

# SGK1 in the Kidney: Disrupted Sodium Transport in Diabetes and Beyond

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## ABSTRACT

Renal complications of diabetes can be severe; however, the mechanisms that underlie the development and progression of diabetic nephropathy are poorly understood. Recent evidence suggests that the serum- and glucocorticoid-induced kinase-1 (SGK1) may be key to this process. SGK1 expression and function are increased in models of diabetes, and polymorphisms of the SGK1 gene are associated with type 2 diabetes mellitus. A key regulator of sodium transport within the renal epithelium of the distal nephron, SGK1 was originally isolated as a glucocorticoid-sensitive gene that regulated the epithelial sodium channel (ENaC; also known as the sodium channel, non-voltage-gated 1, SCNN1). It is now apparent that SGK1 modulates sodium reabsorption by a number of sodium transporters/channels throughout the length of the nephron including the Na<sup>+</sup>/H<sup>+</sup> exchange isoform 3 (NHE3), the Na<sup>+</sup>Cl<sup>-</sup> co-transporter (NCC), and the Na<sup>+</sup>/K<sup>+</sup>-ATPase. In addition, SGK1 is regulated by a diverse range of factors including insulin, glucose, intracellular calcium, transforming growth factor- $\beta$ 1, flow rate, and osmolality. This brief review examines the evidence supporting an involvement of SGK1 in diabetic nephropathy and discusses how dysregulated sodium transport may account for the development of secondary hypertension associated with the condition. Furthermore, the article examines how aberrant SGK1 expression and activity may be responsible for the cellular changes seen in the damaged nephron.

Keywords: SGK, hypertension, diabetic nephropathy, glucose, sodium transport

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## INTRODUCTION

Diabetic nephropathy is the most common cause of endstage renal disease and the requirement for renal replacement therapy. The condition is characterized by both structural and functional disturbances including renal hypertrophy, fibrosis, altered glomerular filtration rate, glomerular hypertension, proteinuria, and systemic hypertension [1–3]. Of the mechanisms that underlie progressive renal damage, dysregulated Na<sup>+</sup> reabsorption is an area that has received considerable attention and is linked to the development of hypertension in diabetes. Serum- and glucocorticoid-induced kinase-1 (SGK1) is one of the key regulators of Na<sup>+</sup> reabsorption in the nephron. In models of diabetic nephropathy, insulin and glucose have been shown to stimulate the expression and phosphorylation of SGK1, and SGK1 polymorphisms are also associated with type 2 diabetes mellitus (T2DM) [4–8]. Furthermore, in models of T2DM, signaling molecules upstream of SGK1 including protein kinase C (PKC), diacylglycerol (DAG), Ca<sup>2+</sup>, and transforming growth factor beta (TGF- $\beta$ ), all show increased expression. This minireview examines SGK1-mediated Na<sup>+</sup> reabsorption and discusses the consequences of disturbed

SGK1 activity and the consequential rise in Na<sup>+</sup> reabsorption, in addition to commenting on the development of those complications associated with diabetic nephropathy.

## SGK1

The serum and glucocorticoid kinase-1 (SGK1) is a serine/threonine kinase, originally cloned as an aldosterone-responsive gene [9, 10]. A number of other roles of SGK1 have also been identified including regulation of apoptosis, ion transport, and cellular differentiation (reviewed in [11]). Expressed in a variety of tissues including the kidney, eye, liver, heart, pancreas, skeletal muscle, and brain, SGK1 expression is regulated through gene transcription and protein degradation, while kinase activity is dependent on phosphatidylinositol-3-kinase (PI3-K) activity and subcellular localization [8, 12–14]. These diverse regulatory mechanisms allow SGK1 to respond to numerous stimuli via cell-type specific pathways [15]. Three SGK1 splice variants have been identified, and it is likely that these also dictate cell-specific functions [16]. In addition to SGK1, two closely related isoforms (80% amino acid identity), SGK2 and SGK3, have also been identified [17].

SGK1 is predominantly localized to the distal region of the nephron, where it is found in the thick ascending limb of the loop of Henle, distal convoluted tubule, and the cortical collecting duct [18]. Present in the cytosol and co-localized with mitochondria under basal conditions [19–21], high glucose or serum evokes a translocation of the kinase to the nucleus [20, 22]. It is also associated with the Na<sup>+</sup>/K<sup>+</sup>-ATPase in the basolateral membrane [18].

### SGK1 and the Regulation of ENaC-mediated Na<sup>+</sup> Transport

Sodium reabsorption is critical in maintaining blood volume and is central to blood pressure control. Defects in the regulation of Na<sup>+</sup> transport underlie all of the known inherited forms of hypertension, and disturbed Na<sup>+</sup> transport is likely to be responsible for the development of secondary hypertension associated with diabetes [23]. Sodium is reabsorbed along the entire length of the nephron by a number of apical transporters [24, 25]. However, it is in the distal nephron and collecting duct where the fine control of Na<sup>+</sup> reabsorption occurs under the auspices of the renin–angiotensin–aldosterone system. Key to this process is the epithelial sodium channel (ENaC). The ENaC (now also known as sodium channel, non-voltage-gated 1; SCNN1) is a member of the ENaC/degenerin gene family [26]. It is an apical amiloride-sensitive channel that facilitates Na<sup>+</sup> transport across the epithelium in a wide variety of tissues including renal tubules, distal colon, skin, lungs, and eyes [13, 14, 27]. Although five ENaC subunits have been cloned,  $\alpha$ -,  $\beta$ -,  $\gamma$ -,  $\delta$ -, and  $\varepsilon$ -ENaC, the formation of a functional channel appears to require only the  $\alpha$ -,  $\beta$ -, and  $\gamma$ - subunits, although recent studies have highlighted additional potential interactions with the  $\delta$ -subunit [28, 29].

Liddle's syndrome, an autosomal dominant form of arterial hypertension characterized by salt sensitivity, hypokalemia, and low aldosterone and renin levels, is associated with activating mutations in the  $\beta$ - and  $\gamma$ -subunits of the ENaC [30–32]. In contrast, loss of function mutations result in pseudohypoaldosteronism type I (PHA-1), a condition associated with salt wasting, hyperkalemia, metabolic acidosis, and hypotension [33, 34]. ENaC expression is increased by glucose, and mineralocorticoid receptor antagonists are effective in reducing renal damage in models of type 1 and 2 diabetes [35–37].

Aldosterone-stimulated Na<sup>+</sup> reabsorption in the collecting duct and distal colon occurs by increasing the rate of Na<sup>+</sup> entry through the ENaC [27]. When aldosterone levels are low, ENaC is reportedly confined to a vesicular pool [38]. It is proposed that the rapid response to aldosterone indicates that early responses are dependent on the action of existing ENaCs. An important regulator of this process is

SGK1. Stimulation of SGK1 by aldosterone causes phosphorylation of SGK1 at serine 422 and threonine 256 via the two downstream 3-phosphoinositide (PIP3)-dependent kinases PDK2 and PDK1 [39, 40]. SGK1 then binds to and phosphorylates Nedd4-2 (neural precursor cell-expressed, developmentally downregulated gene 4 isoform), a ubiquitin ligase that directs proteasome-mediated degradation of ENaCs and inhibits cell surface expression of ENaCs [41, 42]. Therefore, phosphorylation of Nedd4-2 by SGK1 promotes apical membrane localization of the ENaC, inhibits ENaC degradation, and stimulates ENaC transcription [43, 44]. Interestingly, this also induces ubiquitination and degradation of SGK1 [45]. In the absence of SGK1, the association of Nedd4-2 and ENaC induces channel retrieval from the plasma membrane and subsequent proteasomal degradation (reviewed in [46]). In Liddle's syndrome, binding of Nedd4-2 to the ENaC is impaired [47]. This effect is augmented by reduced Nedd4-2 protein expression as a consequence of a low salt diet or raised aldosterone [48].

Genetic variants of the *SGK1* gene correlate with slightly increased blood pressure [49, 50]. However, it is interesting to note that the effects of SGK1 on salt wasting and blood pressure are not as severe as seen in either mineralocorticoid or ENaC mutants [51, 52]. This may be explained by studies that have indicated that SGK1–Nedd4-2 interactions are not the sole regulators of ENaC function. While aldosterone increases SGK1-mediated Nedd4-2 phosphorylation, it does so to a lesser extent than SGK1 phosphorylation [53]. Likewise, studies in SGK1 knockout mice have indicated that ENaC-mediated changes in blood pressure are not solely mediated by SGK1 (reviewed in [11]). Under normal dietary conditions, lack of SGK1 has little effect on salt or fluid retention. However, when fed a low salt diet, SGK1<sup>-/-</sup> mice are unable to retain sufficient Na<sup>+</sup> to maintain their blood pressure [54]. Similarly, in SGK1<sup>-/-</sup> mice fed a high salt diet, blood pressure was not increased [55, 56]. More recently, it has been shown that, in SGK1<sup>-/-</sup> mice, ENaC processing, but not activity, is attenuated [57].

### SGK1 in the Proximal Tubule

To date, the majority of studies have focused on the role of SGK in ENaC-mediated Na<sup>+</sup> reabsorption in the collecting duct, and little is known about the role of SGK in the proximal tubule, a major site of glycaemic injury. The principal route by which Na<sup>+</sup> is reabsorbed in this region of the nephron is through the Na<sup>+</sup>/H<sup>+</sup> exchange isoform 3 (NHE3), and experiments in NHE3 knockout mice have confirmed that it also mediates blood pressure [58]. Several studies have confirmed that the expression of NHE3 is stimulated by SGK1 in response to high glucose [59–61]. In addition, SGK1 has also been shown to increase proximal tubular cell proliferation and reduce cell apoptosis [62]. These

effects are, in part, mediated through the epidermal growth factor receptor (EGFR) [62]. It is known that the glucose-mediated increase in the synthesis of angiotensin II in the proximal tubule increases NHE3-mediated Na<sup>+</sup> reabsorption in diabetic nephropathy [63], and Stevens *et al* recently demonstrated that this response is also regulated by SGK1 [63].

### SGK1 and Cell Volume Regulation

Renal epithelial cells have developed a range of mechanisms to regulate osmotically induced cell volume changes. A volume-regulated isoform of SGK (hSGK), sensitive to hypertonic cell shrinkage, mediates the hyperosmotic induction of SGK1 transcription [64, 65]. Activation of this pathway in response to hypertonic cell shrinkage is mediated via p38 mitogen-activated protein kinase (MAPK) with phosphorylated levels of p38 detected 1–2 h after hyperosmotic induction [66]. Furthermore, application of pharmacological inhibitors of p38 MAPK significantly reduced the induction of SGK1 expression in response to hypertonicity [65]. Glucosuria will result in an osmotic diuresis, leading to high urine flow, and hyperosmotic urine will cause cell shrinkage of renal epithelial cells. These changes activate SGK1, increasing ENaC-mediated Na<sup>+</sup> reabsorption, water uptake, and chloride channel expression, thereby restoring cell volume [66, 67]. SGK1 also alters the expression and insertion of the glucose transporters, GLUT1 and SGLT1, into cell membranes and increases glucose transport [59, 68–70]. Metabolism of intracellular glucose to sorbitol will increase intracellular osmolarity [71]. Likewise, it has been shown that SGK1 stabilizes the myo-inositol transporter (SMIT1) in the plasma membrane [72]. The accumulation of myo-inositol and sorbitol will instigate an osmotic cell volume increase, which would in turn initiate a Ca<sup>2+</sup>-dependent cell volume decrease. This is likely to be mediated by increased TRPV4 (a mechanosensitive transient receptor potential channel), a Ca<sup>2+</sup>-permeable channel that responds to numerous stimuli including increased flow and cell swelling and initiates a concomitant reduction in SGK1 activity [73, 74].

Elevated levels of cytosolic calcium in proximal and distal tubular cells have been linked to hyperglycemia [20, 75, 76], and cell swelling in the proximal tubule is also associated with increased intracellular Ca<sup>2+</sup> [77]. Mechanical stimulation (a surrogate form of osmotic stress) of cells of the human collecting duct (HCD cells) evokes a rapid, TRPV4-mediated increase in [Ca<sup>2+</sup>]<sub>i</sub>, which propagates to adjacent cells via gap junctions [76]. This response counteracts the hyperosmotic induction of SGK. However, in diabetes, sustained expression of SGK1 and TRPV4 may compromise this counter-regulatory mechanism. A rise in [Ca<sup>2+</sup>]<sub>i</sub> from constitutive TRPV4 action will further induce both SGK1 and  $\alpha$ -ENaC expression, exacerbating aberrant renal Na<sup>+</sup> handling.

### SGK1 and TGF- $\beta$ 1

The molecular and cellular events that give rise to both structural and functional complications of diabetic nephropathy include the release of a number of different growth factors and cytokines. Among these regulators is transforming growth factor beta (TGF- $\beta$ ). A ubiquitous cytokine that has a broad spectrum of biological functions in a variety of cell types, of the three TGF- $\beta$  isoforms ( $\beta$ 1,  $\beta$ 2, and  $\beta$ 3), TGF- $\beta$ 1 is thought to be the principal mediator of diabetic complications [78–82]. TGF- $\beta$ 1 initiates its cellular response by binding to its distinct receptor, TGF- $\beta$  receptor II (T $\beta$ RII), which activates the T $\beta$ RI kinase prior to phosphorylation of the receptor-regulated Smads (R-Smads). Activated R-Smads form oligomeric complexes with the common Smad (Co-Smad). These oligomeric complexes then translocate into the nucleus, where they may regulate gene transcription by binding to DNA directly and acting as transcriptional activators [83]. Alternatively, they may associate with nuclear transcription factors such as AP-1 [84]. In many cell lines, TGF- $\beta$ 1 positively regulates its own expression [85]. Autoinduction of TGF- $\beta$ 1 transcription appears to be mediated through binding of an AP-1 complex to the TGF- $\beta$ 1 promoter [84].

Increased expression of TGF- $\beta$ 1 and its receptor has been described in experimental models of renal disease including membranous nephropathy, obstructive nephropathy, and diabetic nephropathy [20, 86]. In both human and experimental diabetes, TGF- $\beta$ 1 gene expression and protein secretion are increased [87]. The resultant phenotypic and morphological changes arising from this maladaptive TGF- $\beta$  signaling contribute to the development of renal fibrosis and the formation of the fibrotic scar, complications that have recently been shown to be reversed by the exogenous application of C-peptide, a cleavage product of the pro-insulin molecule that has numerous renoprotective effects [88–90]. The increased levels of TGF- $\beta$ 1 observed in hyperglycemia arise from the activation of key signaling molecules whose expression is promoted in response to high circulating glucose levels. These include UDP-N-acetylglucosamine, PKC, and members of the MAPK pathway. Although the downstream targets of TGF- $\beta$ 1, which mediate the pathophysiology of diabetic nephropathy, remain largely elusive, the cell hypertrophy observed in response to these elevated levels of circulating TGF- $\beta$ 1 may in part be mediated by induction of SGK1. A downstream target of TGF- $\beta$ 1, SGK1 has been shown to be transcriptionally upregulated by TGF- $\beta$ 1 in various cell types [5, 20, 91, 92]. Furthermore, both exhibit elevated levels of expression in response to high glucose [20]. Studies have demonstrated that augmented SGK1 expression in response to exogenous TGF- $\beta$ 1 is negated in the presence of a p38 MAPK inhibitor [91]. This would suggest that activation of SGK1

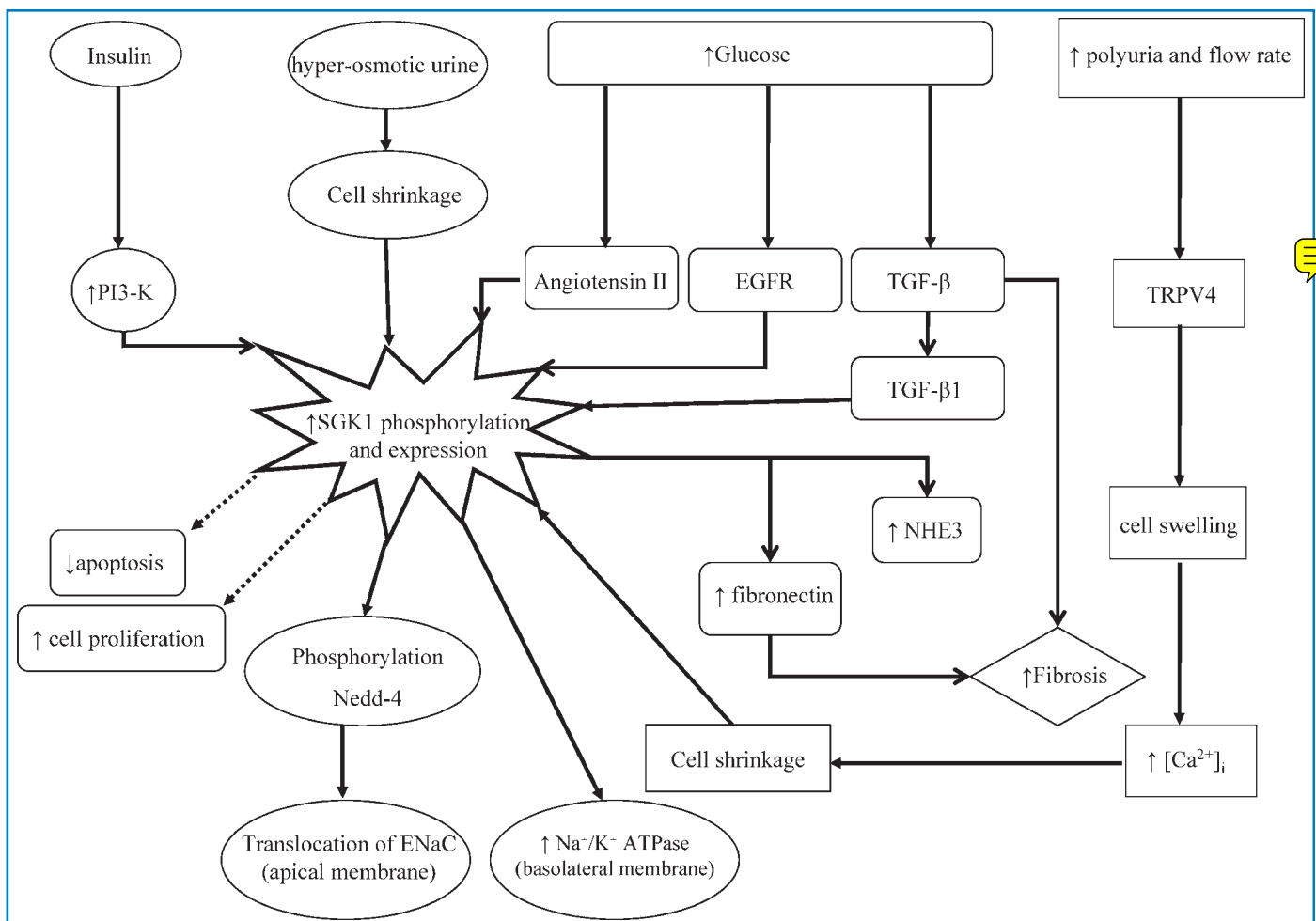
transcription via TGF- $\beta$ 1 is mediated by, and reliant on, activation of the p38 MAPK signaling pathway. Activation of SGK1 via p38 MAPK occurs as a result of cross-talk between the TGF- $\beta$ 1 Smad signaling pathway and the MAPK signaling cascade, thus suggesting synergy between the induction of SGK1 in response to either TGF- $\beta$ 1 or hyperosmotic stress [65]. In addition, in the collecting duct, both mechanical and glucose-evoked increases in cell-cell communication are TGF- $\beta$ 1 dependent [93]. The ability of TGF- $\beta$ 1 to function as a key transcriptional regulator of SGK1 has led to its implication as a signaling component whose enhanced expression may exacerbate the cell hypertrophy associated with the constitutive pathophysiological induction of SGK1 seen in diabetes.

The role of TGF- $\beta$  in the kidney is more commonly associated with the extracellular matrix and its role in fibrosis [94]. Renal fibrosis is the leading cause of endstage renal disease in patients with diabetic nephropathy and, although there are more than a dozen fibrogenic factors, TGF- $\beta$ 1 is generally considered to be the major or predominant isoform involved in the fibrogenic process. While the role of TGF- $\beta$ 2 and TGF- $\beta$ 3 remains less clear, published studies to date support a pro-fibrotic role for all three isoforms, with the upregulation of all three described in both animal and human models of diabetes [95–98]. The contribution of TGF- $\beta$  in the progression of renal fibrogenesis is highlighted by studies demonstrating that improved renal function coincides with a reduction in TGF- $\beta$  expression, especially that of the  $\beta$ 1 and  $\beta$ 2 isoforms [99]. These observations make the pro-fibrotic actions of TGF- $\beta$  an ideal target for therapeutic intervention and have led to a great deal of emphasis being placed on blockade of the TGF- $\beta$  pathway [100]. Inhibition of TGF- $\beta$ 1, TGF- $\beta$ 2, or TGF- $\beta$ 3 by isoform-specific neutralizing antibodies is accompanied by a reduction in renal scarring and improved kidney function [101–104]. Furthermore, intervention of the downstream signaling effects of TGF- $\beta$ , through exogenous application of various agonists including BMP7, HGF and, more recently, the PPAR $\gamma$  agonist troglitazone and C-peptide, dramatically improves renal function, reducing inflammation and fibrosis [105–108]. However, the underlying events that mediate TGF- $\beta$ -induced fibrosis are complicated, with numerous cell types and multiple signaling pathways together promoting development of the fibrotic lesion. SGK1 has been shown to be expressed in numerous fibrosing tissues including cases of Crohn's disease, lung fibrosis, liver cirrhosis, fibrosing pancreatitis, diabetic nephropathy, and glomerulonephritis [5, 108–112]. As SGK1 has been proven to act as a downstream target of TGF- $\beta$ 1, it seems sensible to suggest that SGK1 may mediate some of these downstream fibrotic effects. Therapeutic intervention using the SGK inhibitor, GSK650394, may inhibit the pro-fibrotic actions of TGF- $\beta$ 1 as mediated by SGK, and thus unmasks SGK1 as a

potential therapeutic target in amelioration of TGF- $\beta$ -induced fibrotic complications [113]. Recent studies by Stevens *et al* have shown that SGK1 potentiates the effect of high glucose on fibronectin formation. In human fibroblasts, this is dependent on the presence and abundance of the EGFR [114]. Furthermore, glucose-evoked changes in SGK1 have been found to mediate fibronectin formation in diabetic mice [115]. Although both TGF- $\beta$ 2 and TGF- $\beta$ 3 exhibit pro-fibrotic actions in the kidney, a role for either TGF- $\beta$ 2 or TGF- $\beta$ 3 in the stimulation of SGK1 in the kidney remains to be confirmed.

## CONCLUDING REMARKS

Expressed in a variety of tissues, SGK is tightly regulated by numerous signaling cascades. This level of control enables SGK to participate in a number of cellular functions that include epithelial transport, excitability, cell proliferation, and apoptosis. Although there are three isoforms of SGK, in the current article, we have focused on SGK1 as localized to the kidney and have discussed its role in the control of electrolyte balance via the epithelial sodium channel (ENaC) and the Na<sup>+</sup>/K<sup>+</sup>-ATPase. Studies using models of salt-sensitive hypertension demonstrate increased SGK1 expression, and variants of the gene correlate with elevated blood pressure, which point to a role for SGK1 in the fine regulation of sodium reabsorption. However, knockout models of SGK1 suggest that the kinase is not the sole determinant of ENaC-mediated changes in blood pressure and that this process relies on a complex interplay of signaling molecules. Similarly, changes in Na<sup>+</sup> reabsorption and the development of secondary hypertension seen in diabetes are not limited to alterations in the ENaC. SGK1 also regulates the NHE3 transporter in the proximal tubule, suggesting that SGK1 may play a pivotal role in sodium retention in the proximal tubule. SGK1 also regulates the expression and activity of the basolateral Na<sup>+</sup>/K<sup>+</sup>-ATPase and the increase in the Na<sup>+</sup>Cl<sup>-</sup> co-transporter (NCC) seen in animals under salt restriction. These effects are attenuated in SGK<sup>-/-</sup> animals. This suggests that SGK1 contributes to subtle alterations in the control of Na<sup>+</sup> reabsorption throughout the nephron. Under normal physiological conditions, these actions will maintain circulating blood volume and, in conjunction with TRPV4, also maintain cell volume. In diabetes, renal epithelial cells are exposed to a number of signals, including hyperinsulinemia and hyperglycemia, that act to increase SGK1 expression and function. Furthermore, hyperglycemic-induced TGF- $\beta$ 1 formation together with flow and osmotically driven increases in SGK1 provide a link between poorly controlled plasma glucose and the development of excess Na<sup>+</sup> reabsorption that underlies secondary hypertension. While SGK1-induced Na<sup>+</sup> reabsorption is clearly important in the pathophysiology of diabetic



**Figure 1.** SGK1 in the kidney. Phosphorylated SGK1 allows for insertion and retention of ENaCs into the apical cell membrane, promoting ENaC-mediated  $\text{Na}^+$  reabsorption from the lumen of the cortical collecting duct. SGK1 also stimulates the  $\text{Na}^+/\text{K}^+$ -ATPase in the basolateral membrane. TRPV4 receptors may be activated either by the high urine flow rates that are associated with polyuria or as a result of osmotically induced cell swelling. This will be compensated for by a regulatory cell volume decrease leading to cell shrinkage. Similarly, glycosuria may initiate cell shrinkage as water is lost to the lumen. Cell shrinkage is a key trigger for SGK1 activation. Insulin and glucose are also able to modify SGK1 activity. Insulin induces SGK1 phosphorylation via PI3-K, whereas glucose results in increased SGK1 expression, an effect mediated by angiotensin II, EGFR, TGF- $\beta$ , and PKC, further contributing to increased  $\text{Na}^+$  reabsorption, increased fibronectin formation, decreased apoptosis, and increased cellular proliferation. We suggest that all aspects of type 2 diabetes promote both SGK-mediated increases in  $[\text{Na}^+]_i$  through stimulation of the ENaC,  $\text{Na}^+/\text{K}^+$ -ATPase or NHE3, an imbalance that may predispose to the development of hypertension, whereas SGK-induced fibronectin and increased cell proliferation will exacerbate the state of hypertrophy and fibrosis contributing towards the loss of cell function and nephron damage that is associated with diabetic nephropathy

nephropathy, SGK1 also plays a part in fibrosis and increased proliferation, which further promote the renal cellular damage seen in diabetes.

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