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Ion Channels and Transporters in Diabetic Kidney Disease

Denisha Spires[*,1], **Anna D. Manis**[*,1], **Alexander Staruschenko**[1,2]

[1]Department of Physiology, Medical College of Wisconsin, Milwaukee, WI 53226, USA

[2]Clement J. Zablocki VA Medical Center, Milwaukee USA

Abstract

Type 1 and 2 diabetes mellitus are major medical epidemics affecting millions of patients worldwide. Diabetes mellitus is the leading cause of a form of chronic kidney disease known as Diabetic Kidney Disease (DKD), which is the most common cause of end-stage renal disease (ESRD). DKD is associated with significant changes in renal hemodynamics and electrolyte transport. Alterations in renal ion transport, triggered by pathophysiological conditions in diabetes, can exacerbate hypertension, accelerate renal injury, and are integral to the development of DKD. Renal ion transporters and electrolyte homeostasis play a fundamental role in functional changes and injury to the kidney during DKD. With the large number of ion transporters involved in DKD, understanding the roles of individual transporters as well as the complex cascades through which they interact is essential in the development of effective treatments for patients suffering from this disease. This chapter aims to gather current knowledge of the major renal ion transporters with altered expression and activity under diabetic conditions, and provide a comprehensive overview of their interactions and collective function in DKD.

Keywords

diabetic nephropathy; diabetic kidney disease; SGLT2; ENaC; TRPC6; TRPM6; NHE; K_{ATP} channel

1. INTRODUCTION

Diabetic Kidney Disease (DKD) is the primary contributor to the development of end stage renal disease (ESRD) and is associated with the onset of cardiovascular disease and stroke (Hagg et al., 2013; Maqbool, Cooper, & Jandeleit-Dahm, 2018; Umanath & Lewis, 2018). DKD is a subtype of chronic kidney disease (CKD) in which hyperglycemia, in combination with other manifestations of diabetes mellitus, leads to the development of severe renal complications. DKD is a steadily growing epidemic, with approximately 660,000 Americans diagnosed annually and Medicare expenditures in excess of $31 billion. In 2014, it was estimated that nearly 29 million Americans suffered from diabetes and an additional 86 million from prediabetes. In 2014, 44% of newly reported ESRD cases resulted from

Correspondence: Alexander Staruschenko, PhD; Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. Phone: (414) 955-8475; staruschenko@mcw.edu.

*these authors contributed equally to this work

diabetes. The Center for Disease Control and Prevention predicted that diabetes could affect nearly 1 in 3 U.S. adults by 2050 if current trends continue. Worldwide, the number of diabetic patients is expected to increase to approximately 350 million by the year 2035, with more than 40% of these patients developing CKD (Gheith, Farouk, Nampoory, Halim, & Al-Otaibi, 2016; Pavkov, Collins, Coresh, & Nelson, 2018). With the increasing urgency of the health risk posed by diabetes-related renal complications, the development of effective therapies and strategies for prevention is paramount. However, the pathogenesis of DKD has not been fully elucidated. Renal ion transporters are central to the intricate pathophysiological mechanisms of DKD and its progression. This article will review research concerning the contribution of key renal transporters to the progression of DKD and assess their utility as candidate therapeutic targets.

2. DIABETIC KIDNEY DISEASE

In DKD, also known as diabetic nephropathy (DN), hyperglycemia overwhelms the kidney's functionality, resulting in a breakdown of the glomerular filtration barrier (GFB) and overall dysfunction of the kidney. Hyperglycemia can lead to a variety of pathological cascades that affect ion transport in the kidney. The defining characteristics of DKD include a greater than 50% decline in glomerular filtration rate (GFR) over the course of the disease, microalbuminuria resulting from progressive GFB deterioration, and histological evidence of renal injury (interstitial fibrosis and glomerulosclerosis) (F. C. Brosius, 3rd et al., 2009; Schena & Gesualdo, 2005; Vallon & Komers, 2011). The substantial reduction in GFR associated with DKD is not observed during the initial stages of the disease. Patients initially exhibit hyperfiltration,an elevation in GFR, which gradually declines as DKD progresses over the course of 5 to 10 years. The initial hyperfiltration stage is an attempt by the kidneys to compensate for the apparent decrease in sodium delivery resulting from hyperglycemia. Once the tubuloglomerular feedback (TGF) system's ability to compensate for increased sodium and glucose reabsorption reaches saturation, kidney function and GFR decline (F. C. Brosius, 3rd et al., 2009; Schena & Gesualdo, 2005; Tuttle, 2017; Vallon & Komers, 2011). The second hallmark of DKD, microalbuminuria, is caused by the breakdown of the GFB during disease progression. The GFB is comprised of podocytes and their foot processes (the slit diaphragm), the glomerular basement membrane, and endothelial cells. These components normally function together with a network of proteins to filter the contents of the glomerular capillaries and prevent the passage of substances larger than approximately 69 kDa (the approximate molecular weight of albumin). As renal function declines and glomerular hypertrophy ensues, the GFB deteriorates. As a result, albumin leaks from the capillaries and is excreted in the urine (Jefferson, Shankland, & Pichler, 2008). Renal histologic changes typical of DKD include cellular and tissue injury, mesangial matrix expansion, nodular glomerular lesions, arteriolar hyalinosis, thickening of glomerular basement membranes, and renal interstitial fibrosis.

Hypertension is a frequent comorbidity in diabetic patients and is implicated in the progression of DKD (Fig 1). Hypertension is typically twice as common in patients with diabetes compared to the general population. Diabetes mellitus interacts synergistically with hypertension to promote kidney injury (Staruschenko, 2017). Therefore, the effects of both hyperglycemia and hypertension are required for kidney injury to occur in DKD (Z. Wang et

al., 2017). For this reason, anti-hypertensive drugs remain the leading treatment for DKD. The development of hypertension in diabetes results from overactivation of the renin-angiotensin-aldosterone system (RAAS), upregulation of endothelin 1 (ET-1; a vasoconstrictor secreted by endothelial cells), overproduction of reactive oxygen species (ROS), downregulation of nitric oxide (NO; a vasodilator), as well as other aberrant signaling (Arora & Singh, 2013; Kohan, Rossi, Inscho, & Pollock, 2011; Patney, Chaudhary, & Whaley-Connell, 2018; Patney, Whaley-Connell, & Bakris, 2015).

In DKD, hyperglycemia leads to the activation of numerous pathways including RAAS, inflammatory cytokines, and oxidative stress cascades (Fig. 2), which ultimately result in the renal impairment characteristic of this disease. The RAAS is particularly important in the progression of DKD, given that the primary treatment for DKD is anti-RAAS drugs, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) (Anders, Huber, Isermann, & Schiffer, 2018; Umanath & Lewis, 2018). In response to hyperglycemic conditions, renal cells begin to secrete angiotensin II (Ang II), an integral member of RAAS. Intrarenal Ang II has been found to be substantially elevated when compared to circulating Ang II in DKD patients. This redistribution of Ang II, which likely has a considerable impact on renal ion transport, has been shown to have a causative influence on multiple distinctive features of DKD, including podocyte injury and apoptosis (Leehey, Singh, Alavi, & Singh, 2000; Vallon & Komers, 2011).

This introduction to DKD represents only a glimpse of the complexity involved in the development and progression of this disease. The variation in renal ion transporter expression and activity and their intersecting pathways, signaling cascades, and feedback loops both respond and contribute to pathophysiological states during the progression of diabetes to DKD. These pathological states, including hyperglycemia, hypertension, and dysfunctional insulin signaling substantially dysregulate renal ion transport and electrolyte homeostasis, accelerating renal injury characteristic of DKD. The intricacy of DKD makes it particularly difficult to fully understand all details involved in its progression.

3. GLUCOSE TRANSPORTERS

3.1. Sodium glucose cotransporters

The kidneys play a major role in glucose regulation in humans, and are responsible for reabsorbing 99% of plasma glucose. Glucose reabsorption in the kidney occurs via sodium-glucose transporter 2 (SGLT2) in the early proximal tubule (PT) and to a lesser extent via sodium-glucose transporter 1 (SGLT1) in the late PT. Several SGLT1, SGLT2 or dual SGLT1/SGLT2 inhibitors have been shown to lower blood glucose by preventing glucose reabsorption at the PT, and act as effective antiglycemic drugs that may have utility in the treatment or prevention of DKD (Fig. 3) (Rieg & Vallon, 2018). These inhibitors are well described and have been marketed for treatment of type 2 diabetes mellitus (T2DM).

Members of the SGLT family of glucose transporters are involved in the re-uptake of glucose across the apical cell membrane. Their structure is composed of 14 transmembrane helices (Deng & Yan, 2016). There are 6 members of the SGLT family (SGLT1–6), but only SGLT1 and SGLT2 are well-characterized and have been shown to be highly expressed in

the kidney (Harada & Inagaki, 2012; Poulsen, Fenton, & Rieg, 2015). Although SGLT1 primarily functions within the small intestine, it does contribute to the maintenance of normal glucose balance in the kidney (Tahrani, Barnett, & Bailey, 2013); whereas SGLT2 is predominantly responsible for glucose uptake within the kidney. SGLT2 is located in the brush border of segments 1 and 2 of the PT and is responsible for approximately 90% of the glucose reabsorption in this part of the nephron. The remaining 10% is reabsorbed via SGLT1 in late segments of the PT (Hediger & Rhoads, 1994; Poulsen et al., 2015). The driving force for these cotransporters is the active movement of sodium via the sodium potassium ATPase (Na^+/K^+ ATPase) causing reuptake of glucose by the cell. In a study of these two cotransporters, it was found that only 1 sodium ion is required by SGLT2 for the reabsorption of 1 glucose molecule through the transporter. In contrast, SGLT1 requires 2 Na^+ ions to be moved for each glucose molecule absorbed, Km ~0.4 mM. Normally, SGLT2 (Km ≤ 6 mM) works at 50% capacity, only becoming fully saturated at a glucose level greater than and/or equal to 35 mM (E. Ferrannini & Solini, 2012; Ghezzi, Loo, & Wright, 2018; Harada & Inagaki, 2012; Hummel et al., 2011; Szablewski, 2017). Together with Na^+/K^+ ATPase, SGLT1 and SGLT2 make up the first stage of glucose transport and prevent excessive loss of glucose in the urine. Powell and colleagues confirmed the important role of the SGLTs in glucose transport showing that in a double knockout mouse model, the absence of both SGLT1 and SGLT2 resulted in the excretion of the entire filtered load of glucose (Ghezzi et al., 2018; Powell, DaCosta, et al., 2013). Given these transporters' substantial impact on overall glucose homeostasis, their implication in the development diabetes mellitus and its progression to DKD is unsurprising.

3.2. SGLT1 and SGLT2 in DKD

In treating diabetes mellitus, controlling blood glucose levels is imperative to prevent disease progression. The tubules reabsorb glucose at a maximal rate of approximately 375 mg/min after which their capacity for transport is saturated. In diabetes, plasma glucose increases to levels of hyperglycemia, bombarding the TGF system and the macula densa with overwhelming quantities of glucose. The overloading of this system causes hyperfiltration, which as previously mentioned, ultimately leads to glucose excretion in the urine and DKD (Abdul-Ghani, Norton, & DeFronzo, 2015; Brenner, 1983; Farber, Berger, & Earle, 1951; Ruggenenti et al., 2012; Vallon et al., 2011). SGLT transporters, especially SGLT2, have been targeted by multiple therapeutics in attempt to regulate hyperglycemia in diabetes. The goal of SGLT inhibitors is to increase the urinary output of glucose, thereby decreasing circulating glucose content and minimizing damage (Spatola, Finazzi, Angelini, Dauriz, & Badalamenti, 2018). Vallon et al. found that administering an SGLT2 inhibitor (empagliflozin) to the Akita mouse, a model of type 1 diabetes mellitus (T1DM), prevented hyperfiltration and reduced kidney hypertrophy and albumin excretion in the early stages of DKD. In the T2DN rat, a model of type 2 diabetic nephropathy (DN), the progression of DKD was slowed using a SGLT2 inhibitor which led to an appreciable reduction in GFR, glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria. Similar results were seen in a mouse model of type 2 DKD with SGLT2 inhibition causing a reduction in mesangial expansion and expression of inflammatory markers (Gembardt et al., 2014; Koepsell, 2017; Kojima, Williams, Takahashi, Miyata, & Roman, 2013). Interestingly, insulin receptor

deletion significantly reduced SGLT2 expression and increased urinary glucose excretion and urine flow (Nizar, Shepard, Vo, & Bhalla, 2018).

Unlike T1DM where insulin treatments are greatly beneficial and contribute to an improved quality of life, insulin treatment in T2DM is not as effective. These patients are, to some extent, insulin resistant. For T2DM patients, research has been focused on therapies targeting glucose transporters, specifically SGLT2 because the bulk of glucose re-uptake occurs through this transporter (Defronzo, 2009; Tahrani et al., 2013). Additionally, this cotransporter is primarily located in the kidney which minimizes off target effects of globally inhibiting SGLT2 (Koepsell, 2017). Patients with T2DM have similar renal protein expression of SGLT1 and SGLT2 compared to normoglycemic patients, although Norton and colleagues found that SGLT1 and SGLT2 mRNA expression levels in T2DM are higher than in normoglycemic patients. SGLT2 inhibitors reduce glucose reabsorption in the PT, ultimately resulting in improved kidney function (Sano, Takei, Shiraishi, & Suzuki, 2016; Zou, Zhou, & Xu, 2017). SGLT2 inhibitors also result in increased sodium delivery to the macula densa, which activates the TGF system to constrict the afferent arteriole and decrease GFR (Cherney et al., 2014; Vallon, Blantz, & Thomson, 2003; Zou et al., 2017). In the late stages of T2DM and DKD, the SGLT2 inhibitor canagliflozin was found to improve glycemic control and reduce albuminuria. Kohan et al. found that dapagliflozin, another SGLT2 inhibitor, reduced the body weight and blood pressure of T2DM patients without the change in glycemic control that Yale et al. observed (Kohan, Fioretto, Tang, & List, 2014; Yale et al., 2013; Zou et al., 2017). Similar results were found by other groups showing multiple benefits of SGLT2 inhibitors in diabetes and DKD, including improvements to renal oxygenation, natriuresis, and oxidative stress (Dekkers, Gansevoort, & Heerspink, 2018; Tanaka et al., 2018; X. X. Wang et al., 2017). SGLT2 expression and/or activity has been found to be upregulated in both type 1 and 2 diabetes, with an increase in the maximum glucose transport of approximately 20%. Administration of these inhibitors decreases this maximum capacity by roughly 30 to 50% (DeFronzo et al., 2013; Gallo, Wright, & Vallon, 2015). In addition, a study by Ferrannini et al found that empagliflozin improved pancreatic beta cell function and insulin sensitivity in T2DM patients (E. Ferrannini et al., 2014). Inhibitors of SGLT2 also reduced urate concentrations in the blood, which may contribute to the protective effects of these inhibitors in the progression of DKD (Ficociello et al., 2010; Haring et al., 2014; Jabbour, Hardy, Sugg, & Parikh, 2014; Koepsell, 2017; Kovacs et al., 2014; Rosenstock et al., 2014; Wilding et al., 2012). Figure 3 summarizes the effects of hyperglycemia on these transporters and the effects of their various inhibitors in DKD.

Although SGLT2 is the primary target for treatment of T2DM, it has been proposed that SGLT1 expression increases as a result of SGLT2 inhibition. As SGLT2 becomes overloaded and is inhibited, saturating glucose transport in the early PT, there is an increased need for SGLT1 contribution to handle the increase in glucose delivery to the later segment of the PT. Also, it has been hypothesized that SGLT2 inhibitors are less effective in T2DM patients with renal impairments, and SGLT1 inhibitors have been found to improve glycemic control in these cases (Gorboulev et al., 2012; J. J. Liu, Lee, & DeFronzo, 2012; Spatola et al., 2018; Yale et al., 2013). SGLT1 inhibitors also improve glucose homeostasis by exerting substantial effects on the gastrointestinal system, increasing the release of glucagon-like

peptide-1 (GLP-1) and reducing the absorption of glucose in the gut (P. Song, Onishi, Koepsell, & Vallon, 2016).

Although broadly beneficial for the treatment of diabetes, there are also complications associated with SGLT inhibitors. (G. Ferrannini & Ryden, 2018; Lupsa & Inzucchi, 2018). Adverse effects of SGLT2 blockers include genital mycotic and urinary tract infections. Euglycemic diabetic ketoacidosis has been found in some cases, likely due to increases in glucagon secretion and stimulation of lipolysis and ketogenesis. Furthermore, SGLT2 inhibitor monotherapy seems to be ineffective at maintaining long-term control of hyperglycemia in some cases of DKD (Hershon, 2016; Zou et al., 2017). Combined inhibitors of SGLT1 and SGLT2, such as sotagliflozin, have been shown to effectively reduce glucose and insulin levels in the plasma of T2DM patients (Powell, Smith, et al., 2013; Zambrowicz et al., 2012). Recent studies also revealed beneficial effects of sotagliflozin in combination with insulin treatment in patients with T1DM (Garg et al., 2017). SGLT2 inhibitors have also shown to be effective in combination with RAAS blockers by reducing cardiovascular events, albuminuria, hyperfiltration, and blood pressure in DKD (Bautista et al., 2004; Kojima et al., 2015; Kojima et al., 2013; Zou et al., 2017). Combining SGLT2 inhibitors with other targets of the glycemic control pathway, specifically dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, has also shown to be beneficial in treating DKD. GLP-1 receptor agonists can potentially counteract increases in glucagon secretion caused by SGLT2 inhibitors; whereas DPP-4 inhibitors combined with SGLT2 inhibitors showed reduced hypoglycemia, albuminuria, hyperglycemia, and blood pressure in DKD (DeFronzo et al., 2015; Scheen & Delanaye, 2018; Secrest, Udell, & Filion, 2017).

3.3. GLUT glucose transporters

In addition to the sodium glucose cotransporters, glucose transporters (GLUTs) are also vital for proper glucose homeostasis, and therefore have implications in the development of DM and DKD. GLUTs along with SGLTs are members of the major facilitator superfamily (S. S. Pao, Paulsen, & Saier, 1998; Thorens & Mueckler, 2010). GLUTs facilitate the energy independent movement of glucose down its electrochemical gradient. They are expressed in every cell in the body and are essential for energy metabolism. There are 17 GLUT proteins in the SLC2 family, which are further divided into three classes based on structure. Class I contains GLUT1–4, Class II contains GLUT5, 7, 9 and 11, and Class III contains GLUT6, 8, 10, 12 as well as the H^+/myo-inositol transporter (HMIT). Expression patterns, regulation, and properties of GLUTs are tissue specific. During different disease stages, GLUT expression levels tend to vary as well (Szablewski, 2017). This review will focus on specific GLUTs with prominent effects in the kidney.

3.4. GLUTs in DKD

GLUTs 1, 2, 4, 5, 8–10, and 12 all function in different segments of the kidney to facilitate glucose transport (Chin et al., 1997; C. Heilig et al., 1995; C. W. Heilig, Brosius, & Cunningham, 2006; Mather & Pollock, 2011). GLUT1 has been found to be upregulated in the renal cortex in diabetes as well as in glomerular hypertension. Similar to SGLT1 in the PT, GLUT1 is a low capacity glucose transporter in the glomerulus with a high affinity for

glucose (C. W. Heilig, Brosius, & Henry, 1997). Wang et al. showed that when GLUT1 is overexpressed in glomerular mesangial cells of the C57BL6 mouse (a relatively DKD resistant strain), the glomerulus develops damage like that of the glomerulosclerosis typically seen in DKD. More interestingly, these mice were not hyperglycemic or hypertensive during overexpression, insinuating that GLUT1 plays a potential role in the development of glomerulosclerosis in DKD (Y. Wang et al., 2010). GLUT1 is also expressed in the podocytes of the glomerulus, where it is widely localized to both the apical and basolateral membrane, within vesicles in the cytoplasm and plasma membrane of the foot processes. GLUT1 plays an important role in the proper function of podocytes in the GFB, which impacts overall kidney function (F. C. Brosius, 3rd, Briggs, Marcus, Barac-Nieto, & Charron, 1992; F. C. Brosius & Heilig, 2005; Coward et al., 2005; Jefferson et al., 2008; Wasik & Lehtonen, 2018). GLUT1 is activated in models of streptozotocin (STZ) induced T1DM as well as in mouse models of T2DM (Chen, Heilig, Brosius, & Heilig, 2003; D'Agord Schaan et al., 2001). Although GLUT1 overexpression in mesangial cells leads to the further development of DKD, its overexpression in podocytes appears to be protective in the progression of DKD (Y. Wang et al., 2010; Wasik & Lehtonen, 2018; Zhang et al., 2010). Several studies also implied that genetic variations in GLUT1 results in a genetic predisposition for DKD (F. C. Brosius & Heilig, 2005; Grzeszczak et al., 2001; Hodgkinson, Millward, & Demaine, 2001; Hsu et al., 2011; Z. H. Liu, Guan, Chen, & Li, 1999; Ng et al., 2002; Tarnow, Grarup, Hansen, Parving, & Pedersen, 2001; Vaulont & Kahn, 1994).

In the later stages of glucose reuptake by the kidney, GLUT2 is the primary transporter responsible for the basolateral movement of glucose on the brush border of the PT (Ghezzi et al., 2018; Mather & Pollock, 2011). In the diabetic kidney, it has been found that there is an increase in GLUT2 expression in the PT. For example, Chin et al. found that GLUT2 mRNA expression in the PT was increased in a T1DM animal model (Chin et al., 1997). Kamran et al. found that GLUT2 is overexpressed in both STZ-treated Sprague Dawley rats and diabetic Zucker rats (Kamran, Peterson, & Dominguez, 1997). Marks et al. found similar results in the PT of STZ-treated rats (Marks, Carvou, Debnam, Srai, & Unwin, 2003). GLUT1 and 2 work within the PT together with SGLT1 and 2 (Fig. 3). However, SGLT1 and 2 work more closely through GLUT2, high capacity and low glucose affinity, to handle the bulk of glucose transport in the PT (Ghezzi et al., 2018; Mather & Pollock, 2011). In contrast to SGLTs, finding specific inhibitors of GLUT2 has proven challenging considering the close homology between members of the GLUT family (Ghezzi et al., 2018; Yan, 2015).

In addition to GLUT1 and 2, GLUTs 4, 5, 8, 9, and 10 have also been detected in the kidney. In podocytes, GLUT4 is located on both the apical and basolateral membranes and within intracellular vesicles in the podocyte foot processes. GLUT4 is also expressed in mesangial cells, whereas GLUT8 is only expressed in podocytes (F. C. Brosius, 3rd et al., 1992; F. C. Brosius & Heilig, 2005; C. W. Heilig et al., 2006; Mather & Pollock, 2011). GLUT4 and 8 are considered to be insulin responsive transporters, another key function linking them to DKD. It was found that GLUT8 mRNA and protein levels are regulated by plasma glucose levels in both normal conditions and in cases of diabetes, including insulin resistant forms of diabetes. GLUT4 relocation to the plasma membrane has been found to be induced by the insulin-stimulated increase in phosphoinositide 3-kinase (PI3K)/AKT pathway (F. C.

Brosius & Heilig, 2005; Marcus et al., 1994; Schiffer et al., 2005; Wasik & Lehtonen, 2018). In a model of STZ-induced T1DM, GLUT4 expression in glomeruli was reduced (Marcus et al., 1994). Additionally, Coward et al. found that GLUT4 redistributes to the basal membrane in podocytes in a T2DM model. This suggests that despite a marked reduction in GLUT4 expression, functionality may not be affected during DKD progression (Coward et al., 2005). Additional studies have found that GLUT1 and 4 are responsive to insulin in the podocyte specifically, being stimulated in some fashion by insulin in these cells. Insulin causes activation of GLUT4 and its translocation from the perinuclear and cytosolic vesicular structures to the plasma membrane of the podocyte. Additional studies of GLUT4 deficient mice with DKD demonstrate that reduced GLUT4 activity protects podocytes from DKD by reducing mechanistic target of rapamycin (mTOR) activity (Coward et al., 2005; Guzman et al., 2014; Wasik & Lehtonen, 2018).

In addition to GLUT expression in glomeruli and the PT, Linden et al. found that GLUT12 is located within the distal tubule and collecting duct (CD) of the nephron. GLUT12 protein was found to be predominantly located in the cytoplasm and apical membranes of these segments. Using STZ-treated Ren-2 transgenic rats as a model of DKD, they saw an increase in both GLUT12 and GLUT1, indicating that both GLUT transporters have some involvement in the progression of this disease (Linden et al., 2006; Mather & Pollock, 2011). Expression levels for GLUT3 were also reported, but protein localization has not been determined (C. Heilig et al., 1995). GLUT5, which has been proposed to be fructose specific, has shown increased mRNA expression in the PT during chronic T1DM induced by STZ. Thus, GLUTs, together with SGLTs, play critical roles in glucose transport and contribute towards DKD progression.

4. SODIUM TRANSPORTERS

Sodium absorption in the kidney is precisely regulated and controlled by numerous physiological mechanisms. Under pathological conditions such as diabetes mellitus, Na^+ transport is significantly altered. Eriguchi *et al.* recently performed a sodium transporter profile immunoblot analysis in wild type mice where T1DM was induced by injection of STZ. After 6 months of STZ injections, the authors found no significant changes in total Na^+/H^+ exchanger (NHE) and Na^+-K^+−$2Cl^−$ cotransporter (NKCC) expression. However, NKCC2 phosphorylation was significantly increased in diabetic mice compared with nondiabetic controls. Similarly, analysis of distal tubule transporters revealed increased expression in both total and phosphorylated sodium-chloride cotransporter (NCC), and in subunits of the epithelial Na^+ channel (ENaC). Diabetic animals exhibited elevations in total α- and β-ENaC as well as cleaved forms of α- and γ-ENaC (Eriguchi et al., 2018). These data demonstrate that STZ-mediated hypoinsulinemia and hyperglycemia cause upregulation of most major sodium transporters. This section will delineate additional details about specific sodium transporters, and their potential contributions to DKD.

4.1. ENaC

Expressed primarily in principal cells of the distal nephron, ENaC plays a central role in maintaining salt and water homeostasis, regulating extracellular fluid volume, controlling

blood pressure, and overall renal function (Hanukoglu & Hanukoglu, 2016; Kleyman, Kashlan, & Hughey, 2018; Pavlov & Staruschenko, 2017; Staruschenko, 2012). Diabetes and DKD have been associated with increased ENaC activity and expression, which may reflect or contribute to the pathophysiology of DKD. Studies in humans and animals present multiple mechanisms by which the diabetic state can elicit changes in ENaC, which interfere with renal blood pressure control, exacerbate hypertension, and thereby contribute to the progression of DKD.

ENaC subunits are located on the apical membrane of principal cells in the aldosterone-sensitive distal nephron where they are tightly controlled by various hormones and mediate fine-tuning of sodium absorption in the kidney (Staruschenko, 2012). We and others have shown that insulin augments ENaC expression and activity (Gonzalez-Rodriguez, Gaeggeler, & Rossier, 2007; Ilatovskaya, Levchenko, Brands, Pavlov, & Staruschenko, 2015; Mansley et al., 2016; A. C. Pao, 2016; Pavlov et al., 2013; Tiwari, Nordquist, Halagappa, & Ecelbarger, 2007). As an example, single-channel analysis in freshly isolated, split-open tubules demonstrated that ENaC activity was acutely activated by insulin. Moreover, insulin receptor knockout mice have significantly lower activity compared to their wild-type littermates (Pavlov et al., 2013). Interestingly, high fat-fed mice had no increase in ENaC activity (Nizar et al., 2016). Recent studies by Irsik *et al.* (Irsik, Blazer-Yost, Staruschenko, & Brands, 2017; Irsik & Brands, 2018) have utilized a sophisticated insulin-clamping technique in rats, which allowed them to test the role of daily variations in insulin on sodium excretion. They found that rats whose insulin was clamped to prevent increases in response to carbohydrate showed elevated sodium excretion over the first 4 hours post carbohydrate administration (Irsik & Brands, 2018).

One proposed mechanism suggests that ENaC involvement with DKD is inexorably linked to the serum and glucocorticoid-regulated kinase (SGK1) protein. SGK1 is stimulated by insulin, which causes more ENaC to be translocated to the membrane (through the Nedd4–2 signaling pathway) increasing sodium reabsorption from the tubule. This may lead to excess renal sodium retention, hypertension, and ultimately renal damage associated with DKD (McCormick, Bhalla, Pao, & Pearce, 2005; Pearce et al., 2015). *In vitro* studies found that both ENaC and SGK1 are up-regulated by high levels of extracellular glucose (Hills, Bland, Bennett, Ronco, & Squires, 2006). It has been well established that the over-activity of ENaC can result in hypertension, and increased ENaC expression has been identified in animal models of both type 1 and type 2 diabetes (C. T. Chang et al., 2007). In a rat model of STZ-induced T1DM, increased glucose was correlated with upregulation of all three ENaC subunits, attributed to elevations in aldosterone and vasopressin (J. Song, Knepper, Verbalis, & Ecelbarger, 2003). Another proposed mechanism of ENaC increases in DKD involves the serine protease, plasmin (Kleyman et al., 2018; Ray et al., 2018). Urinary plasmin has been found to be elevated in human subjects with DKD as well as in the puromycin aminonucleoside rat model of nephrotic syndrome. Dysfunction of the GFB in DKD causes plasmin to be filtered to the tubules where it activates ENaC and increases sodium reabsorption (Svenningsen, Skott, & Jensen, 2012). In a study of patients with T2DM, microalbuminuria, a hallmark of GFB breakdown, is associated with increased aberrant filtration of plasmin. This surge of filtered plasmin was shown to be sufficient to increase the open probability for ENaC, and was proposed as a possible mechanism

contributing to hypertension in diabetes (Buhl et al., 2014). Clinical studies have also found that amiloride, an ENaC blocker, may be protective in DKD as it significantly increased sodium excretion, and reduced blood pressure, albuminuria, and plasmin in urine of diabetic patients (Andersen et al., 2015). Recently a pilot randomized cross-over study comparing the effects of daily administration of either oral amiloride or the NCC inhibitor, hydrochlorothiazide (HCTZ), to patients with type 2 diabetes and proteinuria revealed similar effects with both drugs resulting in reduced systolic blood pressure (Unruh et al., 2017).

It is widely accepted that oxidative stress plays a central role in diabetes-induced renal injury. Prolonged hyperglycemia causes excess glucose to contact and react with proteins and lipids resulting in advanced glycation end-products (AGEs), which are known to cause multiple complications in diabetic patients and are implicated in DKD. The role of AGEs in DKD may be especially important to understand as they are capable of having substantial effects, including oxidative stress, that persists long term even after blood glucose control is regained in the patient (Singh, Bali, Singh, & Jaggi, 2014). AGEs have been shown to be upregulated in diabetic subjects with hypertension, with an especially pronounced elevation in the distal nephron where ENaC is highly expressed (Schleicher, Wagner, & Nerlich, 1997). When applied to cultured tubular epithelial cells in concentrations comparable to what occurs in diabetes, AGEs increased ENaC mRNA and protein and stimulated ENaC activity by inhibiting catalase and increasing intracellular ROS production (Q. Wang et al., 2015). The effect on ENaC activity persisted for more than 72 hours after removal of AGEs. This sustained ENaC elevation may be key to understanding why DKD often continues to progress despite adequate glucose control and provide key insights necessary for the development of more effective treatments. From these studies, it is evident that diabetes creates pathophysiological conditions that affect ENaC via multiple pathways, causing a sustained increase in activity or expression, ultimately resulting in blood pressure elevation (Fig. 4). As hypertension is one of the most important risk factors in the progression from diabetes to DKD, ENaC is a critical mechanistic and potential therapeutic target in DKD research.

4.2. Sodium hydrogen exchanger (NHE)

Sodium-hydrogen exchangers (NHE) directly and indirectly contribute to the maintenance of blood volume and whole body acid-base homeostasis. The inward movement of Na^+ down its electrochemical gradient supplies the energy for the active transport of H^+ against its gradient. In the human genome there are 9 isoforms of NHE belonging to one of 3 subfamilies: cation-proton antiporters (CPA1 and CPA2) and Na-transporting carboxylic acid decarboxylase (NaT-DC). NHE1–4 and 6–9 are members of the CPA1 family and are found in various parts of the kidney (Bobulescu, Di Sole, & Moe, 2005; Bobulescu & Moe, 2009; Brett, Donowitz, & Rao, 2005; A. B. Chang, Lin, Keith Studley, Tran, & Saier, 2004; Orlowski & Grinstein, 2004). NHE isoforms 1–4 and 8 are located on either the apical or basolateral membranes of renal epithelial cells, whereas NHE6, 7, and 9 are found only on membranes of organelles. NHE3 and NHE8 are located on the apical membrane of the PT; NHE2 and NHE3 are on the apical membrane of the thick ascending limb (TAL) of the loop of Henle; NHE 2 is on the apical membrane of the distal convoluted tubule (DCT) and

connecting tubule; NHE4 is on the basolateral membrane of the entire nephron; and NHE1 is located on the basolateral membrane everywhere except the macula densa and intercalated cells (Chambrey et al., 2001; Chambrey et al., 1998; Goyal, Mentone, & Aronson, 2005; Nakamura, Tanaka, Teko, Mitsui, & Kanazawa, 2005; Orlowski & Grinstein, 2004; Xu, Chen, & Ghishan, 2005).

Given the location and the general function of NHE exchangers, it is expected that certain NHE isoforms are involved in the progression of DKD. STZ-induced T1DM in a mouse model with a loss of function mutation in NHE1 (*swe/swe* mouse created on the C57BL/6 mouse background) resulted in the development of DKD characteristics. *Swe/swe* mice without STZ-induced T1DM exhibited renal tubular epithelial cell atrophy, and STZ treatment resulted in the additional development of albuminuria and increased tubulointerstital pathology (Khan, Wu, Sedor, Abu Jawdeh, & Schelling, 2006; Wu et al., 2003). Numerous studies have found that NHE3 in particular is implicated in DKD development. A link between SGLT2 and NHE3 has been proposed to contribute to the renoprotective effects of SGLT2 inhibitors and to potentially contribute to the reduction in sodium reabsorption during treatment with SGLT2 inhibitors. However, contradictory explanations have been reported, suggesting that SGLT2 inhibitors increase rather than reduce sodium absorption and that the nephro-protective effects of these inhibitors is not dependent on the TGF system (Wakisaka, 2016; Wakisaka, Nagao, & Yoshinari, 2016; Wright, Loo, & Hirayama, 2011; Zeni, Norden, Cancarini, & Unwin, 2017). The connection between NHE3 and SGLT2 has even been hypothesized to have benefits in treating some of the characteristics of DKD, including the alteration of renal hemodynamics (Pessoa, Campos, Carraro-Lacroix, Girardi, & Malnic, 2014; Tonneijck et al., 2017). The “tubular theory” for hyperfiltration (a hallmark of DKD) suggests that the relationship between the glomerulus and the tubule is the key to explaining diabetes-induced renal dysfunction and abnormalities, and proposes that hyperfiltration is caused by increased sodium reabsorption combined with tubular hypertrophy and up-regulation of SGLTs and NHE3. The theory suggests that the combination of these factors inhibit TGF (Tonneijck et al., 2017; Tuttle, 2017; Zeni et al., 2017). It has also been discovered that the GLP-1 receptor agonist, liraglutide, reduces GFR and albumin excretion in patients with T2DM by GLP-1 mediated inhibition of NHE3 and DPP-4 assembly in the PT brush border. Inhibiting this relationship causes a reduction in sodium reabsorption and GFR by activating the TGF system (Muskiet, Smits, Morsink, & Diamant, 2014; Tonneijck et al., 2017).

4.3. NKCC2 and NCC

The furosemide-sensitive cotransporter NKCC2 and the thiazide-sensitive cotransporter NCC play important roles in renal salt handling and extracellular volume regulation in the TAL and DCT, respectively. Similar to other sodium transporters, expression of both total and active forms of NKCC2 and NCC is increased under diabetic conditions, which has been reported in several rodent models (Cipriani et al., 2012; Eriguchi et al., 2018; Riazi, Khan, Tiwari, Hu, & Ecelbarger, 2006; Riazi, Maric, & Ecelbarger, 2006). Metformin, an antidiabetic drug that is widely used to treat patients with diabetes mellitus, was shown to increase urinary sodium excretion by reducing phosphorylation of NCC. Interestingly, the activity of other renal sodium transporters, such as NKCC2, ENaC, and NHE3 did not show

significant changes during metformin treatment (Hashimoto et al., 2018). Similar to this finding, our data also revealed that metformin-treated Dahl SS rats fed a high salt diet had no difference in the activity of ENaC (Pavlov et al., 2017).

Hyperinsulinism is associated with increased expression of NCC along with Na^+/K^+ ATPase and ENaC (Bickel, Verbalis, Knepper, & Ecelbarger, 2001). *In vitro* studies of insulin effects revealed that insulin induces activation and phosphorylation of NCC, which could contribute to sodium balance and the progression of DKD in hyperinsulinemic states (Chavez-Canales et al., 2013). Therefore, there is some evidence demonstrating the potential contribution of sodium cotransporters in the TAL and DCT (especially for thiazide-sensitive transporter NCC). However, additional studies are warranted.

5. POTASSIUM CHANNELS

Although renal potassium channels have not been definitively identified as causal in the development of DKD, it is likely that some of these channels are involved in the disease progression. The kidney is responsible for maintaining whole-body potassium homeostasis, which is essential for the proper control of blood glucose, as insulin is secreted from pancreatic beta cells in response to a potassium induced depolarization (Ekmekcioglu, Elmadfa, Meyer, & Moeslinger, 2016). Various clinical studies indicate that insufficient serum potassium or dietary potassium intake is associated with the onset of T2DM. Low potassium diets and hypokalemia contribute to impaired insulin secretion and glucose intolerance (Rowe, Tobin, Rosa, & Andres, 1980; Sagild, Andersen, & Andreasen, 1961). It has also been shown that the treatment of hypertension with thiazide diuretics, which commonly cause potassium depletion as a side-effect, has been associated with increased risk of new-onset diabetes (Zillich, Garg, Basu, Bakris, & Carter, 2006). In addition to diabetes onset, potassium may also play a role in the progression of diabetes to more severe cardiovascular and renal impairment. High potassium diets have been established to reduce the risk of development of cardiovascular disease in healthy patients. However, it has been less clear whether increasing dietary potassium intake in patients with diabetes would have similar protective results. A study by Smyth et al. examined how potassium intake may correlate with renal outcomes in nearly 30,000 patients with established diabetes or other vascular disease. This study found that higher potassium was associated with decreased risk for all renal outcomes in these patients. Interestingly, they found that only potassium, not sodium, was predictive for renal outcome (Smyth et al., 2014). A similar study involving over 600 Japanese patients with T2DM also showed that high urinary excretion of K^+ (indicative of higher potassium intake), but not sodium, was associated with better cardiorenal outcomes (Araki et al., 2015). These studies together indicate that the improper maintenance of potassium homeostasis, and possible dysfunction of renal K^+ channels, may be involved in the development of renal impairments in diabetes. For example, the voltage-gated potassium channel gene subfamily, KCNQ1, which localizes to the brush border of the PT, has been proposed as a marker for DKD. Genetic variants in this gene have significant association with susceptibility for DKD and microalbuminuria in multiple studies involving East Asian and European populations (Lim et al., 2012; Ohshige et al., 2010; Unoki et al., 2008).

The Ca^{2+} - activated K^+ channel 3.1 ($K_{Ca}3.1$) has been identified as a potential target in DKD. This voltage-independent potassium channel is expressed in multiple cell types implicated in tubulointerstitial fibrosis including renal PT cells, fibroblasts, inflammatory cells, and endothelial cells (Huang, Pollock, & Chen, 2014b). *In vitro*, as well as *in vivo* studies in diabetic mouse models have shown that $K_{Ca}3.1$ is activated by high glucose and produces a proinflammatory response that contributes to renal damage in DKD. Moreover, blocking $K_{Ca}3.1$ suppresses the proinflammatory cytokine chemokine ligand 20 (CCL20), which prevents macrophage accumulation and improves renal fibrosis in diabetic mice, making it a potential therapeutic target for the treatment of DKD (Huang, Pollock, & Chen, 2014a; Huang et al., 2013). One study found that renal injury in DKD may be exacerbated by insufficient autophagy in proximal tubular cells, and that blocking $K_{Ca}3.1$ restores normal autophagy, which may prevent some degree of renal injury in diabetic kidney disease (Huang et al., 2016). $K_{Ca}3.1$ blockers have been studied in clinical trials to treat sickle cell disease and although results showed it may be ineffective for this purpose, these drugs were safe and well-tolerated by patients in the trial (Wulff & Castle, 2010). This supports the claim that $K_{Ca}3.1$ blockers may be beneficial in the treatment of DKD.

As previously discussed, the malfunction of podocytes and loss of nephrin in the GFB is a hallmark of DKD. Studies show that both insulin and exposure to high glucose affect the activity and expression of the large-conductance Ca^{2+}-activated K^+ (BK) channel present in podocytes. Treatment of mouse podocytes with high glucose caused a marked reduction of BK channel current and a decrease in surface expression of BK channels, as well as nephrin, which likely interacts with the channel. However, insulin acts to stimulate BK channel activity and expression, which is blocked by the presence of high glucose. BK channels have been shown to interact with transient receptor potential canonical (TRPC) channels and their large conductance may provide the driving force facilitating movement of Ca^{2+} into the podocyte through TRPC channels. BK channels in the podocytes are responsive to insulin and glucose and interact with TRPC channels and nephrin, both of which are implicated in DKD. Thus it is feasible that the malfunction of these channels is involved in the progression of DKD (Kim & Dryer, 2011).

In addition to tubular potassium channels, there are renal vascular K^+ channels which also contribute to DKD (Salomonsson, Brasen, & Sorensen, 2017). As an example, the involvement of ATP-sensitive K^+ channels (K_{ATP} channels) in renal afferent arteriolar dilation was reported during STZ-induced T1DM (Ikenaga, Bast, Fallet, & Carmines, 2000). Similarly, we have shown recently that Dahl salt-sensitive rats with STZ-induced diabetes had an increased vasodilator response to the K_{ATP} channel activator, pinacidil (Miller et al., 2018). In addition to increased K_{ATP} channel activity in diabetes, it was also shown that other renal vascular K^+ channels, including BK channels and members of the inward rectifier (K_{ir}) family, contribute to afferent arteriolar dilation in diabetic animal models (Brindeiro, Fallet, Lane, & Carmines, 2008; Carmines & Fujiwara, 2002).

6. CALCIUM AND MAGNESIUM CHANNELS

6.1. Transient receptor potential (TRP) channels

The TRP superfamily of cation channels vary in permeability, selectivity, and mode of activation. TRP channels play a pivotal role in the influx of calcium, magnesium, and other ions across the plasma membrane and contribute to a diversity of functions, including their physiological and pathophysiological roles in the kidney (Abramowitz & Birnbaumer, 2009; Marko, Mannaa, Haschler, Kramer, & Gollasch, 2017; Tomilin, Mamenko, Zaika, & Pochynyuk, 2016). The TRP family is sub-divided into the following groups based on function and sequence: melastatin-related TRP (TRPM), ankryin transmembrane TRP (TRPA), vanilloid-receptor-related TRP (TRPV), mucolipin TRP (TRPML), polycystin TRP (TRPP), and canonical TRP (TRPC). Each group has a varied number of members and are expressed in all cell membranes, excluding mitochondrial membranes, throughout tissue types including the brain, lungs, smooth muscle, and kidneys. Abnormal activity and mutations in these channels have been linked to an assortment of kidney disorders such as nephrotic syndromes, glomerular diseases, polycystic kidney disease (PKD), and DKD (Abramowitz & Birnbaumer, 2009; Harris & Torres, 2009; Nilius & Owsianik, 2011; Tomilin et al., 2016; Woudenberg-Vrenken, Bindels, & Hoenderop, 2009). More recently the TRPC subfamily has become a target for research into possible therapeutic treatments for DKD.

The TRPC subfamily is composed of seven channels that are non-selectively permeable to calcium and sodium (Abramowitz & Birnbaumer, 2009; Vazquez, Wedel, Aziz, Trebak, & Putney, 2004; Woudenberg-Vrenken et al., 2009). TRPC 1–7 are all activated through phospholipase C (PLC) coupled receptors; however, they differ in mode of operation. Some are store-operated, whereas others operate via receptors (Dietrich, Mederos y Schnitzler, Kalwa, Storch, & Gudermann, 2005). Store-operated calcium entry (SOC) occurs when inositol 1,4,5-trisphosphate (IP_3) or another signal causes the release of intracellular calcium stores from the endoplasmic reticulum (ER), reducing the calcium concentration in the ER. This Ca^{2+} decrease leads to the activation of SOC channels (Dietrich et al., 2005). Receptor-operated calcium entry (ROC) occurs when an agonist binds to and activates the PLC coupled receptor, which is located on the cell membrane separate from the actual channel (Dietrich et al., 2005). Activation of both SOC and ROC TRPC channels lead to increased intracellular calcium levels (Abramowitz & Birnbaumer, 2009). In the kidney, TRPC channels are present in renal tubules and the glomerulus where their malfunction, overexpression, or mutation is linked to certain renal diseases. Of these channels, only TRPC6 has been genetically linked to a renal disease (Reiser et al., 2005; Winn et al., 2005).

6.2. TRPC6 and DKD

Numerous gain-of-function mutations in *Trpc6* gene have been identified to ultimately lead to the development of Focal Segmental Glomerulosclerosis (FSGS) (Heeringa et al., 2009; Reiser et al., 2005; Winn et al., 2005). A recent analysis of human disease-causing *Trpc6* mutations also revealed a loss-of-function mutation in TRPC6 as an additional cause of hereditary FSGS (Riehle et al., 2016), which demonstrates that not only activation, but also inhibition of TRPC6 activity might lead to FSGS. With its location on the membrane of the

podocyte, TRPC6 participates in unison with other integral players of the slit diaphragm such as podocin and nephrin (Dryer & Reiser, 2010; Ilatovskaya & Staruschenko, 2015; Reiser et al., 2005). TRPC6 normally remains dormant in the cell membrane until activated by a stimulus (Fig. 5) (Ilatovskaya & Staruschenko, 2015). Ang II is increased during the progression of DKD and has been found to activate TRPC6 channels (Anderson, Roshanravan, Khine, & Dryer, 2014; Ilatovskaya et al., 2018; Ilatovskaya, Levchenko, Lowing, et al., 2015; Ilatovskaya et al., 2014; Ilatovskaya, Palygin, Levchenko, Endres, & Staruschenko, 2017; Nijenhuis et al., 2011; Sonneveld et al., 2014). In addition, hyperglycemia together with Ang II leads to overexpression of the TRPC6 channel in the podocyte and the subsequent drastic increase in intracellular calcium flowing through TRPC6. Hyperglycemia alone is insufficient to cause this same response (Sonneveld et al., 2014). Ang II influences TRPC6 mRNA and protein levels by increasing the expression of the channel in the podocyte. The Ang II-mediated activation of the TRPC6 channel leads to engorgement of the podocyte with calcium, which causes podocyte cell death and breakdown of the GFB. This inevitably leads to albuminuria which is a hallmark of DKD (Fig 5) (Adebiyi, Soni, John, & Yang, 2014; Eckel et al., 2011; Evans, Lee, & Ragolia, 2009; Ilatovskaya, Levchenko, Lowing, et al., 2015; Ilatovskaya et al., 2014; Ilatovskaya et al., 2017; Nijenhuis et al., 2011; Qin Zou, 2015; Reiser et al., 2005; Sonneveld et al., 2014; Zhang, Ding, Fan, & Liu, 2009). Our recent studies using a TRPC6 knockout on the Dahl SS rat background ($SS^{Trpc6-/-}$) indicate that TRPC6 channel inhibition may have at least partial renoprotective effects in the context of type 1 DN (Spires et al., 2018). Further studies revealed the contribution of Nox4-mediated oxidative stress in the regulation of TRPC6 in DKD (Ilatovskaya et al., 2018). In agreement with our studies, Kim *et al.* reported that the genetic inactivation of TRPC6 in Sprague-Dawley rats confers this protection in a model of severe nephrosis (Kim, Yazdizadeh Shotorbani, & Dryer, 2018). Interestingly, Wang *et al.* reported that TRPC6 KO Akita mice exhibit prominent mesangial expansion in the diabetic group, which suggests enhanced susceptibility of glomerular cell types to the adverse effects of the TRPC6 KO with regards to hyperglycemia (Staruschenko, 2019; L. Wang, Chang, Buckley, & Spurney, 2019).

6.4. Voltage-gated calcium channels

Although less thoroughly studied than TRPC channels, voltage-gated calcium channels have also been shown to play a role in DKD. In the clinic, calcium channel blockers are commonly prescribed in conjunction with RAAS inhibitors to achieve better control over blood pressure, which is required for hypertensive patients with renal complications. These drugs are promising candidates in the treatment of DKD as they have been shown to be effective antihypertensive medications that are safe and well-tolerated with few reported side effects. The antihypertensive effect of calcium channel blockers is mainly attributed to the blockade of L-type Ca^{2+} channels, but N- and T-type channels may play a role in renal protective action due to their effects on glomerular capillary pressure, renal fibrotic process, sympathetic nerve activity and aldosterone synthesis (Sugano, Hayashi, Hosoya, & Yokoo, 2013). Blockers of both the N- and L-type calcium channels have been tested in patients with diabetes to determine whether they impacted renal function. Multiple clinical studies have found that N- and L- type calcium channel blockers are renoprotective and improve proteinuria/microalbuminuria in diabetic patients. However, there is debate as to whether a

specific L-type blocker, amlodipine, or a general N-/L-type blocker, cilnidipine, is more protective in the progression of DKD. Ando *et al.* compared the results of administering the antagonist of both the N- and L-type channels, cilnidipine, and the specific L-type calcium channel blocker, amlodipine, to patients with hypertension and T2DM with microalbuminuria over a 12-month duration and did not find a substantial difference in renal outcomes (Ando et al., 2013). In contrast, a different study in hypertensive diabetic patients found significant differences in patient outcomes between the two drugs. Masuda *et al.* found that cilnidipine treatment resulted in significantly lower insulin resistance, higher estimated GFR, lower urinary albumin, and lower urinary creatinine. These parameters indicate better renal function and less renal damage, suggesting that cilnidipine rather than amlodipine, better preserves kidney function and is a more appropriate candidate for slowing the progression of DKD (Masuda et al., 2011). Both calcium channel blockers are already safely being prescribed to diabetic patients with hypertension who are at the highest risk for developing DKD; however, more clinical research is needed to determine which drug is most renoprotective. Basic science research on these channels indicates that inhibiting the N-type channel is especially important for the protection against kidney injury and the preservation of function. Thus, it has been predicted that antagonizing the N-type channel would produce a more balanced dilation of the afferent and efferent arterioles, more effectively reducing glomerular pressure. The N-type voltage-gated calcium channel, $Ca_v2.2$, is expressed in podocytes in the glomerulus as well as in the DCT. A global deletion of this channel in the *db/db* diabetic mouse ameliorates many of the renal manifestations of diabetes that are known to contribute to DKD. This knockout mouse had a significant reduction in hyperfiltration, renal injury, blood pressure, and proteinuria. Similarly, applying pharmaceutical antagonists to $Ca_v2.2$ resulted in renoprotection. Blocking this channel in cultured podocytes caused a reduction in transforming growth factor beta (TGF-β) mediated nephrin loss. These studies suggest that treatment with specific $Ca_v2.2$ channel blockers may slow the progression of DKD by protecting podocytes and reducing glomerular injury (Ohno et al., 2016).

6.5. Magnesium homeostasis and TRPM6 and TRPM7 channels

Renal magnesium handling is not classically associated with DKD, as magnesium has long been considered to be independent of endocrine control, often termed an “orphan ion” (Yee, 2018). However, recent studies suggest that magnesium should not be overlooked in the context of DKD. Next to potassium, magnesium is the second most abundant intracellular cation and the kidney is responsible for maintaining its homeostasis. Like potassium, magnesium is associated with increased longevity and cardiovascular health, and is also an important anti-inflammatory molecule. Several studies have found an association between serum magnesium and diabetes. Earlier studies have suggested a link between hypomagnesemia and hyperglycemia, as well as an association between hypomagnesemia and the complications of diabetes (White & Campbell, 1993). A meta-analysis including over 500,000 patients found an inverse correlation between serum magnesium levels and risk for cardiovascular disease (Qu et al., 2013). Furthermore, this protection has been shown to extend to patients with CKD, who are at heightened risk for cardiovascular events (Kanbay, Goldsmith, Uyar, Turgut, & Covic, 2010), and hypertension where magnesium supplementation has been shown to be effective in reducing blood pressure. Additionally,

patients with diabetes have lower serum magnesium, on average, than healthy controls. Diabetic patients with microalbuminuria, indicative of progression towards DKD, have significantly lower magnesium than those without (Corsonello et al., 2000). Poor glycemic control in these patients likely causes enhanced urinary magnesium loss, which is associated with a more rapid progression from diabetes to DKD.

There is considerable evidence suggesting that Mg^{2+} deficiency is a significant risk factor for the development of insulin resistance and T2DM (Barbagallo & Dominguez, 2007). A recent population-based cohort study by Kieboom *et al.* revealed that low serum Mg^{2+} levels are associated with an increased risk of prediabetes. Furthermore, common variants in magnesium-regulating genes, including the magnesium transporters, SLC41A2 (Solute Carrier Family 41 Member 2) and TRPM6, modify diabetes risk through altering serum Mg^{2+} levels (Kieboom et al., 2017). Transient receptor potential melastatin 6 and 7 (TRPM6 and TRPM7) channels play a central role in magnesium homeostasis, which is critical for maintaining glucose and insulin metabolism. Several loss-of-function mutations in *Trpm6* have been identified among patients with an autosomal-recessive form of hypomagnesemia with secondary hypocalcemia (Lainez et al., 2014; Schlingmann et al., 2002; Walder et al., 2002). Various factors and hormones, including epidermal growth factor, pH, and insulin, contribute to the expression and function of this important channel (de Baaij, Hoenderop, & Bindels, 2015). There is also genetic evidence establishing the potential contribution of TRPM6 channels to the development of diabetes. For instance, Song *et al.*, reported that two common non-synonymous SNPs in *Trpm6* might confer susceptibility to T2DM in women with low magnesium intake (Y. Song et al., 2009). Another study revealed that SNPs in *Trpm6* have been associated with gestational diabetes. Loss of insulin-induced activation of TRPM6 channels results in impaired glucose tolerance during pregnancy (Nair et al., 2012). Insulin binding causes the activation of two cascades resulting in more TRPM6 channels as well as NCC transporters to be inserted in the apical membrane. Hyperinsulinemia and insulin resistance may cause an uncoupling of these cascades, in which NCC increases concomitantly with insulin activity while TRPM6 becomes unresponsive to insulin activity, both effectively contributing to hypertension. A recent genome-wide meta-analysis of Mg^{2+} homeostasis and metabolic phenotypes identified two loci associated with urinary magnesium near *Trpm6* (Corre et al., 2018). TRPM6 activity may also be inhibited by oxidative stress, further reducing Mg^{2+} uptake in diabetic patients. Diabetic rat models have also shown altered expression levels of TRPM6. Hyperfiltration and increased urinary flow rates in DKD patients are inversely correlated with Mg^{2+} reabsorption in the TAL and DCT and may also affect osmotic diuresis and passive reabsorption in the PT (Gommers, Hoenderop, Bindels, & de Baaij, 2016). In addition to TRPM6 and TRPM7 channels, there are other magnesium carriers in the kidney which might contribute to Mg^{2+} handling under normal conditions as well as during DKD. Therefore, current studies provide evidence supporting the critical contribution of magnesium channels in diabetes and the potential beneficial role of Mg^{2+} supplementation in diabetic patients. However, additional clinical and fundamental research is needed to identify specific mechanisms contributing to magnesium deficiency in diabetes. Despite gaps in research on the complicated role of renal magnesium handling in DKD, it is certain that magnesium imbalance contributes to or is

affected by multiple pathways integral to the progression of DKD including blood pressure control, oxidative stress, inflammation and hyperfiltration.

7. CONCLUSIONS AND FUTURE PERSPECTIVES

DKD as a result of diabetes mellitus is a medical pandemic affecting many patients today. Due to the critical role of renal ion transport in kidney damage caused by DKD, these transporters and their pathways represent promising targets for therapeutics. Understanding the roles of the numerous transporters in the disease progression of DKD requires knowledge of both their individual functions as well as their collective interactions, cascades, and mechanisms of regulation. This review provides only a brief description of the involvement of some of the most influential transporters in DKD. More studies are certainly necessary to further validate and evaluate the roles of these and other ion transporters in the pathogenesis of DKD.

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ABBREVIATIONS

AGEs	Advanced glycation end-products
BK	Large-conductance Ca^{2+}-activated K^+ channel
CD	collecting duct
CKD	Chronic kidney disease
DCT	Distal convoluted tubule
DKD	Diabetic kidney disease
DN	Diabetic nephropathy
DPP-4	Dipeptidyl peptidase-4
ENaC	Epithelial Na^+ channel
ESRD	End stage renal disease
ET-1	Endothelin 1
FSGS	Focal Segmental Glomerulosclerosis
GFB	Glomerular filtration barrier
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1

GLUT	Glucose transporter
K_{ATP}	ATP-sensitive K^+ channels
mTOR	Mechanistic target of rapamycin
Na^+/K^+	**ATPase** Sodium potassium ATPase
NCC	Na^+-2Cl^- cotransporter
NHE	Na^+/H^+ exchanger
NKCC	Na^+-K^+-2Cl^- cotransporter
NO	nitric oxide
PT	Proximal tubule
RAAS	Renin-angiotensin-aldosterone system
ROS	Reactive oxygen species
SGK1	Serum and glucocorticoid-regulated kinase
SGLT1	Sodium-glucose transporter 1
SGLT2	Sodium-glucose transporter 2
SLC41A2	Solute carrier family 41 member 2
STZ	streptozotocin
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAL	Thick ascending limb
TGF	Tubuloglomerular feedback
TGF-β	Transforming growth factor beta
TRP	Transient receptor potential channel
TRPC	Transient receptor potential canonical channel
TRPM	Transient receptor potential melastatin channel

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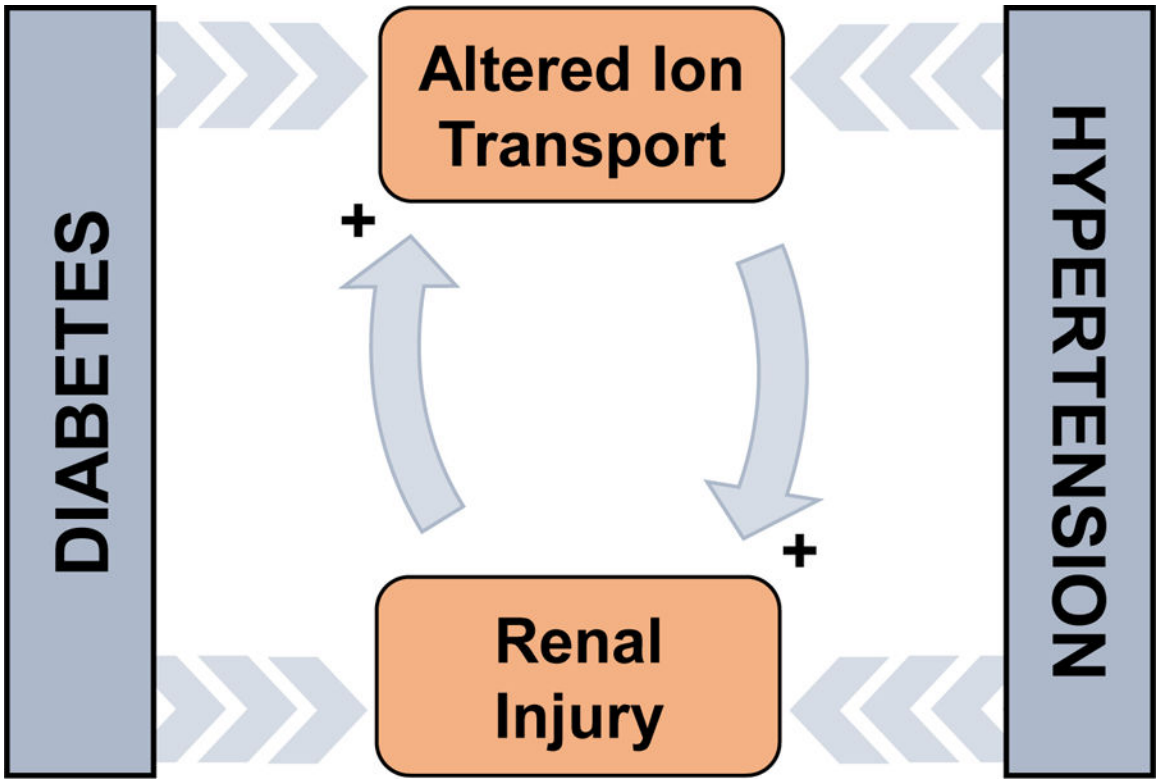

Figure 1.

The positive feedback relationship between diabetes, hypertension, altered ion transport, and renal injury. This represents a simplified explanation for a very complex relationship that defines diabetic kidney disease (DKD).

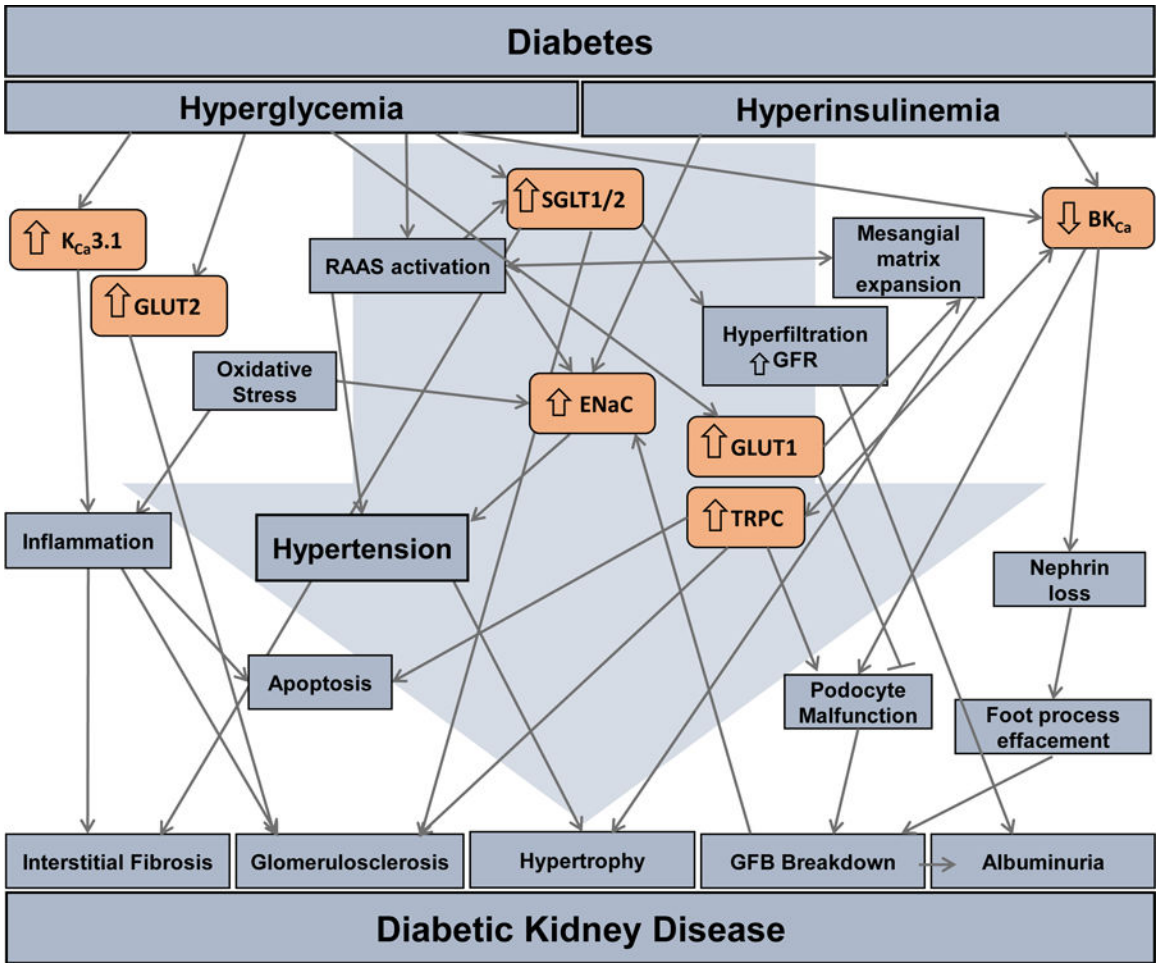

Figure 2.

Schematic for pathogenesis of diabetic kidney disease (DKD). Hyperglycemia and hyperinsulinemia induced by diabetes leads to the activation and expression of the different channels and transporters located along the various nephron segments. These changes are exercised either directly or indirectly upon the channel. The multitude of these channel alterations result in interstitial fibrosis, glomerulosclerosis, hypertrophy, breakdown of the glomerular filtration barrier (GFB) and albuminuria. The culmination of the damage to various portions of the nephron is the development of DKD. Abbreviations: calcium activated potassium channel 3.1 ($K_{Ca}3.1$); glucose transporters (GLUT1 and 2); sodium glucose cotransporter (SGLT1 and 2); large conductance Ca^{2+}-activated K^+ channel (BK_{Ca}); epithelial Na^+ channel (ENaC); transient receptor potential canonical (TRPC) channel.

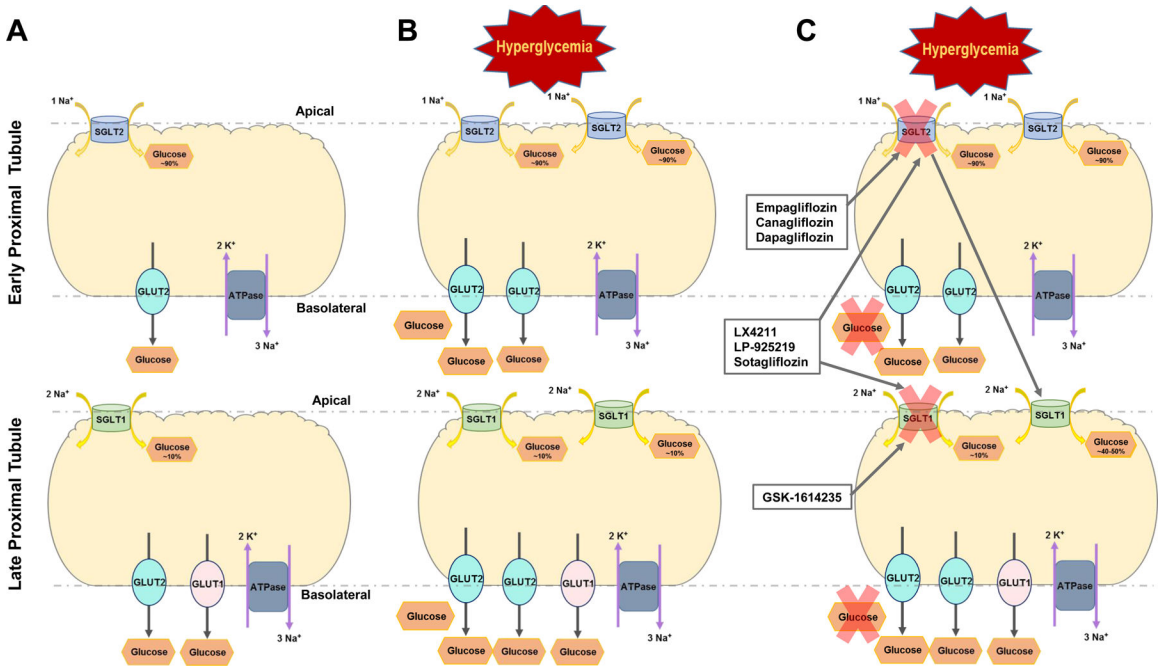

Figure 3.

Tubular view of glucose transport within the proximal tubule of the kidneys. **A**. Healthy proximal tubule segments and normal function of sodium glucose cotransporters (SGLT1 and SGLT2) and their glucose transporter (GLUT1 and GLUT2) counterparts. **B**. The altered function of SGLT and GLUT transporters under DKD conditions. **C**. Examples of the inhibitors specific for SGLT2, SGLT1, and dual inhibitors for both transporters and their general effects under DKD conditions.

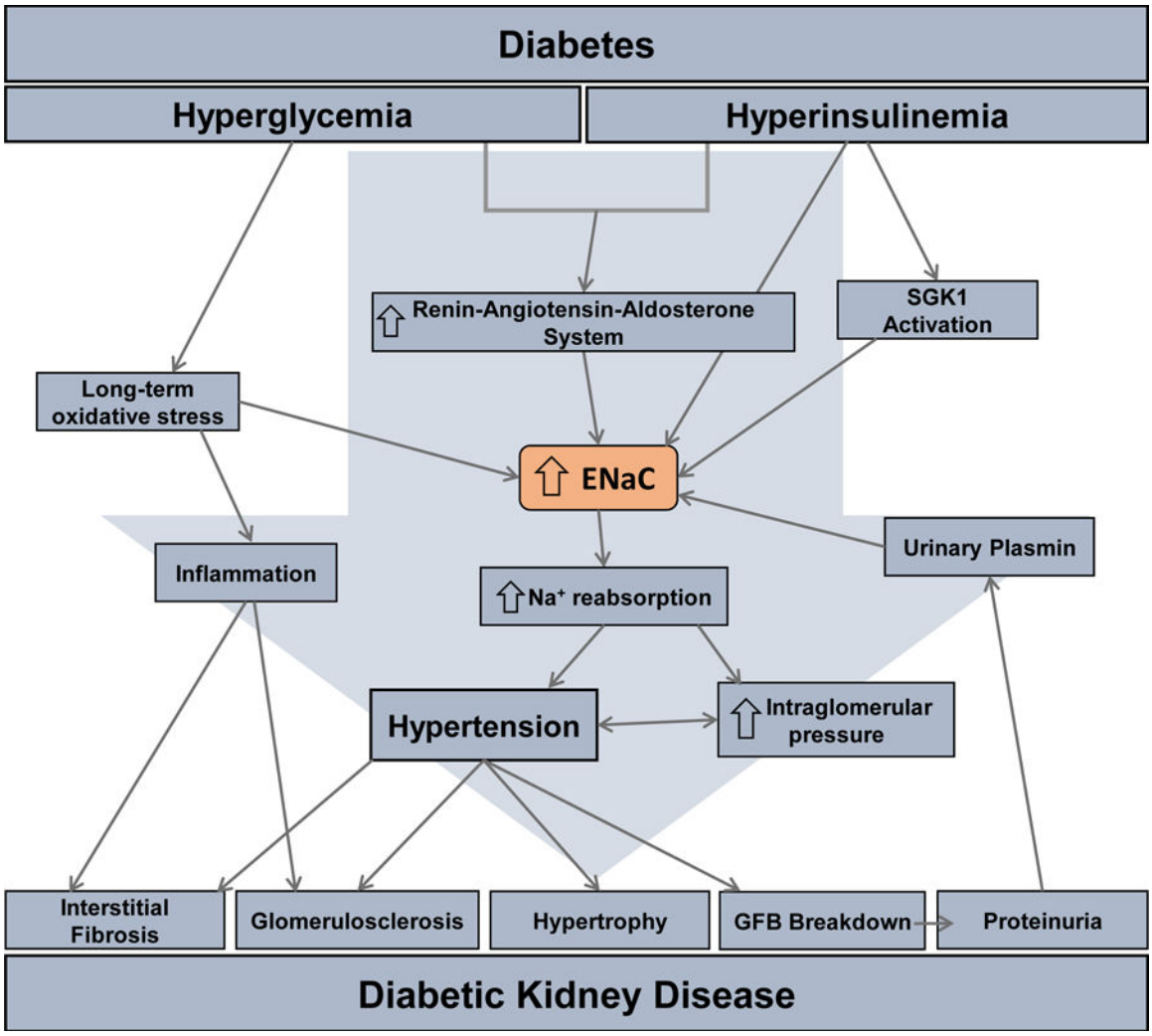

Figure 4.

Schematic for epithelial Na^+ channel (ENaC) induced tubular renal injury in DKD. Hyperglycemia and hyperinsulinemia induced via diabetes cause over-activation of the renin-angiotensin-aldosterone system (RAAS), long-term oxidative stress, and serum and glucocorticoid-regulated kinase (SGK) 1 activation that all directly cause the increase in the ENaC activation and/or expression. This increase in ENaC leads to various factors shown in the above pathway, such as hypertension. The culmination of these factors result in the development of the major characteristics of DKD.

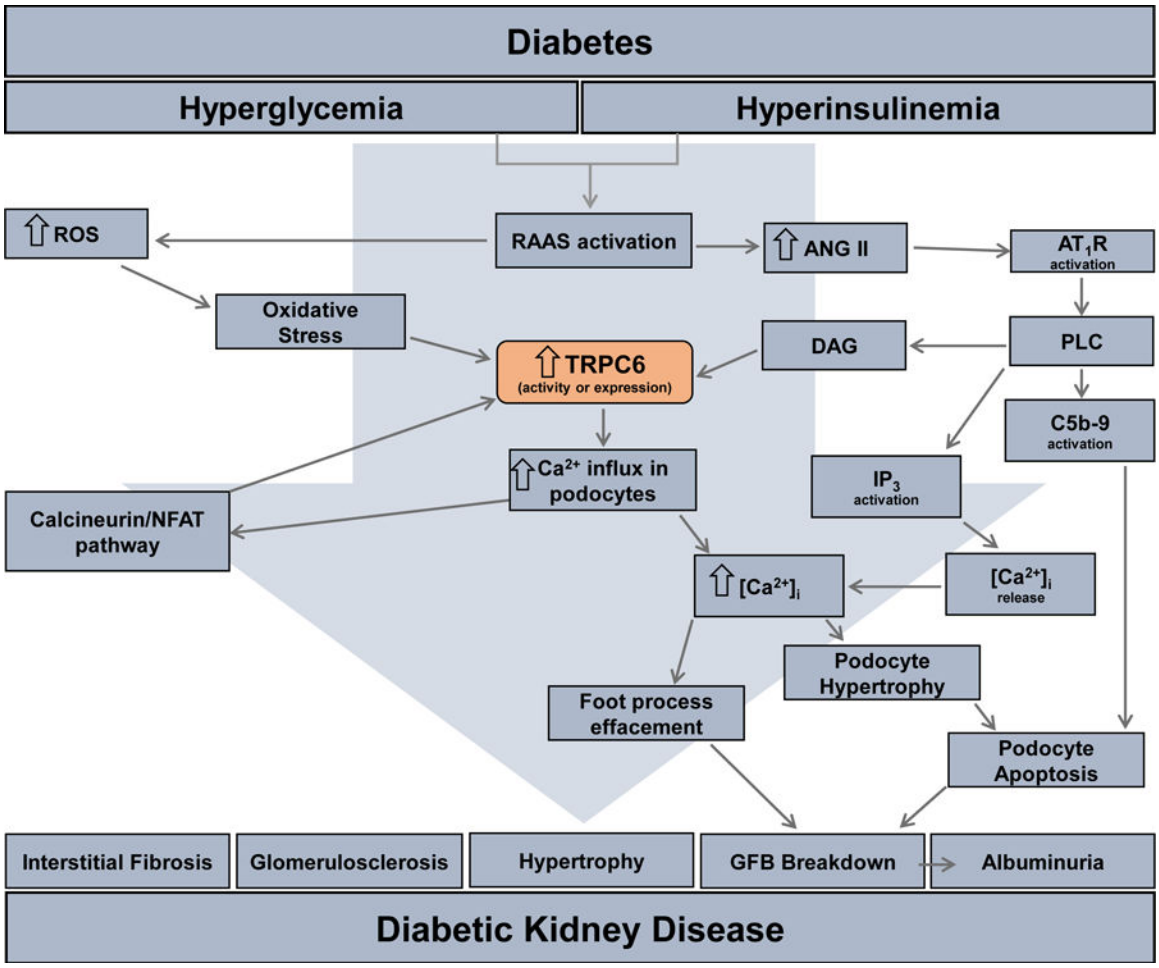

Figure 5.

Schematic for TRPC6-induced glomerular renal injury in the progression of DKD. Activation of the renin-angiotensin-aldosterone system (RAAS) cause an increase in angiotensin II (ANG II) that acts through the angiotensin II receptor type 1 (AT_1R). This receptor activates phospholipase C (PLC) on the podocyte cell membrane. PLC activates 3 additional targets/pathways in the podocyte: diacylglycerol (DAG) that cause calcium influx through the transient receptor potential canonical 6 (TRPC6) channel which in turn increases intracellular calcium $[Ca^{2+}]_i$; inositol triphosphate (IP_3) activates calcium release from the intracellular stores; the membrane attack complex of complement C (C5b-9), a transmembrane channel involved in some immune responses, induces podocyte apoptosis. Increases in RAAS also leads to an increase in reactive oxygen species (ROS) that begets oxidative stress activating the calcineurin/NFAT pathway that increases the transcription of *Trpc6*. The culmination of the increase in $[Ca^{2+}]_I$ from over-activation of TRPC6 leads to podocyte hypertrophy/apoptosis and foot process effacement ending in breakdown of the glomerular filtration barrier (GFB). The ultimate result of this pathway is the development of the DKD characteristic albuminuria.