decreased rate of mitochondrial damage.[66] This demonstrates that the down-regulation of $K_{Ca3.1}$ channel can control diabetic renal tubule damage by improving autophagy in DKD tubule cells and restoring mitochondrial function.

These results show that different types of potassium channels play different roles in different kidney cells and tissues. The same ion channels may play different roles in different cells and participate in different pathophysiological processes (*e.g.*, as it happens for BK_{Ca} channels). Thus, the functions and roles of potassium channels in kidney tissues are complex and important (Table 2). However, few studies have investigated the role of potassium channels in DKD. A follow-up study of potassium channels in DKD is worth further exploration, and there may be crucial discoveries. For example, existing reports have suggested that $K_{Ca3.1}$, which plays a key role in tubular inflammation and interstitial fibrosis, also regulates inflammatory factor secretion and TGF-β1 expression.[65] Inflammation and TGF-β1 up-regulation worsen DKD or induce progression to CKD, where their effects go beyond tubules and interstitium to cause podocyte injury and endothelial cell damage, among others. However, until now there has been little research about kidney $K_{Ca3.1}$ channel in cells other than tubular cells.

The role of potassium channels in the genetic susceptibility to DKD

Genetic factors play significant roles in the occurrence and development of DM and DKD. Hyperglycemia, hyperlipidemia, hypertension, and proteinuria are affected by genetic factors to varying degrees.[67] Current studies suggest that DKD is, to some extent, a polygenic genetic disease. Of note, not all patients with diabetes develop DKD, and some genetic changes are involved in the occurrence of DKD.[68,69] Based on previous studies,[70–75] the potassium channels KCNQ1 (potassium voltage-gated channel subfamily Q member 1) and KCNJ11 (potassium inward-rectifier channel subfamily J member 11) have been found to play important roles in the genetic susceptibility of DM[70–74,76] and their variants are related to new-onset diabetes in tacrolimus-treated renal transplant patients.[77–79] KCNQ1 is the most studied of these channels and is genetically associated with both DM and DKD.[71] KCNQ1 encodes a subunit of voltage-gated potassium channels, which are mainly found in the heart and inner ear and are expressed to a lesser degree in the stomach, intestine, liver, and kidney. In the kidney, KCNQ1 and KCNE1 assemble to form a potassium channel complex located at the brush border of the proximal renal tubules. This potassium channel maintains the dynamics of Na^+ uptake through membrane repolarization and influences Na^+ secretion in the proximal tubules.[80]

Single-nucleotide polymorphisms in KCNQ1 have been proposed to be associated with DKD occurrence. In a preliminary study from Japan, 33 single-nucleotide polymorphisms were detected in KCNQ1 via genotyping analysis of 754 patients with T2DM and significant nephropathy and 558 control participants. It was found that rs123381, rs163183, rs2299620, rs2237896, and rs2237897 may be associated with DKD, with rs2237897 showing the strongest correlation.[81] The involvement of KCNQ1's single-nucleotide polymorphisms in DKD was validated in another study by analyzing rs2237895, rs2237897, and rs2283228 in the KCNQ1 locus. It was found that the rs2283228 polymorphism was significantly associated with proteinuria in 752 Chinese patients with T2DM living in Singapore.[82] Another review also showed rs2283228 and rs2237895 have significant gene—environment interactions with environmental factors such as smoking, waist circumference, and sex in DKD patients in Malaysia.[75]

However, the previously reported rs2237897 locus was found to have no obvious correlation with proteinuria after several tests and corrections.[82] In another study from India, venous blood samples were collected from 50 patients with DKD and 20 control participants with T2DM without nephropathy to detect the rs2237897 polymorphism in the *KCNQ1* gene. The results showed that there was a significant difference in the genotype frequency of rs2237897 in patients with DKD compared with the controls.[83] Of note, all the above-mentioned studies suggesting associations

Table 2 Different potassium channels involved in the physiological activities of the normal kidney and diabetic kidney injury.

Location	Physiological or pathophysiological conditions	Potassium channel
Afferent arterioles	Normal vasodilation	K_V, $K_{ir2.1}$, BK_{Ca}
	Early glomerular hyper-perfusion in DKD	K_{ATP}, ROMK
	DKD advanced ischemic kidney damage	$K_{ir6.1}$
Mesangial cells	Glomerular hyper-filtration	BK_{Ca}
	The proliferation of mesangial cells and release of cell—matrix proteins	K_{ATP}
Podocytes	Podocyte damage and increased permeability	BK_{Ca}
Endothelial cells	Endothelial cell-mediated vasodilation	K_{Ca}
	Endothelial cell injury	BK_{Ca}
Tubulointerstitial fibrosis	Release of inflammatory factors	$K_{Ca3.1}$
	Epithelial cell trans-differentiation	$K_{Ca3.1}$
	Autophagy deficiency and mitochondrial dysfunction	$K_{Ca3.1}$

between single-nucleotide polymorphisms of KCNQ1 and DKD were conducted in Asia.

Studies conducted in Europe and North America depict a different picture from that of Asian studies. In a Spanish genotyping study, six common KCNQ1 variants (rs2237892, rs2237895, rs231362, and three intronic variants) were identified in 681 healthy elderly individuals (>65 years old) from the Spanish Renastur cohort. The results suggested that these six variants were not related to T2DM (180 participants with diabetes *vs*. 581 without diabetes). However, the intron 12-rs2237895 locus was associated with a reduced glomerular filtration rate.[84] Again, a perspective different from that depicted in Asian studies has been proposed based on studies conducted in North America and the Netherlands. More specifically, these studies indicated that the variants of KCNQ1 are only related to genetic susceptibility to diabetes and not to DKD. In a study analyzing the genetic effects of KCNQ1 loci (namely, rs2237892, rs231362, rs2237895, and rs2299620) in Pima Indians in North America, it was found that among 7351 Pima Indians from 4549 families, 34% had diabetes, and all mutants were significantly associated with the genetic effects of T2DM.[85] The strongest association was observed at the rs2299620 locus. A study from the Netherlands conducted genotype testing in 4620 patients with T2DM and 5285 healthy control participants and found that the three loci rs151290, rs2237892, and rs2237895 were significantly associated with T2DM. This may be related to the influence of insulin secretion and lipid metabolism; however, the researchers found no evidence of an association between KCNQ1 and diabetic complications.[71]

In conclusion, although there are certain differences in research results from different regions, the above-mentioned results indicate that KCNQ1 is a genetic susceptibility-associated gene for DKD, especially at the rs2237895, rs2237892, and rs2237897 loci. According to the literature, KCNJ11 is not closely associated with DKD. However, the rs5219 loci participate in susceptibility to DM and new-onset diabetes in tacrolimus-treated renal transplant patients (Table 3). Thus, there have been reports from North America, Europe, and Asia on the relationship between potassium channels and DM or DKD; however, data from countries in Africa and Australia are limited. As genetic factors play an important role in the pathogenesis of DM and DKD, this area of research is also worthy of scientific attention.

Application of potassium channel agonists or inhibitors in the treatment of DKD

The K^+ current formed after the opening of the K^+ channel provides a basis for the cell to maintain or restore the resting potential, or weaken the depolarization caused by the excitatory current. Thus, drugs capable of opening potassium channels have broad clinical application potentials in cardiovascular, endocrine, and other areas of treatment[86] (Fig. 3). For the two main categories of K^+ channels (BK_{Ca} and K_{ATP}), synthetic potassium channel openers exist,[87] but therapeutic effects on DKD have mainly been observed using inhibitors or antagonists of these two ion channels.[87]

In one study,[88] wild-type $K_{Ca3.1}{}^{-/-}$ and $eNOS^{-/-}$ mice were subjected to streptozotocin-induced diabetes, and the therapeutic effects of TRAM34, a selective inhibitor of the $K_{Ca3.1}$ channel, were monitored.[88] Results of the study showed that compared with diabetic wild-type mice, (i) the albumin/creatinine ratio in diabetic $K_{Ca3.1}{}^{-/-}$ mice was significantly lower, and (ii) the ratio of albumin to creatinine in diabetic $eNOS^{-/-}$ mice treated with TRAM34 was significantly reduced. Also, compared with diabetic wild-type mice, the expression levels of monocyte chemotactic protein-1, intercellular adhesion molecule 1, EGF-like module-containing mucin-like hormone receptor-like 1, plasminogen activator inhibitor type 1, and type III/IV collagen were significantly lower in the kidneys of diabetic $K_{Ca3.1}{}^{-/-}$ mice. Similarly, treatment with TRAM34 reduced the expression of markers of inflammation and fibrosis in diabetic $eNOS^{-/-}$ mice.[88] In addition, blocking the $K_{Ca3.1}$ channel in animal models resulted in the down-regulation of TGF-β1, TGF-β1 type II receptor (TβRII), and the

Table 3 The role of potassium channels in the genetic susceptibility of DKD.

K^+ channel	Related diseases	Single-nucleotide polymorphisms	Country	Population
KCNQ1	New-onset diabetes in tacrolimus-treated renal-transplanted patients	rs2237895	Spain	Spanish[77]
	DM	rs2237892, rs231362, rs2237895, rs2299620	USA	Pima Indians[85]
		rs151290, rs2237892, rs2237895	Netherlands	Dutch[71]
	DKD	rs123381, rs163183, rs2299620, rs2237896, rs2237897	Japan	Japanese[81]
		rs2237895, rs2237897, rs2283228,	Singapore	Chinese[82]
		rs2237897	India	Indian[83]
		rs2237895	Spain	Spanish[84]
		rs2237895, rs2283228,	Malaysia	Malaysia[75]
KCNJ11	New-onset diabetes in tacrolimus-treated renal-transplanted patients	rs5219	Spain	Spanish[78]
		rs1805127	Turkey	Turkish[79]
	DM	rs5219	India	Indian[73]
		rs5219	Japan	Japanese[74]

Note: The underlined loci are the sites with the strongest effect in the study.

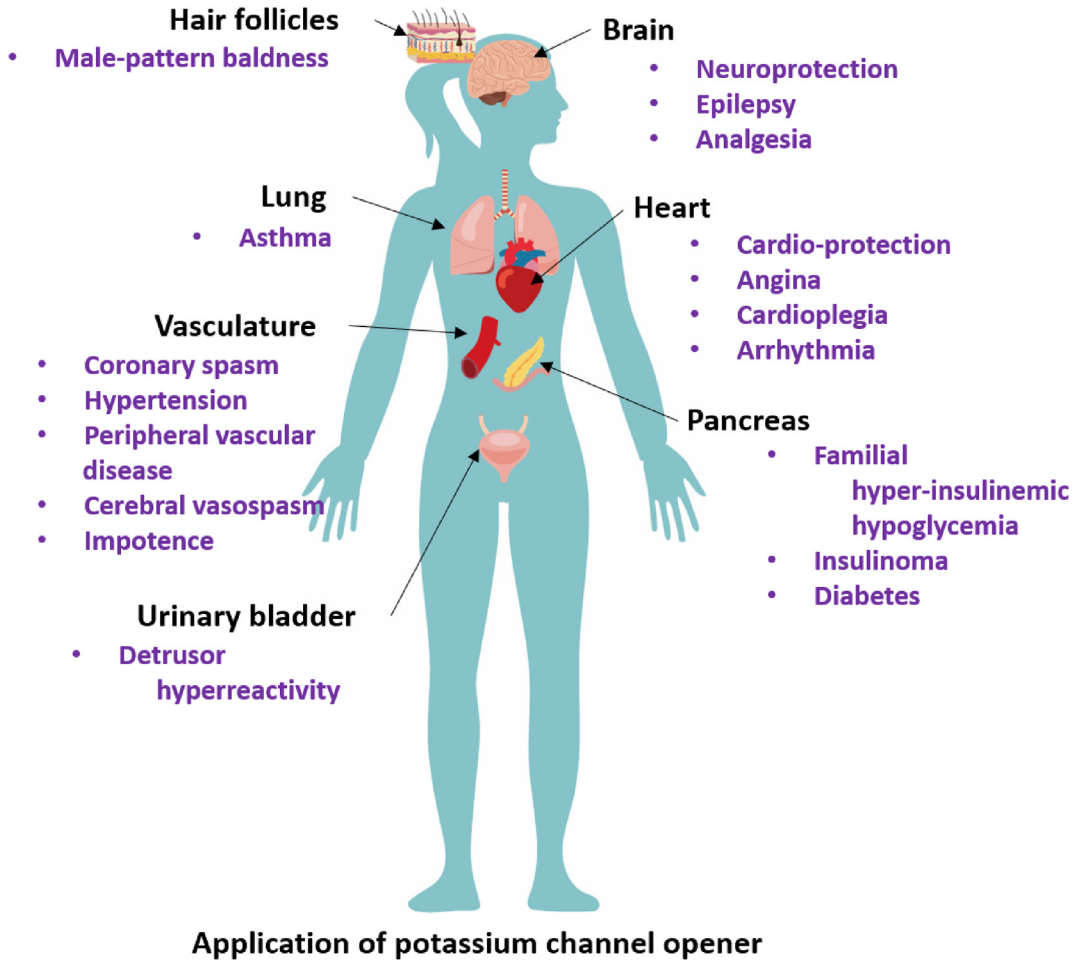

Figure 3 The broad clinical potential applications of potassium channel openers.

phosphorylation of Smad2/3. These results indicate that the $K_{Ca3.1}$ channel mediates inflammation and renal fibrosis in DKD through the TGF-β1/Smad signaling pathway.[62] Thus, the blockade of the $K_{Ca3.1}$ channel might be considered a new therapeutic intervention goal for patients with DKD.

The effects of the K_{ATP} channel blocker U37883A (4-morpholinecarboximidine-N-1-adamantyl-N′-cyclohexylhydrochloride) on renal function were observed in a DM rat model. In control rats, the application of U37883A (1.5 mg/kg body weight, intravenous bolus) significantly reduced the heart rate but did not affect or even slightly increase the mean arterial blood pressure. Furthermore, U37883A did not significantly affect renal vascular resistance, renal blood flow, or glomerular filtration rate but caused diuresis and reduced plasma renin activity. Diabetic rats showed basically the same response to U37883A two or six weeks after streptozotocin induction. In particular, the renal vascular resistance and glomerular ultrafiltration remained unchanged.[89] These results indicate that in diabetic and control rats, the renin excretion function of the kidney and heart rhythm are sensitive to U37883A, signifying the important role of K_{ATP} channels in these physiological activities. However, U37883A did not alter renal vascular resistance, renal blood flow, or glomerular filtration rate in non-diabetic and diabetic rats,[89] indicating that the role of the K_{ATP} channel in renal hemodynamics is not as important as highlighted in other studies.

The renal protection offered by nicorandil differed from what was mentioned above for U37883A. Nicorandil is a clinically proven anti-angina drug that causes vasodilation through the dual action of releasing nitric oxide and binding to and opening of K_{ATP} channels. It also reduces the incidence of cardiovascular events in patients with coronary artery disease. In addition, nicorandil can reduce proteinuria in hypertensive patients receiving low-dose angiotensin receptor blockers. Nicorandil was administered to *eNOS*$^{-/-}$ streptozotocin-induced diabetic mice. These mice also suffered from advanced DKD.[90] After eight weeks, it was found that nicorandil did not affect the blood glucose level, blood pressure, or systemic endothelial function of the mice but significantly reduced proteinuria and glomerular damage. Additionally, nicorandil reduced podocyte loss and podocyte oxidative stress.[91] In cultured podocytes, it was further demonstrated that nicorandil may protect against glucose-mediated oxidative stress through K_{ATP} channels, possibly due to a reduction in nitrotyrosine rather than a decrease in nitric oxide.[90,91] Thus, nicorandil may alleviate DKD by protecting podocyte function and can be considered a new treatment modality for advanced DKD. The structure and the effects of potassium channel inhibitors or openers are shown in Figure 4 and Table 4.

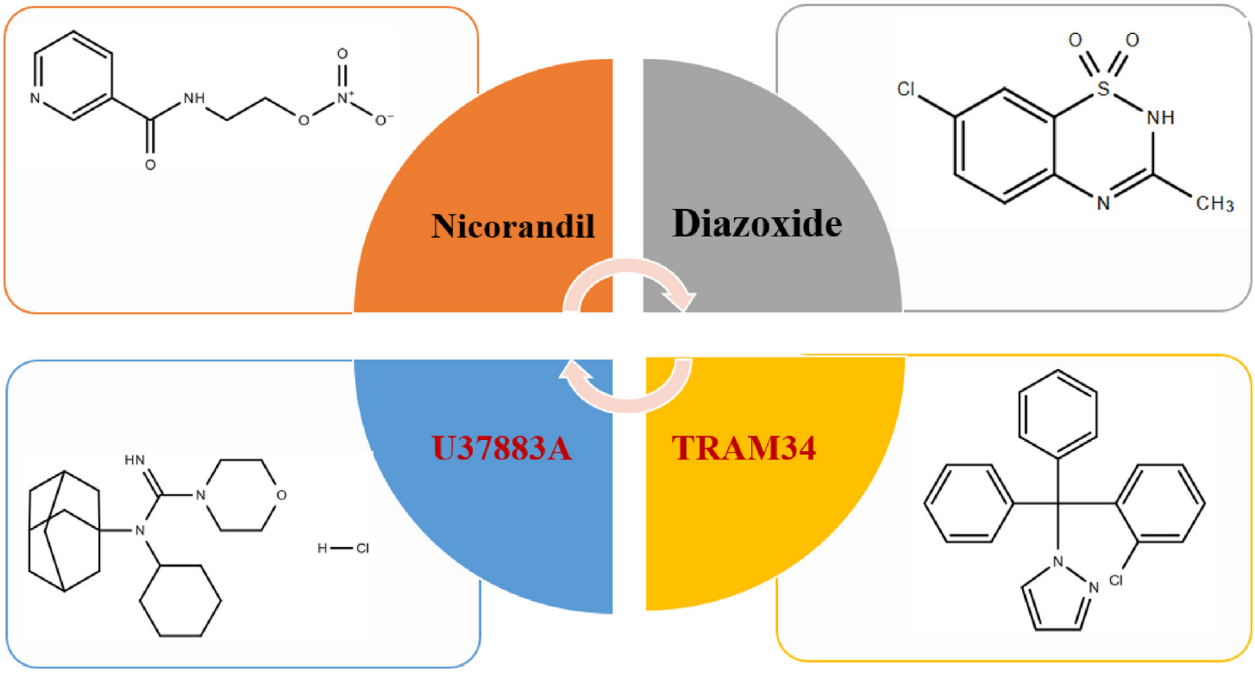

Figure 4 Structures of opener, agonist, and inhibitors of K^+ channels listed in Table 4.

Table 4 Effects of potassium channel opener, agonist, and inhibitors in DKD.

Type	Potassium channel	Name	Effects
Opener	K_{ATP}	Diazoxide	Inhibition of cell proliferation and suppression of the release of matrix metalloproteinase-2, fibronectin, and type IV collagen[42]
Agonist	K_{ATP}	Nicorandil	Reduction in proteinuria and glomerular damage[90] Protection of podocytes against glucose-mediated oxidative stress[91]
Inhibitors	$K_{Ca3.1}$	TRAM34	Reduction in the expression of markers of inflammation and fibrosis in diabetic *eNOS*$^{-/-}$ mice[88] Reduction in the expressions of TGF-β1 and TGF-β1 type II receptor (TβRII) and the phosphorylation of Smad2/3[62]
	K_{ATP}	U37883A	Regulation of the renin excretion function of the kidney and the heart rhythm[89]

Conclusion

As the leading cause of ESRD, DKD has resulted in an increasing social and economic burden. Research on the pathogenesis of DKD and the development of new treatments are hot topics in medical research. Currently, the main clinical treatments for DKD include the use of glucagon-like peptide 1 agonists, sodium-glucose cotransporter-2 inhibitors, renin-angiotensin system inhibitors, and dipeptidyl peptidase 4 inhibitors to alleviate kidney damage from the perspective of metabolism and hemodynamics. However, these methods have certain limitations. Thus, there is a need to identify other drugs to alleviate the disease while delaying the progressive deterioration of renal function. In this review, we discussed how the abnormal expression and function of potassium channels are closely related to the occurrence and development of DKD and its genetic susceptibility. Therefore, the role of potassium channels in diabetes warrants further investigation, where drugs targeting these channels could be developed to delay DKD.

Author contributions

J.G. designed the review, analyzed, and interpreted data, and wrote the manuscript. C.Z., H.Z., Y.Y., and Z.L. took part in selecting the research papers and preparing the manuscript. All authors contributed to and approved the final submitted version of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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