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Targeting SGK1 in diabetes

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Abstract

Compelling evidence is accumulating pointing to a pathophysiological role of the serum-and-glucocorticoid-inducible-kinase-1 (SGK1) in the development and complications of diabetes. SGK1 is ubiquitously expressed with exquisitely high transcriptional volatility. Stimulators of SGK1 expression include hyperglycemia, cell shrinkage, ischemia, glucocorticoids and mineralocorticoids. SGK1 is activated by insulin and growth factors via phosphatidylinositol-3-kinase, 3-phosphoinositide dependent kinase PDK1 and mTOR. SGK1 activates ion channels (including ENaC, TRPV5, ROMK, KCNE1/KCNQ1 and CLCKa/Barttin), carriers (including NCC, NKCC, NHE3, SGLT1 and EAAT3), and the Na⁺/K⁺-ATPase. It regulates the activity of several enzymes (e.g. glycogen-synthase-kinase-3, ubiquitin-ligase Nedd4-2, phosphomannose-mutase-2), and transcription factors (e.g. forkhead-transcription-factor FOXO3a, β -catenin, nuclear-factor-kappa-B NF κ B). A common SGK1 gene variant (~3–5% prevalence in Caucasians, ~10% in Africans) is associated with increased blood pressure, obesity and type 2 diabetes. In patients suffering from type 2 diabetes, SGK1 presumably contributes to fluid retention and hypertension, enhanced coagulation, and increased deposition of matrix proteins leading to tissue fibrosis such as diabetic nephropathy. Accordingly, targeting SGK1 may favourably influence occurrence and course of type 2 diabetes.

Keywords

Coagulation; Fibrosis; Hypertension; Inflammation; Metabolic syndrome

1. Introduction

The serum- and glucocorticoid-inducible kinase 1 (SGK1) was discovered as a gene regulated transcriptionally by serum- and glucocorticoids in rat mammary tumor cells [1]. The human isoform was cloned as an immediate early gene upregulated by cell shrinkage [2].

SGK1 transcripts are found in virtually all tissues, but their level varies between different cell types in brain [3], eye [4], inner ear [5–7], semicircular canal duct epithelium [6], lung [3,8,9], kidney [10], liver, intestine, pancreas and ovary [4]. Expression patterns depend on the developmental state [4,11].

In humans, the SGK1 encoding gene is localised in chromosome 6q23 [4]. Several translational SGK1 variants have been identified, which differ in regulation of expression, subcellular localization and function [12–14]. SGK1 forms dimers by two intermolecular disulfide bonds between Cys258 in the activation loop and Cys193 [15].

SGK1 stimulates a variety of ion channels, transporters, transcription factors and enzymes [4]. The kinase thus participates in the regulation of a wide variety of functions (for earlier

reviews see [4,16]). In the present review, the case is made that SGK1 plays a dual role in the pathophysiology of diabetes. At the one hand, it facilitates the development of obesity, which in turn predisposes to the development of type 2 diabetes. On the other hand, it is upregulated by hyperglycemia and contributes to the development of hypertension, excessive coagulation and fibrosis in the affected patients.

2. Transcriptional SGK1 regulation

As evidenced from Northern blotting, RT-PCR and/or *in situ* hybridisation, SGK1 transcription is stimulated by glucocorticoids [1,17], mineralocorticoids [18,19], gonadotropins [4], progesterone [20], progesterone, 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), transforming growth factor β (TGFβ), interleukin 6, fibroblast and platelet-derived growth factor [4], thrombin [21], endothelin [4,22], advanced glycation end products (AGE), further cytokines and activation of peroxisome proliferator-activated receptor γ [4,23].

Additional stimulators include cell shrinkage [4], excessive glucose concentrations [4], A6 cell swelling [24], chelation of Ca²⁺ [24], metabolic acidosis [25], salt loading of spontaneously hypertensive mice [26], oxidative stress [17,27], heat shock, UV radiation, DNA damage, ischemia, neuronal injury, neuronal excitotoxicity, neuronal challenge by exposure to microgravity, fear conditioning, plus maze exposure, enrichment training, amphetamine, lysergic acid dimethylamide LSD, electroconvulsive therapy, sleep deprivation and fluoxetine [4,28].

Moreover, enhanced SGK1 transcript levels were observed in diabetic nephropathy [29], Rett syndrome, organ rejection, dialysis, wound healing, glomerulonephritis, liver cirrhosis, fibrosing pancreatitis, Crohn's disease, lung fibrosis and cardiac fibrosis [4,30].

SGK1 transcription is downregulated by heparin, mutations in the gene encoding methyl-CpG-binding protein 2 (MECP2), dietary iron and nucleosides [4,31].

Signalling molecules participating in the regulation of SGK1 transcription include cyclic AMP [20], reactive oxygen species and NADPH oxidases [21], protein kinase C, protein kinase Raf, big mitogen-activated protein kinase 1 (BMK1), mitogen-activated protein kinase (MKK1), stress-activated protein kinase-2 (SAPK2, p38 kinase), phosphatidylinositol-(PI)-3-kinase, extracellular signal-regulated kinase (ERK1/2), p53, cytosolic Ca²⁺, nitric oxide, EWS/NOR1 (NR4A3) fusion protein [4,32].

The promoter of the rat SGK1 gene contains binding sites for several transcription factors including receptors for glucocorticoids (GR), mineralocorticoids (MR), progesterone (PR), the vitamin D receptor (VDR), retinoids (RXR), farnesoids (FXR), as well as sterol regulatory element binding protein (SREBP), peroxysome proliferator activator receptor gamma (PPARγ), cAMP response element binding protein (CREB), p53 tumor suppressor protein, Sp1 transcription factor, activating protein 1 (AP1), activating transcription factor 6 (ATF6), heat shock factor (HSF), reticuloendotheliosis viral oncogene homolog (c-Rel), nuclear factor κB (NFκB), signal transducers and activators of transcription (STAT), TGFβ dependent transcription factors SMAD3 and SMAD4, and fork-head activin signal transducer (FAST) [1].

3. Posttranscriptional localization and regulation of SGK1

According to immunohistochemistry, serum may trigger importin-alpha mediated entry of SGK1 into the nucleus [4] and hyperosmotic shock or glucocorticoids may increase the cytosolic SGK1 abundance [1,4]. SGK1 has further been localized to the mitochondrial membrane [33,34].

Activation of SGK1 is accomplished by phosphorylation at the threonine 256 by the 3-phosphoinositide (PIP3)-dependent kinase PDK1 [35]. The effect of PDK1 requires prior phosphorylation at serine 422 [35]. Further kinases involved in the activation of SGK1 include the mammalian target of rapamycin mTOR and the serine/threonine kinase WNK1 (with no lysine kinase 1) [4,36–40]. PIP3 is degraded and thus PDK1 dependent SGK1 activation is disrupted by the phosphatase and tensin homolog PTEN [4]. The assembly of SGK1 and PDK1 and the subsequent SGK1 activation is supported by the scaffold protein Na⁺/H⁺ exchanger regulating factor 2 (NHERF2) [4].

PDK1 dependent activation of SGK1 is triggered via PI3-kinase by insulin, IGF1, hepatic growth factor (HGF), follicle stimulating hormone (FSH) and thrombin [4]. SGK1 is further activated by bone marrow kinase/extracellular signal-regulated kinase 5 (BK/ERK5), p38 α , feeding, increased cytosolic Ca²⁺ activity with subsequent activation of calmodulin-dependent protein kinase kinase (CaMKK), the G-protein Rac1, neuronal depolarization, cAMP, lithium, oxidation and adhesion to fibronectin [4,21,41].

SGK1 is ubiquitinated by the ubiquitin ligase Nedd4-2 (neuronal precursor cells expressed developmentally downregulated) and is rapidly degraded leading to a half-life of some 30 minutes [4].

4. SGK1 regulated proteins

SGK1 may phosphorylate proteins at the consensus sequence R-X-R-X-X-(S/T)-phi (X = any amino acid, R = arginine, phi = hydrophobic amino acid), which is similar to that of related kinases [4]. The only proteins hitherto known to be exclusive SGK1 targets are N-myc downregulated genes NDRG1 and NDRG2. Accordingly, most SGK1 sensitive functions are similarly regulated by the SGK and protein kinase B isoforms or other related kinases. A specific inhibitor against SGK1 would thus not be expected to abrogate those functions [4].

SGK1 stimulates a wide variety of channels including the epithelial Na⁺ channel ENaC [4, 42–51], the voltage gated Na⁺ channel SCN5A [4], the renal outer medullary K⁺ channel ROMK1 [4], the voltage gated K⁺ channels KCNE1/KCNQ1 [52], KCNQ4 [4], Kv1.3, Kv1.5 [53] and Kv4.3 (K⁺ channel) [4], the epithelial Ca²⁺ channels TRPV5 [4] and TRPV6 [54], the kainate receptor GluR6 [4], the unselective cation channel 4F2/LAT [4], the Cl[−] channels ClCka/barttin [55], ClC2 [4], CFTR (Cystic fibrosis transmembrane conductance regulator) [56,57] and VSOAC (volume-sensitive osmolyte and anion channel) [4], as well as the acid sensing ion channel ASIC1 [58].

SGK1 stimulates a number of carriers including the the NaCl cotransporter NCC [59], the Na⁺,K⁺,2Cl[−] cotransporter NKCC2 [4], the Na⁺/H⁺ exchanger NHE3 [60,61], the glucose transporters SGLT1 [62–64], GLUT1 [65] and GLUT4 [66], the amino acid transporters ASCT2 [66], SN1 [4], EAAT1 [4], EAAT2 [4], EAAT3 [4], EAAT4 [67] and EAAT5 [4], the peptide transporter PepT2 [68], the Na⁺,dicarboxylate cotransporter NaDC-1 [4], the creatine transporter CreaT [4], the Na⁺, myoinositol cotransporter SMIT [69], as well as the phosphate carrier NaPiIb [4]. SGK1 further stimulates the Na⁺/K⁺-ATPase [4,70].

SGK1 may regulate channels, carriers and the Na⁺/K⁺-ATPase by modification of expression [71], by phosphorylating the target proteins or by phosphorylating the ubiquitin ligase Nedd4-2 [16]. Following SGK1-dependent phosphorylation, Nedd4-2 binds to a heterodimeric protein complex composed of 14-3-3beta and 14-3-3epsilon [72] and is thus unable to ubiquitinate its targets [73,74]. The result is reduced degradation of the target proteins, such as ENaC. Both 14-3-3 isoforms are upregulated by aldosterone [72]. Silencing of the proteins abrogates the stimulating effect of aldosterone on ENaC [72].

SGK1 may further be effective by inhibiting inducible nitric oxide synthase iNOS leading to decreased formation of nitric oxide, which in turn may modify transport [75]. Moreover, SGK1 may regulate carriers and channels through activation of the phosphatidylinositol-3-phosphate-5-kinase PIKfyve and subsequent formation of PIP2 [64,76,77] or by inhibition of WNK4, which in turn inhibits ENaC [78].

Beyond its effect on Nedd4-2, iNOS [75], PIKfyve [64,76,77] and WNK4 [78], SGK1 may phosphorylate and thus inhibit several further enzymes, including the mitogen-activated protein kinase/ERK kinase kinase 3 MEKK3, the stress activated kinase SEK1 [17], the B-Raf kinase, the phosphomannose mutase 2, and the glycogen synthase kinase 3 GSK3 [4].

SGK1 regulates a number of transcription factors, including the cAMP responsive element binding protein (CREB), the nuclear factor kappa B (NFκB) [79,80], and the forkhead transcription factor FKHR-L1 (FOXO3a) [4,21,81].

SGK1 phosphorylates several additional proteins including the type A natriuretic peptide receptor (NPR-A), Ca²⁺ regulated heat-stable protein of apparent molecular mass 24 kDa CRHSP24, the adaptor precursor (APP) Fe65, NDRG1 and NDRG2, mosinVc, filamin C, microtubule-associated protein tau and huntingtin [4,46,82].

It should be pointed out again, that most targets are shared by related kinases, which usually play a leading part over SGK1 in the regulation of the respective targets [4]. SGK3-regulated target proteins include ENaC, TRPV5,6, SCN5A, GluR1, the rapid delayed voltage gated cardiac K⁺ channels (HERG), several voltage gated (Kv) channels, KCNE1/KCNQ1, CLC-Ka/barttin, the carriers SGLT1, several amino acid carriers, creatine transporter SLC6A8, Na⁺ dicarboxylate cotransporter and the Na⁺/K⁺-ATPase [4,54,69]. SGK3 further phosphorylates glycogen synthase kinase 3 beta (GSK-3beta) [4]. Less is known about functions of SGK2, which, however, similarly regulates ENaC, Kv channels, KCNE1/KCNQ1, CLCKa/barttin, several amino acid transporters, the Na⁺ dicarboxylate cotransporter 1 and the Na⁺/K⁺-ATPase [4,69,83].

5. SGK1 sensitive functions

SGK1 dependent regulation affects a wide variety of physiological and pathophysiological functions [4] including regulation of cell volume [84], cell survival and tumor growth [85], cell proliferation, aldosterone release, insulin release [86], induction and maintenance of neuropathic and inflammatory pain [87], glucose metabolism, function of decidualizing cells [20], cellular K⁺ uptake [88], gastric acid secretion [89–91], intestinal transport, renal tubular salt- [47], K⁺- and Ca²⁺-transport as well as salt appetite [4,92]. In *Caenorhabditis elegans*, knockout of SGK1 leads to substantial prolongation of life span [4]. Data addressing the putative role of SGK1 as a determinant of life span in other species have not been published. Mice lacking SGK3 have impaired hair growth [93,94] and reduced locomotion [4].

6. Pathophysiological role of SGK1 in diabetes

Compelling evidence points to a role of SGK1 in the development of diabetes and the pathophysiology of its complications.

SGK1 participates in the development of obesity [4], which is well known to cause insulin resistance and ultimately impair insulin release leading to type 2 diabetes [95]. The mechanisms involved in the development of insulin resistance in obese individuals include intracellular lipid-induced inhibition of insulin-stimulated insulin-receptor substrate (IRS)-1 tyrosine phosphorylation resulting in reduced IRS-1-associated phosphatidylinositol 3 kinase activity and subsequent decrease of insulin-stimulated GLUT4 activity [96].

SGK1 fosters the development of obesity at least partially by stimulation of the Na⁺ coupled glucose transporter SGLT1, which accelerates the intestinal uptake of glucose [4]. The rapid intestinal glucose absorption leads to excessive insulin release and fat deposition, with subsequent decrease of plasma glucose concentration, which triggers repeated glucose uptake and thus obesity. Conversely, obesity could be counteracted by inhibitors of SGLT1 [4]. The role of SGK1 in the development of obesity is underscored by the observation that a variant of the SGK1 gene (the combined presence of distinct polymorphisms in intron 6 [I6CC] and in exon 8 [E8CC/CT]) is associated with increased body weight. The same SGK1 gene variant is more prevalent in patients with type 2 diabetes than in individuals without family history of diabetes [97]. The gene variant is common, affecting 3–5 % of a Caucasian population and some 10 % of an African population [97]. In diabetes mellitus, the excessive plasma glucose concentrations could, at least in theory, upregulate intestinal SGK1 expression and the enhanced SGK1-dependent stimulation of SGLT1 could contribute to the maintenance of obesity.

SGK1 is similarly important in the development of diabetic complications. As indicated above, SGK1 transcription is stimulated by excessive glucose concentrations and strong SGK1 expression has been observed in renal tissue of diabetic patients [4,29].

Excessive SGK1 expression in diabetic nephropathy leads to stimulation of SGLT1 in proximal renal tubules which blunts the glucosuria [98]. Moreover, SGK1 could stimulate proximal renal tubular glucose transport by stimulation of the K⁺ channels KCNQ1/KCNE1, which establish the electrical driving force for electrogenic glucose transport.

The same SGK1 gene variant, which predisposes to obesity, is associated with moderately enhanced blood pressure. Individuals carrying the SGK1 gene variant display a particularly strong correlation between insulinemia and blood pressure [4], pointing to a decisive role of SGK1 in the hypertension paralleling hyperinsulinemia. In wild type mice, hyperinsulinemia by pretreatment with a high-fructose diet or a high fat diet sensitizes arterial blood pressure to high-salt intake, an effect completely lacking in SGK1-knockout mice (*sgk1*^{-/-}) [4]. Accordingly, SGK1 is required for the stimulation of renal tubular salt reabsorption by insulin. SGK1 further participates in the hypertensive effects of glucocorticoids [99]. The excessive expression of SGK1 during hyperglycemia or diabetes mellitus could, at least in theory, sensitize the renal tubules for the salt retaining effects of insulin and thus foster the development of hypertension.

Similar to excessive SGK1 activity, lack of Nedd4-2 leads to hypertension [100]. Moreover, the Nedd4-2 gene variant ^{P355L}Nedd4-2 with enhanced SGK1 sensitivity, predisposes to the development of renal salt retention, hypertension and development of end-stage renal disease (ESRD).

SGK1-sensitive renal salt retention may not only predispose to hypertension but contribute to fluid retention and edema formation during treatment with PPAR γ agonists [101] or in nephritic syndrome [102]. Along those lines, SGK1 expression is increased during ascites formation in cirrhotic rats [103].

Increased SGK1 expression and activity may further contribute to the risk of kidney stones, which are more prevalent in individuals with type II diabetes. Despite the stimulating effect of SGK1 on TRPV5 Ca²⁺ channels, the renal Ca²⁺ excretion is decreased in *sgk1*^{-/-} mice [4]. Conversely, enhanced SGK1 activity is expected to foster calciuria. The stimulation of NaCl cotransport and ENaC by SGK1 leads to extracellular volume expansion, which decreases Na⁺ and Ca²⁺ reabsorption in the proximal tubule and in the thick ascending limb of the loop of Henle, thus increasing renal Ca²⁺ excretion. Conversely, inhibition of NaCl cotransport by

thiazide diuretics leads to anticalciuria protecting against the development of Ca^{2+} stones, an effect involving upregulation of proximal tubular Ca^{2+} reabsorption [104].

SGK1 is expressed in glomerular podocytes [27,105] and upregulated in those cells by aldosterone and oxidative stress [27]. SGK1 is thus thought to participate in the development of proteinuria during mineralocorticoid excess and inflammation. Accordingly, the proteinuria following DOCA treatment is significantly blunted in SGK1 knockout mice [4]. Lack of SGK1 does, however, not protect against doxorubicin induced glomerular injury [102]. Hitherto, no experiments have been published on the role of SGK1 in proteinuria of diabetic nephropathy.

SGK1 has been shown to potentiate the effect of excessive glucose concentrations on fibronectin formation [4]. Hitherto, excessive SGK1 transcription during diabetes has only been demonstrated in renal tissue and isolated cells [4]. Excessive SGK1 expression has been reported to prevail in several other tissues during fibrosing disease such as in intestinal Crohn's disease, lung fibrosis, liver cirrhosis, and fibrosing pancreatitis [4]. Besides diabetic nephropathy, glomerulonephritis and puromycin aminonucleoside induced experimental rat nephritic syndrome are paralleled by excessive renal expression of SGK1 [4].

As indicated above, SGK1 transcription is strongly stimulated by transforming growth factor $\text{TGF}\beta$ [4], which has been identified as the etiologic agent of renal hypertrophy and the accumulation of mesangial extracellular matrix components in diabetes [106]. Accordingly, renal hypertrophy and fibrosis of diabetic mice could be reversed by neutralizing anti-TGF-beta antibodies, antisense TGF-beta1 oligodeoxynucleotides or knocking out the Smad3 gene [106].

Epidermal growth factor (EGF) has similarly been shown to play a role in the nephromegaly and enhanced sodium reabsorption observed in diabetic nephropathy [107,108]. Experiments in primary cultures of human cortical fibroblasts revealed that high glucose concentrations stimulate the epidermal growth factor receptor EGF-R, which enhances the expression of SGK1 with subsequent stimulation of fibronectin formation [107,108].

SGK1 stimulates the nuclear translocation of $\text{NF}\kappa\text{B}$, a transcription factor stimulating the expression of connective tissue growth factor (CTGF) [4]. CTGF is a strong stimulator of fibrosis and contributes to the stimulation of matrix protein synthesis and the development of a variety of fibrosing disorders [4]. The cardiac stimulation of CTGF formation and cardiac fibrosis following mineralocorticoid excess are completely abrogated by knockout of SGK1, an observation underscoring the causal role of SGK1 in fibrosing disease [4]. In addition, SGK1 participates in α -adrenergically induced cardiac hypertrophy [4].

The profibrotic effect of SGK1 may come as a surprise in view of the known anti-inflammatory effect of glucocorticoids. However, the synthetic glucocorticoid dexamethasone has previously been shown to enhance the expression of CTGF and collagen and to foster fibrosis [4].

Excessive SGK1 expression in diabetes further contributes to a prothrombotic state since SGK1 has been shown to be activated and upregulated by thrombin in a redox-dependent manner [21]. Interestingly, SGK1 can induce the expression of tissue factor, the activator of the extrinsic coagulation cascade, and promotes procoagulant activity [21].

7. Conclusions

The serum- and glucocorticoid-inducible kinase SGK1, a potent regulator of metabolism, transport, transcription and enzyme activity, plays a dual role in the pathophysiology of diabetes mellitus. At the one hand, it fosters the development of obesity, which in turn predisposes to type 2 diabetes. On the other hand it participates in the pathophysiology of

diabetic complications. It is upregulated by hyperglycemia and could account for insulin induced hypertension. It presumably contributes to the enhanced incidence of nephrolithiasis, glomerular injury and the hypercoagulable state in diabetic individuals. Most importantly, it participates in the stimulation of fibrosis leading particularly to the development of diabetic nephropathy.

8. Expert Opinion

The triggering of obesity, hypertension and coagulation by SGK1 renders the kinase a signaling molecule fostering the development of metabolic syndrome, a condition associated with enhanced morbidity and mortality from cardiovascular disease [4]. Metabolic syndrome shares several clinical features with glucocorticoid excess or Cushing's syndrome despite normal glucocorticoid plasma concentrations [4]. It is tempting to speculate that at least in some individuals, an increased glucocorticoid independent SGK1 expression accounts for metabolic syndrome. Along those lines, maternal SGK1 appears to be critically important for the fetal programming of hypertension in the offspring in response to malnutritive stress of the mother [109].

Accordingly, pharmacological SGK1 inhibition may be an attractive strategy to counteract obesity, metabolic syndrome and the complications of diabetes mellitus. As SGK1 is apparently not required for house keeping functions [4], side effects of specific SGK1 inhibitors are expected to be modest. Accordingly, the phenotype of SGK1 knockout mice is mild [4]. SGK1 may be a particularly attractive therapeutic option in patients carrying the gain of function variant of the SGK1 gene.

Combined inhibition of SGK1 and SGK3 may still be tolerated, as the phenotype of the SGK1-SGK3 double knockout mouse is similarly mild. SGK1 inhibitors are useful, however, only, if they do not inhibit the PKB/Akt isoforms, which would impede cellular glucose uptake and thus be expected to aggravate diabetic hyperglycemia.

SGK1 inhibitors may be similarly useful in the prophylactic, metaphylactic and curative treatment of tumor growth and several fibrosing diseases. Along those lines, the SGK1 inhibitor GSK650394 has been proposed for anticancer therapy [110].

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Fig. 1.
Regulation of SGK1 expression and activity

Fig. 2. Diagram summarizing the role of SGK1 in the development (red arrows) and consequences (blue arrows) of type 2 diabetes