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REVIEW

Intermediate conductance, Ca^{2+}-activated K^+ channels: a novel target for chronic renal diseases

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Abstract **Renal failure is a medical condition in which the kidneys are not working properly. There are two types of kidney failure: 1) acute kidney failure, which is sudden and often reversible with adequate treatment; and 2) chronic renal failure, which develops slowly and often is not reversible. The last stage of chronic renal failure is fatal without dialysis or kidney transplant. The treatment for chronic renal failure is focusing on slowing the progression of kidney damage. Several reports have described a promising approach to slow the loss of renal function through inhibition of the basolateral membrane, Ca^{2+}-activated K^+ (KCa3.1) channel with a selective and nontoxic blocker TRAM-34. This review summarizes pathophysiological studies that describe the role of KCa3.1 in kidney diseases.**

Keywords Ca^{2+}-activated K^+ channels, KCa3.1, renal fibrosis, polycystic kidney disease, diabetes nephropathy, transplant, cell proliferation, Cl^- secretion, renal failure

Introduction

Ca^{2+}-activated K^+ channels of intermediate conductance (KCa3.1) are activated in response to increases in cytosolic Ca^{2+} and are involved in numerous Ca^{2+}-dependent signaling pathways and in the regulation of membrane potential in both excitable and nonexcitable cells. Although KCa3.1 is expressed in a wide variety of tissues, no human disease has been associated with mutations in KCa3.1. KCa3.1 channels have been identified in epithelial tissues such as lung, intestinal tract, kidney and glands; hematopoietic-derived cells such as erythrocytes, lymphocytes, mast cells and monocytes/macrophages; immune tissue such as thymus, spleen, bone marrow and lymph node; fibroblasts; vascular endothelia, smooth muscle cells among others (Rufo et al., 1996; Devor et al., 1996; Ishii et al., 1997; Logsdon et al., 1997; Pena et al., 1999; Neylon et al., 1999; Chen et al., 2004; Grgic et al., 2005; Tharp et al., 2005). Accumulated evidence has shown that one of the roles of KCa3.1 channels is to directly mediate Ca^{2+} entry into cells. Elevated intracellular Ca^{2+} leads to activation of KCa3.1, efflux of K^+ and cell hyperpolarization, thus maintaining the electrochemical driving force needed for sustained Ca^{2+} entry into the cell (Ghanshani et al.,2000; Nilius et al., 2001; Cruse et al., 2006). KCa3.1-mediated elevation of intracellular Ca^{2+} is involved in the migratory, inflammatory and proliferative responses and in the production of chemokines and cytokines in many cell types (Ghanshani et al., 2000; Pena et al., 2000; Grgic et al. 2005; Si et al., 2006).

Within epithelia, the main role of KCa3.1 is to recycle K^+ out of the cell thereby maintaining the electrochemical driving force for Cl^- secretion across the apical membrane (Rufo et al., 1996; Devor et al., 1999). Utilizing Biotin Ligase Acceptor Peptide (BLAP)-tagged KCa3.1, we demonstrated that KCa3.1 is exclusively targeted to the basolateral membrane in different polarized epithelia cells (Bertuccio et al., 2014). Although other reports also determined that KCa3.1 is typically expressed on the basolateral side of the epithelium, Rajendran and coworkers have demonstrated that one splice variant of KCa3.1 (KCa3.1c) was localized to the apical membrane of rat colonic epithelial cells (Barmeyer et al., 2010).

Since pharmacological inhibition or knockdown of KCa3.1 showed suppression of mitogen-driven cell proliferation, decreased Cl^- secretion in epithelia and attenuated disease progression in different cell types (Grgic et al., 2005; Wang et al., 2007; Tharp et al., 2008; Toyama et al., 2008), several investigators studied the processes of proliferation and

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interstitial/tubular fibrosis produced in kidney diseases. Thus, this review briefly summarizes the pathophysiological role of KCa3.1 in kidney diseases.

Polycystic kidney disease

Autosomal-dominant polycystic kidney disease (ADPKD), one of the most common monogenetic diseases, is the third most frequent cause of end stage kidney disease in humans. It is characterized by the progressive development and enlargement of multiple bilateral fluid-filled cysts in the kidneys. A large body of evidence suggests that cyst formation in ADPKD is produced by tubular cell proliferation, anomalies in the extracellular matrix and a net fluid secretion toward the cyst lumen (Ye et al., 1993; Wallace et al., 1996; Li et al., 2004; Mangos et al., 2010). Pioneering work demonstrated that cysts in ADPKD become totally independent from the tubule from which they derive and intracystic secretory fluid accumulation is originated by the cystic epithelium itself (Lambert et al., 1947; Grantham et al., 1987). The fluid accumulation in the lumen of ADPKD cysts is driven by the transepithelial secretion of Cl^-, mediated by 1) the basolateral Na^+-K^+-$2Cl^-$ cotransporter (NKCC1), which is responsible for Cl^- entry into the cell; and 2) the apical Cl^- channels (CFTR and Ca^{2+}-activated Cl^- channels), which allow Cl^- transport into the cyst lumen. To maintain sustained Cl^- secretion, a continuous recycling of K^+ and Na^+ is necessary at the basolateral membrane, as well as the maintenance of a hyperpolarized membrane potential (Sullivan et al., 1998; Torres et al., 2007). The continuous activity of the basolateral Na^+-K^+-ATPase and KCa3.1 are responsible for recycling Na^+ and K^+ ions out of the cell, thereby maintaining the hyperpolarized cell membrane potential favorable for Cl^- efflux into the cyst lumen through the cAMP-sensitive Cl^- channel CFTR (cystic fibrosis transmembrane conductance regulator) (Sullivan et al., 1998; Torres et al., 2007). This apical Cl^- secretion, and the resultant negative transepithelial voltage, contributes to the transepithelial movement of Na^+ and water into the cyst lumen resulting in cyst growth.

Albaqumi et al. (2008) confirmed that fluid secretion was stimulated by adenylyl cyclase agonists in monolayers of kidney cells derived from patients with ADPKD. It has further been shown that pharmacological inhibitors of the CFTR slowed progression of disease in patients with ADPKD (Davidow et al., 1996; O'Sullivan et al., 1998; Li et al., 2004; Xu et al., 2006) and mutation in the CFTR channel in patients with ADPKD reduced disease severity (O'Sullivan et al., 1998; Xu et al., 2006). In conclusion, apical Cl^- secretion is the driving force for fluid secretion in ADPKD cysts.

In addition, it was observed that the stimulation of Cl^- secretion requires activation of basolateral KCa3.1 channels in airway and intestinal epithelia (Devor et al., 1996; Devor et al., 2000; Singh et al., 2001; Izu et al., 2002; Mall et al., 2003). To confirm that KCa3.1 plays a critical role in apical Cl^- secretion in the kidney, ADPKD cells were incubated with DCEBIO, a KCa3.1 activator. The addition of DCEBIO stimulated net chloride secretion in ADPKD cells. Moreover, the increase in Cl^- secretion and the enlargement and cyst formation were markedly attenuated by treatment with TRAM-34, a specific KCa3.1 potassium channel blocker, in absence or presence of forskolin (Albaqumi et al., 2008).

Since cyst growth is the major feature for the progressive deterioration and loss of renal function in ADPKD (Grantham et al., 2008), the objective in ADPKD treatment is to slow or stop the growth of the cysts (Grantham et al., 2006). Thus, inhibiting the dysregulated Cl^- secretion associated with ADPKD represents a major therapeutic target. Based on this tenet, the use of pharmacological inhibitors of KCa3.1 may provide a novel therapy for inhibiting increased transepithelial Cl^- secretion and slowing renal cyst progression in patients with ADPKD.

Renal fibrosis

Renal fibrosis is the endpoint of most forms of progressive renal disease. If the damage is prolonged, the result is irreversible renal injury, although renal injury may be prevented or reversed if the insult is removed. Independent of the principal cause leading to renal damage, the pathogenesis of renal fibrosis is characterized by an excessive accumulation of extracellular matrix components (ECM), monocyte/macrophage cell infiltration, transformation of tubular epithelial cells to myofibroblasts through epithelial-mesenchymal transition (EMT) and fibroblast proliferation (Iwano et al., 2004; Neilson et al., 2006). The mechanism that causes the fibrogenic response after damage is incompletely understood and lacks a successful therapeutic strategy. It was proposed that inhibition of fibroblast proliferation may moderate the damaged tissue in the injured kidney (Grgic et al., 2009). It has also been proposed that only injured proximal tubular epithelia induced interstitial fibrosis and glomerulosclerosis (Grgic et al., 2012). Based on this, controlling fibroblast proliferation and/or tubular injury represent potential therapeutic options to prevent and arrest the progression of renal fibrosis.

Several investigations have shown that fibroblast activation and proliferation in the kidney are activated by local growth factors, cytokines and metabolic toxins including TGF-β1, PDGF, CTGF, and βFGF (Strutz et al. 2000; Gore-Hyer et al., 2002; Eitner et al., 2003; Yu et al., 2003). However, transforming growth factor-β1 (TGF-β1) has been accepted as a main mediator in the pathogenesis of renal fibrosis in both experimental and human kidney diseases, by stimulating ECM production and by inducing EMT (Zeisberg et al., 2003; Ruiz-Ortega et al., 2006). These processes are activated when TGF-β binds to TGF-β1 type II receptor (TβRII), which recruits TGF-β1 type I receptor (TβRI). Then, this complex activates both intracellular signaling pathways of Smads

(small mothers against decapentaplegic) and mitogen-activated protein kinase (MAPK) such as p38 and ERK (Biernacka et al., 2011; Gewin et al., 2012; López-Hernández et al., 2012). Other reports described that TGF-β1 is also involved in inflammatory responses by increasing expression of monocyte chemoattractant protein-I (MCP-1) in chronic kidney diseases (Zhang et al., 2009; Huang et al., 2010). MCP-1 is the most potent chemotactic factor for monocytes, which induces monocyte migration and differentiation to macrophages (Amann et al., 2003). MCP-1 expression is stimulated by TGF-β1 in human proximal tubular cells (Qi et al., 2006) and by Smad3 in cardiac fibroblasts (Huang et al., 2010).

KCa3.1 channels have been proposed to play an important role in promoting mitogenesis in several tissues (Ghanshani et al., 2000; Kohler et al., 2003; Jager et al., 2004; Grgic et al., 2005; Si et al., 2006) and pharmacological inhibition or knockdown of KCa3.1 suppressed mitogen-driven cell proliferation and decreased disease progression (Kohler et al., 2003; Grgic et al., 2005; Wang et al., 2007; Toyama et al., 2008). Interestingly, local mitogens such as βFGF, PDGF or VEGF produced upregulation of KCa3.1 in different cell types (Grgic et al., 2005; Si et al., 2006). From all these findings, Grgic et al. proposed that KCa3.1 channels may promote renal fibroblast proliferation in the kidney and the control of KCa3.1 may modulate the progression of renal fibrosis (Grgic et al., 2009). Thus, these authors observed upregulation of KCa3.1 mRNA expression and protein levels when murine fibroblasts of renal origin were stimulated with βFGF. In addition, TRAM-34, a highly selective KCa3.1 blocker, inhibited fibroblast proliferation by arresting mitogenic stimulated fibroblasts at the G_0/G_1 transition. In addition, they found that mitogenic upregulation of KCa3.1 in murine renal fibroblasts was mediated by receptor tyrosine kinase activity and the Ras/Raf/MEK/ERK-signaling cascade (Grgic et al., 2009). Furthermore, blockade of KCa3.1 inhibited fibroblast activation and increased extracellular matrix in human renal fibroblasts exposed to TGF-β1 (Huang et al., 2013). Finally, Huang et al. recently demonstrated that treatment of human proximal tubular cells (HK2 cells) with TGF-β1 induced a significant KCa3.1 expression and it was reversed by TRAM-34 and KCa3.1 siRNA (Huang et al., 2014). The exposure of HK2 cells to TGF-β1 significantly increased monocyte chemoattractant protein-1 (MCP-1) expression, which was reverted to control values in the presence of KCa3.1 siRNA. The same authors demonstrated that both the Smad3 and the MAPK pathways (p38 and ERK1/2) were activated in HK2 cells exposed to TGF-β1 and was inhibited in the presence of KCa3.1 siRNA or TRAM-34. Equally, HK2 cells overexpressing KCa3.1 increased MCP-1 expression through Smad3, p38 and ERK1/2 signaling pathways. The same group discovered that human interstitial fibroblasts exposure to TGF-β1 also increased Smad phosphorylation, which was reverted by exposure to TRAM-34 (Huang et al., 2013).

Based on these findings, Grgic et al. proposed that the regulation of KCa3.1 in kidney may prevent the mechanisms involved in the progression of renal fibrosis (Grgic et al., 2009). Then, as KCa3.1 has a significant function in driving renal fibroblast proliferation and inflammatory process *in vitro*, Grgic et al. examined whether KCa3.1 expression was altered in mice with unilateral ureteral obstruction (UUO), a progressive renal fibrosis model (Grgic et al., 2009). It was demonstrated that KCa3.1 is upregulated in parallel with a rise in TGF-β1 expression levels in induced UUO mice. Analysis of kidneys from UUO mice deficient for KCa3.1 exhibited a significant reduction in the expression of fibrotic marker, the deposition of collagen, αSMA-expressing cells, chronic tubulointerstitial damage, and better preservation of proximal tubules and total renal parenchyma. Similarly, pharmacological treatment with TRAM-34 attenuated the progression of renal fibrosis in UUO-induced in wild-type mice. Taken together, these data demonstrate that pharmacological KCa3.1 inhibition can reduce the inflammatory and fibrotic processes in the kidney and may alleviate the progression of renal fibrosis.

Because most renal disorders lead to renal fibrosis, there is a desperate need to identify novel key molecular players that may prevent or reverse this process. it is unknown if the pharmacological inhibition of KCa3.1 in kidney is one of these players.

Diabetic nephropathy

Diabetes mellitus is a chronic disease in which glucose levels are elevated in the blood. Diabetes mellitus is the cause of approximately one-third of the cases of end stage renal disease (ESRD) worldwide, and it is the most common cause of ESRD in the United States (Centers for Disease Control and Prevention (CDC), 2005). *Diabetic nephropathy* (DN) is a chronic complication of diabetes that affects around 30% of patients with diabetes mellitus (Reddy et al., 2008). DN is a progressive disease that takes several years to develop. Although currently available pharmacotherapies, such as glycemic control, blood pressure control and renin-angiotensin-aldosterone system inhibitor slow down the progression of diabetic diseases, the number of patients with diabetes that develop renal damage remains high (Rosolowsky et al., 2011; Zheng et al., 2011). DN is well characterized by renal hypertrophy, ECM accumulation and tubulointerstitial fibrosis.

TGF-β1 has become a key cytokine involved in the development of renal hypertrophy and accumulation of extracellular matrix in diabetes (Border et al., 1994; Wolf et al., 1999; Wolf et al., 2003). Tubular and glomerular upregulation of renal TGF-β1 has been well described in human and experimental diabetes (Yamamoto et al., 1993; Pankewycz et al., 1994; Iwano et al., 1996; Park et al., 1997; Sharma et al., 1997) and the increased expression of TGF-β1

was closely correlated with the degree the progression of diabetic nephropathy in these patients (Iwano et al., 1996). In early stages of DN, TGF-β1 is stimulated by hyperglycemia and glomerular stretch; while in later stages, TGF-β1 is increased by glycated proteins (e.g., AGEs), angiotensin II (Ang II), platelet-derived growth factor (PDGF) and TGF-β auto-induction (Sharma et al., 2000). Recent works found that Ang II and AGEs upregulate KCa3.1 expression in cardiac fibroblasts and vascular smooth muscle, triggering cell proliferation and migration (Zhao et al., 2012; Wang et al., 2013). In addition, as was mentioned in the previous section, cell proliferation and migration are also modulated by Smad3 and MCP-1 in DN. Thus, several groups demonstrated that Smad3 plays an essential role in this process and is upregulated in experimental DN (Isono et al., 2002; Fujimoto et al., 2003; Li et al., 2010). In addition, augmented amounts of MCP-1 (Banbaet et al., 2000; Mezzano et al., 2004) have been implicated in the pathogenesis of DN producing activation of monocytes/macrophages (Wada et al., 2000; Morii et al., 2003) and suppression of MCP-1 markedly decreased albuminuria, renal injury and fibrosis in streptozotocin (STZ)-induced DN (Amann et al., 2003; Zheng et al., 2009).

Since tubulointerstitial fibrosis plays a key role in the development and progression of diabetic nephropathy and KCa3.1 mediates cellular proliferation of many cell types, Huang et al. studied if KCa3.1 provokes renal scarring in diabetes (Huang et al., 2013). Thus, Huang et al. examined whether the expression of KCa3.l is altered in kidney biopsies from patients with DN and found that KCa3.1 protein expression was upregulated in proximal tubular cells of diabetic kidneys (Huang et al., 2013). The same observation was found in two STZ-diabetic mouse models and the administration of TRAM-34 significantly reversed the increased KCa3.1 expression in the proximal tubule of diabetic mice. The TGF-β1/TβRII/Smad signaling pathway was strongly activated in diabetic KCa3.1$^{+/+}$ mice. However, KCa3.1 deficiency or blockade of KCa3.1 with the administration of TRAM-34 significantly reduced TGF-β1/TβRII/Smad levels in diabetic mice. The impaired renal function of wild type diabetic mice was significantly attenuated in diabetic KCa3.1$^{-/-}$ mice. Subsequently, these authors demonstrated that KCa3.1 deficiency attenuated inflammatory regulation, suppressed interstitial matrix production and reduced renal interstitial fibrosis in KCa3.1 knockout mouse models of DN. The treatment with TRAM-34 also alleviated all indices of renal injury in diabetic animals. These data show that expression of TGF-β1 and its receptor TβRII is mediated by KCa3.1, acting through the Smad pathway, regulating renal dysfunction and renal fibrosis in diabetic kidneys. Therefore, the inhibition of the KCa3.1 signaling pathway may provide a novel approach to prevent the development of DN and may attenuate the progression of renal fibrosis.

Chemokines constitute a family of chemotactic cytokines that are involved in the migration of leukocytes throughout the body (Yoshie et al., 2001). One of them is Chemokine ligand 20 (CCL20) also known as macrophage inflammatory protein-3a. CCL20 has been implicated in inflammatory responses (Dieu-Nosjean et al., 2000; Nakayama et al., 2001) and has an important role in the development of DN (Qi et al., 2011). CCL20 expression is induced by cytokines such as TGF-β1 (Homey et al., 2000) and nuclear factor-κB (NF-κB) (Sugita et al., 2002). Renal biopsy from patient and renal cortical tissue of animals with DN presented elevated NF-kB levels (Schmid et al., 2006; Ohga et al., 2007). Qi et al. (2007) identified significantly increased levels of CCL20 in either TGF-β1-induced or high glucose (HG)-induced renal proximal tubule cells and in the kidney of diabetic rats. Exposure to HG presented decreased CCL20 expression when TGF-β1 gene was silenced using small interfering RNA (Qi et al., 2007). These findings suggest that controlling CCL20 expression may delay the development of DN.

To identify whether KCa3.1 has a role in the inflammatory responses inherent to DN, Huang et al. studied whether the blockade of KCa3.1 would inhibit the cytokine CCL20 expression induced by HG in proximal tubular cells (Huang et al., 2014). This study showed that increased CCL20 expression was accompanied by increasing of macrophage number into the tubulointerstitium, demonstrating that CCL20 is involved in renal macrophage infiltration in DN. In addition, blockade of KCa3.1 by TRAM-34 was able to attenuate the upregulation of CCL20 expression and macrophage infiltration and it was mediated through the inhibition of NF-κB activation in *in vitro* proximal tubular cells and STZ-induced diabetic mouse models. Taken together, these findings suggest that TRAM-34, may exert a protective effect via inhibition of the NF-κB signaling pathway.

Kidney allograft rejection

Transplantation has become the treatment of various irreversible organ failures. An allograft is a transplant of an organ between two subjects not genetically identical. However, management of the immune system has always been the major obstacle. The immune system of the recipient develops mechanisms that recognized the new organ as a strange tissue and tries to combat it and thus induces transplant rejection. For that reason, after any transplantation, an appropriate immunosuppressive treatment is essential. The primary target cells of most immunosuppressants are T-lymphocytes. Currently, a classical calcineurin inhibitor, cyclosporine A (CsA), which inhibits T cell activation, is used as immunosuppressant to prevent kidney transplant rejection in the long term, but it is associated with a number of negative side-effects (Leichtman, 2007).

In the eighties, patch clamp studies revealed the existence of K^+ channels in human lymphocytes (DeCoursey et al., 1984; Matteson and Deutsch, 1984; Cahalan et al., 1985; Schlichter et al., 1986). Recently, several reports have identified that T-lymphocytes express two types of K^+ channels: Kv1.3 and KCa3.1 (Grissmer et al., 1990; Logsdon et al., 1997) and the expression of both channels depends on the T-lymphocytes activation and differentiation states. In the resting state, T cells express around 250 Kv1.3 and less than 20 KCa3.1 channels per cell (Beeton et al., 2003; Wulff et al., 2003). Indeed, T-lymphocyte activation and proliferation were associated with upregulation of these K^+ channels (Ghanshani et al., 2000; Wulff et al., 2003). The activation of immune cells depends on Ca^{2+} influx from the extracellular space. T cell activation leads to the activation of store-operated Ca^{2+}-release-activated Ca^{2+} (CRAC) channels, resulting in the rapid influx of extracellular Ca^{2+}. Rapid influx of Ca^{2+} induces K^+ channel activation, which mediates the efflux of K^+ and maintains the hyperpolarized membrane potential that is critical for sustained calcium entry into the T cells via CRAC. Interestingly, following activation, T cells transcriptionally upregulate KCa3.1 to 500 channels and Kv1.3 to ~1500 channels per cell (Rus et al., 2005). Pharmacological blockade of T-lymphocyte K^+-channels have shown to attenuate the T cell activity in autoimmune diseases (Beeton et al., 2001, 2006). The discovery of new channel blockers that selectively target lymphocyte K^+ channels may be a novel therapeutic strategy to improve renal graft survival. Based on this hypothesis, Grgic et al. postulated that blockade of T-lymphocyte K^+-channels may be useful in preventing kidney allograft rejection. Thus, the combination of TRAM-34 with ShK, a K_V 1.3 blocker, reduced T-lymphocyte and macrophage infiltration in a kidney allograft transplant of rats and the efficacy of this treatment was comparable to that of CsA (Grgic et al., 2009). Importantly, no adverse effects were observed with this treatment. These data suggest that KCa3.1 blockers may be a new alternative immunosuppressant for kidney allograft rejection.

Clinical trials with KCa3.1 blockers

Although it has not been discussed in this review, KCa3.1 plays an essential role in the physiology of a wide variety of cells including red blood cells, immune cells, vascular endothelium, airway epithelium, and neurons; and in disease states such as inflammatory bowel disease, multiple sclerosis, arthritis, asthma, atherosclerosis and restenosis, in which the progress of these diseases were suppressed in the presence of KCa3.1 blockers (Wojtulewski et al., 1980; Rufo et al., 1996; Devor et al., 1996; Ishii et al., 1997; Logsdon et al., 1997; Pena et al., 1999; Neylon et al., 1999; Ghanshani et al., 2000; Kohler et al., 2003; Chen et al., 2004; Grgic et al., 2005; Tharp et al., 2005; Toyama et al., 2008; Bradding et al., 2009; Di et al., 2010). In all these studies, it was proposed that the development of a KCa3.1 channel inhibitor would be of pharmaceutical interest for the treatment of one or more of the disorders described above.

The first clinical trial was focused on the treatment of sickle cell anemia by the KCa3.1 blocker, Senicapoc. In Phase I and II trials, Senicapoc was found to be safe and well tolerated, to be able to reduce hemolysis and increase hemoglobin levels in sickle cell patients (Ataga et al., 2008). A subsequent Phase III study was terminated early because of lack of efficacy in reducing sickling crisis. Senicapoc was also explored in patients with allergic asthma. In this trial, Senicapoc enhanced lung function, however, the effect of Senicapoc on exercise-induced asthma did not improve lung function (Robinette et al., 2008). Another KCa3.1 inhibitor, clotrimazole, was reported to improve the rheumatoid arthritis symptoms in a small clinical trial (Wojtulewski et al., 1980). Although pharmacological KCa3.1 blockers appear to be safe, well-tolerated in humans and biologically active at the doses given, there is concern that KCa3.1 blockers might increase blood pressure as was observed in animals with deletion of the KCa3.1 gene (Si et al., 2006; Brahler et al., 2009). However, mice receiving TRAM-34 (Toyama et al., 2008) or over 500 human volunteers and patients taking Senicapoc for up to 2 years (Ataga et al., 2008) did not present with increased blood pressure.

We believe that the KCa3.1 channel is a prominent new pharmacological target for several diseases including renal disorders that, at this moment, do not have successful treatment options. We expect that within the next 10 years drugs targeting of KCa3.1 will start to come to the market.

Conclusions

Although much is known about the molecular and cellular mechanisms that lead to renal failure, the events that initiate this process remain unknown. Discovering and targeting these key signals would help investigators to stop the progressive loss of renal function that affects many individuals worldwide. The intermediate-conductance Ca^{2+}-activated K^+ channel (KCa3.1) could be one of these candidates given that its selective pharmacological inhibition, or knockdown of expression, ameliorates renal disease progression, as was summarized in this review. Although initial clinical trials have assessed the effects of blocking KCa3.1 in human diseases such as sickle cell and asthma, there are no clinical trials related to kidney disease. The hypothesis that KCa3.1 inhibitors may be potential renal therapeutics needs to be evaluated in the near future.

Compliance with ethics guidelines

Dr. Bertuccio and Dr. Devor declare that they have no conclict of interest. This manuscript is a review article and does not involve a

research protocol requiring approval by the relevant institutional review board or ethics committee.

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