Published in final edited form as:
Curr Opin Nephrol Hypertens. 2009 September ; 18(5): 439–448. doi:10.1097/MNH.0b013e32832f125e.

The Physiological Impact of the Serum- and Glucocorticoid-inducible Kinase SGK1

Florian Lang, **Ferruh Artunc**, and **Volker Vallon**
Department of Physiology, University of Tuebingen, Germany; Departments of Medicine and Pharmacology, University of California San Diego, San Diego, USA

Abstract

Purpose of review—The role of SGK1 in renal physiology and pathophysiology is reviewed with particular emphasis of recent advances.

Recent findings—The mammalian target of rapamycin complex 2 (mTORC2) has been shown to phosphorylate SGK1 at Ser^{422} (the so-called hydrophobic motif). Ser^{397} and Ser^{401} are two additional SGK1-phosphorylation sites required for maximal SGK1-activity. A 5′ variant alternate transcript of human Sgk1 has been identified that is widely expressed and shows improved stability, enhanced membrane association, and greater stimulation of epithelial Na^+ transport. SGK1 is essential for optimal processing of the epithelial sodium channel and also regulates the expression of the Na^+-Cl^- cotransporter. With regard to pathophysiology, SGK1 participates in the stimulation of renal tubular glucose transport in diabetes, the renal profibrotic effect of both angiotensin II and aldosterone, and in fetal programming of arterial hypertension.

Summary—The outlined recent findings advanced our understanding of the molecular regulation of SGK1 as well as the role of the kinase in renal physiology and the pathophysiology of renal disease and hypertension. Future studies using pharmacological inhibitors of SGK1 will reveal the utility of the kinase as a new therapeutic target.

Keywords

Metabolic syndrome; hypertension; fibrosis; inflammation; coagulation

Introduction

The **s**erum- and **g**lucocorticoid-inducible **k**inase 1 (SGK1) was originally cloned as an immediate early gene transcriptionally stimulated by serum and glucocorticoids in rat mammary tumor cells [1]. The human isoform has been discovered as a gene upregulated by cell shrinkage [2]. As listed in Table 1, SGK1 is under transcriptional control of a variety of further stimuli.

Corresponding author: Florian Lang, Dept. of Physiology, University of Tuebingen, Gmelinstrasse 5, 72076 Tuebingen, Germany; Tel. +4970712972194, Fax +497071295618, florian.lang@uni-tuebingen.de.

Disclosure: The study in the laboratories of the authors is funded by the Deutsche Forschungsgemeinschaft (DFG, IRTG to F.L.) and the National Institutes of Health (NIH-R01DK56248 and NIH-P30DK079337 to V.V.). The authors declare that they have no conflict of interest.

The gene encoding human SGK1 has been localised to chromosome 6q23 [36]. Distinct translational isoforms of SGK1 have been disclosed differing in regulation of expression, subcellular localization and function [37-39]. The kinase forms dimers by two intermolecular disulfide bonds between Cys258 in the activation loop and Cys193 [40]. SGK kinases were detected in a variety of species including shark and *Caenorhabditis elegans* [7]. Yeast express two orthologues, Ypk1 and Ypk2, kinases involved in the regulation of endocytosis and required for survival [7].

Regulation of SGK1 expression and activity

SGK1 expression is virtually ubiquitous [2], but varies between different cell types, as observed in brain [7,41,42], eye [7], inner ear [3,4,43], semicircular canal duct epithelium [4], lung [7, 44-48], kidney [7,49], liver [7], intestine [7], pancreas [7] and ovary [7]. Moreover, typical expression patterns are found during embryonic as well as postnatal development [41,50-52]. The subcellular localisation of SGK1 may depend on the functional state of the cell. Activation of SGK1 following exposure of cells to serum has been suggested to trigger importin-alpha mediated entry of SGK1 into the nucleus [7] whereas activation by hyperosmotic shock or glucocorticoids enhances cytosolic localization of the kinase [1]. SGK1 may further localize to the mitochondrial membrane [53,54].

SGK1 transcription is rapidly regulated by a wide variety of stimulators and inhibitors (Table 1). Transcription factor binding sites have been identified in the promoter of the rat SGK1 gene for the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the progesterone receptor (PR), the vitamin D receptor (VDR), the retinoid X receptor (RXR), the farnesoid X receptor (FXR), the sterol regulatory element binding protein (SREBP), peroxisome proliferator-activated receptor γ (PPARγ), the cAMP response element binding protein (CREB), the p53 tumor suppressor protein, the Sp1 transcription factor, the activating protein 1 (AP1), the activating transcription factor 6 (ATF6), the 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].

SGK1 is activated by the phosphatidylinositol-3-kinase (PI3-kinase) pathway involving the 3-phosphoinositide (PIP3)-dependent kinase PDK1 [7]. PIP3 is degraded and thus SGK1 activation discontinued by the phosphatase and tensin homolog PTEN [55]. SGK1 activation by PDK1 may involve the scaffold protein Na^+/H^+ exchanger regulating factor 2 (NHERF2), which mediates the assembly of SGK1 and PDK1 via its PDZ domains and PIF consensus sequence [7]. Activation of SGK1 by PDK1 may further involve the mammalian target of rapamycin mTOR [56-59] and the serine/threonine kinase WNK1 (with no lysine kinase 1) [60-62].

PI3-kinase pathway dependent activation of SGK1 is triggered by insulin, IGF1 , hepatic growth factor (HGF), and follicle stimulating hormone (FSH) [7]. SGK1 can further be activated by bone marrow kinase/extracellular signal-regulated kinase 5 (BK/ERK5) or by p38α [7], by feeding [63], by an increase of cytosolic Ca^{2+} activity with subsequent activation of calmodulin-dependent protein kinase kinase (CaMKK) [7], and by the small G-protein Rac1 [7]. SGK1 is further activated by neuronal depolarization, cAMP, lithium, oxidation and adhesion to fibronectin [7].

SGK1 is degraded with a half-life of 30 minutes [7]. SGK1 may be ubiquitinated [64,65] by the ubiquitin ligase Nedd4-2 (**n**euronal precursor cells **e**xpressed **d**evelopmentally **d**ownregulated) [66].

SGK1 dependent regulation of cellular functions

The SGK1 kinase consensus sequence R-X-R-X-X-(S/T)-phi (X stands for any amino acid, R for arginine and phi indicates a hydrophobic amino acid) is shared by other kinases [7] and the only exclusive SGK1 targets known are the N-myc downregulated genes NDRG1 and NDRG2 [7,67]. Thus, most SGK1 sensitive functions are similarly regulated by SGK and protein kinase B isoforms or other related kinases. As listed in Table 2, SGK1 regulates a wide variety of channels and carriers.

SGK1 regulates the channels and carriers partially by phosphorylating the target proteins [7]. Alternatively, SGK1 phosphorylates the ubiquitin ligase Nedd4-2 [7], which otherwise ubiquitinates channel and transport proteins thus preparing them for clearance from the cell membrane and subsequent degradation [7]. Phosphoprylated Nedd4-2 is bound to 14-3-3, and is thus unable to ubiquitinate its targets [108-111]. The ^{P355L}Nedd4-2 variant, found in patients with end-stage renal disease (ESRD) suffering from arterial hypertension, was shown to be more sensitive to phosphorylation by SGK1 and, accordingly, to exert a weaker negative effect on ENaC [7]. Furthermore, SGK1 may phosphorylate WNK4, a kinase inhibiting ENaC activity [112], and inhibit inducible nitric oxide synthase, and the decreased formation of nitric oxide may then disinhibit ENaC [114]. SGK1 may also be effective through modification of channel or carrier expression [113]. SGK1 may further regulate carriers and channels through activation of the phosphatidylinositol-3-phosphate-5-kinase PIKfyve and subsequent formation of PIP2 [95,115,116].

SGK1 phosphorylates and thus inhibits several enzymes, including the ubiquitin ligase Nedd4-2 [7,66], the mitogen-activated protein kinase/ERK kinase kinase 3 (MEKK3) [7], the kinase SEK1 [21], the B-Raf kinase [7], the phosphomannose mutase 2 [117], inducible nitric oxide (NO) synthase [114] and the glycogen synthase kinase 3 GSK3 [7,118], which, however, may be regulated by PKB/Akt rather than SGK1 [7].

SGK1 regulates several transcription factors, including the cAMP responsive element binding protein (CREB) [119], nuclear factor kappa B (NFκB) [32,120,121], and the forkhead transcription factor FKHR-L1 (FOXO3a) [7,122].

SGK1 phosphorylates a variety of further proteins such as the type A natriuretic peptide receptor (NPR-A) [7], Ca^{2+} regulated heat-stable protein of apparent molecular mass 24 kDa CRHSP24 [123], the adaptor precursor (APP) Fe65 [72], NDRG1 and NDRG2 [67], mosinVc [124], filamin C [7], microtubule-associated protein tau [125] and huntingtin [7]. In most cases, the functional significance of SGK1 dependent phorphorylation of those proteins is still elusive. A wide variety of functions have, however, been described, which are regulated by SGK1 (Table 3). Most of those functions have been reviewed previously [7].

In the following the role of SGK1 in the regulation of electrolyte metabolism and blood pressure will be discussed in more detail.

The role of SGK1 in renal function and salt appetite

SGK1 stimulates a variety of renal tubular ion channels and transporters (Table 2) and thus participates in the regulation of renal electrolyte excretion (for earlier references see [7, 151-154]).

Specifically, SGK1 participates in the regulation of renal Na^+ excretion by aldosterone, insulin and IGF1 [91,155]. The effect of aldosterone is only partially dependent on the presence of SGK1 and effects of aldosterone and SGK1 are additive. In contrast, antidiuretic hormone (ADH) or insulin do not further stimulate ENaC in cells expressing active SGK1 [156].

Experiments in SGK1-knockout (*sgk1*$^{-/-}$) mice indeed revealed subtle but relevant impairment of renal salt retention [90]. In salt replete conditions arterial blood pressure and renal salt output is similar in *sgk1*$^{-/-}$ mice and their wild-type littermates (*sgk1*$^{+/+}$). The maintenance of salt balance and blood pressure requires, however, increased plasma aldosterone levels in *sgk1*$^{-/-}$ mice [7]. Under NaCl-deficient diet, NaCl excretion decreases in both *sgk1*$^{-/-}$ and *sgk1*$^{+/+}$ mice, the renal NaCl retention remains, however, insufficient in *sgk1*$^{-/-}$ mice, despite an increase of plasma aldosterone concentration, decrease of arterial blood pressure, decrease of glomerular filtration rate and enhanced proximal tubular Na^+ reabsorption [7]. The renal salt loss of *sgk1*$^{-/-}$ mice may not be only due to decreased stimulation of ENaC as enhanced ENaC activity has been observed in salt depleted *sgk1*$^{-/-}$ mice [90], presumably as a result of stimulation of ENaC expression by hyperaldosteronism [90]. Similarly, despite the lack of SGK1 ENaC activity is enhanced in the colon of *sgk1*$^{-/-}$ mice, which is again likely due to hyperaldosteronism [157]. The enhanced renal salt loss despite increased ENaC activity may be due to decreased expression of the NaCl cotransport in early distal tubule [90]. Inhibition of ENaC by triamterene leads to excessive, eventually lethal salt loss in *sgk1*$^{-/-}$ but not in *sgk1*$^{+/+}$ mice, an observation again pointing to a renal transport defect other than ENaC in *sgk1*$^{-/-}$ mice [158]. SGK1 is particularly important for the antinatriuretic effect of insulin, which is significantly blunted in *sgk1*$^{-/-}$ mice [136]. Renal salt loss does not appear to be more pronounced in mice lacking both SGK1 and SGK3 [159].

In dehydration, the enhanced medullary osmolarity upregulates the expression of SGK1, which in turn stimulates the expression of the natriuretic peptide receptor type A thus sensitizing the epithelial cells to natriuretic peptides and triggering natriuresis [16]. The renal loss of Na^+ counteracts hyperosomolarity during water deprivation [16].

Lack of SGK1 further impairs the ability of the kidney to excrete a K^+ load. Despite enhanced plasma levels of aldosterone, which should increase renal K^+ excretion, *sgk1*$^{-/-}$ mice do not adequately increase the renal K^+ excretion following an acute K^+ load [7]. Following a chronic K^+ load, *sgk1*$^{-/-}$ mice enhance renal K^+ excretion only upon marked increase of plasma K^+ and aldosterone concentrations [7]. SGK1 is further critically important for the effect of insulin on cellular K^+ uptake [160].

The *sgk1*$^{-/-}$ mice express significantly less TRPV5 Ca^{2+} channels [132], an observation consistent with a stimulating effect of SGK1 on TRPV5 [7]. However, despite decreased TRPV5 expression, the renal Ca^{2+} excretion is decreased in *sgk1*$^{-/-}$ mice [132]. The extracellular volume contraction following renal salt loss due to impaired stimulation of NaCl cotransport and ENaC enhances Na^+ [7] and presumably Ca^{2+} reabsorption in the proximal tubule and in the thick ascending limb of the loop of Henle, thus decreasing renal Ca^{2+} excretion. It is noteworthy that inhibition of NaCl cotransport by thiazide diuretics regularly leads to anticalciuria [161] by a mechanism that involves upregulation of proximal tubular Ca^{2+} reabsorption [162].

In normal kidneys, the proximal tubular SGK1 expression is low [7] and SGK1 is thus not considered to participate in the regulation of proximal tubular transport. In diabetic nephropathy, however, SGK1 is expressed throughout the kidney including proximal renal tubules and thus stimulates renal tubular glucose transport [163]. The effect may be due to stimulation of SGLT1 [7] or due to activation of KCNQ1/KCNE1 [7], which maintains the electrical driving force for electrogenic glucose transport [164].

SGK1 is expressed in glomerular podocytes [22,165] and is upregulated in those cells by aldosterone and oxidative stress [20,22]. Thus, SGK1 may participate in the development of proteinuria during mineralocorticoid excess and inflammation. As a matter of fact, the proteinuria following DOCA treatment is significantly blunted in SGK1 knockout mice

[133]. The *sgk1*$^{-/-}$ mice are, however, not protected against doxorubicin induced glomerular injury [135]. SGK1-dependent renal salt retention favor the development of edema during treatment with PPARγ agonists [166] or in nephrotic syndrome [135]. Furthermore, increased SGK1 expression has been found during ascites formation in cirrhotic rats [167].

SGK1 does not only participate in the regulation of salt excretion but contributes to the regulation of salt intake [168]. Treatment of animals with the mineralocorticoid DOCA is followed by excessive salt intake in *sgk1*$^{+/+}$ but not in *sgk1*$^{-/-}$ mice. Thus, SGK1 plays a *dual* role in mineralocorticoid-regulated NaCl homeostasis, stimulating both, intake and renal retention of salt.

Role of SG1 in hypertension, obesity and metabolic syndrome

The effect of SGK1 on renal salt excretion and salt intake is expected to impact on blood pressure control. As a matter of fact, a certain variant of the SGK1 gene (the combined presence of distinct polymorphisms in intron 6 [I6CC] and in exon 8 [E8CC/CT]) is associated with moderately enhanced blood pressure [7]. The gene variant is common, affecting 3-5 % of a Caucasian population [7]. While one study failed to detect a correlation of the gene variant with blood pressure in patients with renal failure [7], a subsequent study on more than four thousand individuals confirmed the association of the gene variant with increased blood pressure [169]. This latter study revealed a particularly strong correlation between insulinemia and blood pressure in individuals carrying the SGK1 gene variant unravelling the decisive role of SGK1 in the hypertension paralleling hyperinsulinemia [169]. Hyperinsulinemia by pretreatment with a high-fructose diet [136] or a high fat diet [137] sensitizes arterial blood pressure to high-salt intake in *sgk1*$^{+/+}$ but not in *sgk1*$^{-/-}$ mice. This observation underscores the role of SGK1 in insulin induced antinatriuresis and blood pressure control. Moreover, SGK1 may participate in the hypertensive effects of glucocorticoids [170]. Lack of Nedd4-2 leads to hypertension in mice thus mimicking overactivity of SGK1 [171]. Beyond the contribution of SGK1 to blood pressure increase in a given individual, maternal SGK1 appears to be critical for the fetal programming of hypertension in the offspring by stress of the mother [172].

As SGK1 is a powerful stimulator of the Na^+ coupled glucose transporter SGLT1 [7], the SGK1 gene variant may further accelerate the intestinal glucose absorption. Enhanced SGLT1 activity accelerates intestinal glucose absorption leading to excessive insulin release, fat deposition, and subsequent decrease of plasma glucose concentration triggering repeated glucose uptake and thus obesity [7]. Conversely, inhibitors of SGLT1 have been shown to counteract obesity [7]. Accordingly, the same SGK1 gene variant associated with enhanced blood pressure proved to be associated with increased body mass index [7]. Moreover, this SGK1 gene variant is more prevalent in patients with type 2 diabetes than in individuals without family history of diabetes [173]

Hypertension, obesity and susceptibility to develop type II diabetes are hallmarks of metabolic syndrome, which is associated with enhanced morbidity and mortality from cardiovascular disease [7]. Metabolic syndrome and Cushing's syndrome share common clinical features , but the plasma cortisol levels are not typically elevated in metabolic syndrome [7]. The disorder is rather caused by inappropriate activity of a downstream signaling element. To the extend that SGK1 mediates effects of glucocorticoids on blood pressure and body weight, a SGK1 gene variant leading to increased SGK1 activity would trigger glucocorticoid actions without enhanced plasma glucocorticoid concentrations. Metabolic syndrome is further typically associated with enhanced coagulation [7], which is again stimulated by SGK1 [13]. Taken together, compelling evidence suggests a participation of SGK1 in the pathophysiology of metabolic syndrome.

Conclusions

The serum- and glucocorticoid-inducible kinase SGK1 is a powerful regulator of metabolism, transport, transcription and enzyme activity and thus participates in the regulation of a wide variety of physiological functions including epithelial transport, excitability, cell proliferation and apoptosis. The phenotype of SGK1 knockout mice is mild and obviously, the function of this kinase is involved in but not critically important for the maintenance of house keeping functions. However, following appropriate challenges the lack of SGK1 becomes obvious and physiologically or pathophysiologically relevant. SGK1 plays a particularly important role in electrolyte balance, extracellular volume regulation, metabolic syndrome, tumor growth, inflammation, and fibrosing disease.

References

1. Firestone GL, Giampaolo JR, O'Keeffe BA. Stimulus-dependent regulation of the serum and glucocorticoid inducible protein kinase (Sgk) transcription, subcellular localization and enzymatic activity. Cell Physiol Biochem 2003;13:1–12. [PubMed: 12649597]
2. Waldegger S, Barth P, Raber G, et al. Cloning and characterization of a putative human serine/threonine protein kinase transcriptionally modified during anisotonic and isotonic alterations of cell volume. Proc Natl Acad Sci U S A 1997;94:4440–4445. [PubMed: 9114008]
3. Kim SH, Kim KX, Raveendran NN, et al. Regulation of Epithelial Sodium Channel (ENaC)-Mediated Sodium Transport by Glucocorticoids in Reissner's Membrane Epithelium. Am J Physiol Cell Physiol. 2009
4. Pondugula SR, Raveendran NN, Ergonul Z, et al. Glucocorticoid regulation of genes in the amiloride-sensitive sodium transport pathway by semicircular canal duct epithelium of neonatal rat. Physiol Genomics 2006;24:114–123. [PubMed: 16263802]
5. van Gemert NG, Meijer OC, Morsink MC, et al. Effect of brief corticosterone administration on SGK1 and RGS4 mRNA expression in rat hippocampus. Stress 2006;9:165–170. [PubMed: 17060050]
6. Yaylaoglu MB, Agbemafle BM, Oesterreicher TJ, et al. Diverse patterns of cell-specific gene expression in response to glucocorticoid in the developing small intestine. Am J Physiol Gastrointest Liver Physiol 2006;291:G1041–G1050. [PubMed: 16825705]
7. Lang F, Bohmer C, Palmada M, et al. (Patho)physiological significance of the serum- and glucocorticoid-inducible kinase isoforms. Physiol Rev 2006;86:1151–1178. [PubMed: 17015487]
8. Bertog M, Cuffe JE, Pradervand S, et al. Aldosterone responsiveness of the epithelial sodium channel (ENaC) in colon is increased in a mouse model for Liddle's syndrome. J Physiol 2008;586:459–475. [PubMed: 18006588]
9. Fakitsas P, Adam G, Daidie D, et al. Early aldosterone-induced gene product regulates the epithelial sodium channel by deubiquitylation. J Am Soc Nephrol 2007;18:1084–1092. [PubMed: 17344426]
10. Feroze-Zaidi F, Fusi L, Takano M, et al. Role and regulation of the serum- and glucocorticoid-regulated kinase 1 in fertile and infertile human endometrium. Endocrinology 2007;148:5020–5029. [PubMed: 17640988]
11. Thomas CP, Liu KZ, Vats HS. Medroxyprogesterone acetate binds the glucocorticoid receptor to stimulate alpha-ENaC and sgk1 expression in renal collecting duct epithelia. Am J Physiol Renal Physiol 2006;290:F306–F312. [PubMed: 16189295]
12. Meng F, Yamagiwa Y, Taffetani S, et al. IL-6 activates serum and glucocorticoid kinase via p38alpha mitogen-activated protein kinase pathway. Am J Physiol Cell Physiol 2005;289:C971–C981. [PubMed: 15917303]
13. Belaiba RS, Djordjevic T, Bonello S, et al. The serum- and glucocorticoid-inducible kinase Sgk-1 is involved in pulmonary vascular remodeling: role in redox-sensitive regulation of tissue factor by thrombin. Circ Res 2006;98:828–836. [PubMed: 16484615]
14. Wolf SC, Schultze M, Risler T, et al. Stimulation of serum- and glucocorticoid-regulated kinase-1 gene expression by endothelin-1. Biochem Pharmacol 2006;71:1175–1183. [PubMed: 16483548]

15. Chang CT, Wu MS, Tian YC, et al. Enhancement of epithelial sodium channel expression in renal cortical collecting ducts cells by advanced glycation end products. Nephrol Dial Transplant 2007;22:722–731. [PubMed: 17192279]
16. Chen S, Grigsby CL, Law CS, et al. Tonicity-dependent induction of Sgk1 expression has a potential role in dehydration-induced natriuresis in rodents. J Clin Invest 2009;119:1647–1658. [PubMed: 19436108]
17. Pfau A, Grossmann C, Freudinger R, et al. Ca2+ but not H2O2 modulates GRE-element activation by the human mineralocorticoid receptor in HEK cells. Mol Cell Endocrinol 2007;264:35–43. [PubMed: 17113706]
18. Hills CE, Bland R, Bennett J, et al. High glucose up-regulates ENaC and SGK1 expression in HCD-cells. Cell Physiol Biochem 2006;18:337–346. [PubMed: 17170520]
19. Faroqui S, Sheriff S, Amlal H. Metabolic acidosis has dual effects on sodium handling by rat kidney. Am J Physiol Renal Physiol 2006;291:F322–F331. [PubMed: 16495212]
20. Nagase M, Yoshida S, Shibata S, et al. Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. J Am Soc Nephrol 2006;17:3438–3446. [PubMed: 17082236]
21. Kim MJ, Chae JS, Kim KJ, et al. Negative regulation of SEK1 signaling by serum- and glucocorticoid-inducible protein kinase 1. EMBO J 2007;26:3075–3085. [PubMed: 17568772]
22. Shibata S, Nagase M, Yoshida S, et al. Podocyte as the target for aldosterone: roles of oxidative stress and Sgk1. Hypertension 2007;49:355–364. [PubMed: 17200434]
23. Feng Y, Wang Y, Xiong J, et al. Enhanced expression of serum and glucocorticoid-inducible kinase-1 in kidneys of L-NAME-treated rats. Kidney Blood Press Res 2006;29:94–99. [PubMed: 16710099]
24. David S, Stegenga SL, Hu P, et al. Expression of serum- and glucocorticoid-inducible kinase is regulated in an experience-dependent manner and can cause dendrite growth. J Neurosci 2005;25:7048–7053. [PubMed: 16049181]
25. Lee CT, Ma YL, Lee EH. Serum- and glucocorticoid-inducible kinase1 enhances contextual fear memory formation through down-regulation of the expression of Hes5. J Neurochem 2007;100:1531–1542. [PubMed: 17241237]
26. Koya E, Spijker S, Homberg JR, et al. Molecular reactivity of mesocorticolimbic brain areas of high and low grooming rats after elevated plus maze exposure. Brain Res Mol Brain Res 2005;137:184–192. [PubMed: 15950777]
27. Conti B, Maier R, Barr AM, et al. Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. Mol Psychiatry 2007;12:167–189. [PubMed: 17033635]
28. Nuber UA, Kriaucionis S, Roloff TC, et al. Up-regulation of glucocorticoid-regulated genes in a mouse model of Rett syndrome. Hum Mol Genet 2005;14:2247–2256. [PubMed: 16002417]
29. Velic A, Gabriels G, Hirsch JR, et al. Acute rejection after rat renal transplantation leads to downregulation of NA+ and water channels in the collecting duct. Am J Transplant 2005;5:1276–1285. [PubMed: 15888031]
30. Friedrich B, Alexander D, Aicher WK, et al. Influence of standard haemodialysis treatment on transcription of human serum- and glucocorticoid-inducible kinase SGK1 and taurine transporter TAUT in blood leukocytes. Nephrol Dial Transplant 2005;20:768–774. [PubMed: 15701671]
31. Wang Q, Zhang A, Li R, et al. High glucose promotes the CTGF expression in human mesangial cells via serum and glucocorticoid-induced kinase 1 pathway. J Huazhong Univ Sci Technolog Med Sci 2008;28:508–512. [PubMed: 18846327]
32. Vallon V, Wyatt AW, Klingel K, et al. SGK1-dependent cardiac CTGF formation and fibrosis following DOCA treatment. J Mol Med 2006;84:396–404. [PubMed: 16604333]
33. Li L, Wingo CS, Xia SL. Downregulation of SGK1 by nucleotides in renal tubular epithelial cells. Am J Physiol Renal Physiol 2007;293:F1751–F1757. [PubMed: 17686958]
34. Turpaev K, Bouton C, Diet A, et al. Analysis of differentially expressed genes in nitric oxide-exposed human monocytic cells. Free Radic Biol Med 2005;38:1392–1400. [PubMed: 15855057]
35. Poulin H, Filion C, Ladanyi M, et al. Serum- and glucocorticoid-regulated kinase 1 (SGK1) induction by the EWS/NOR1(NR4A3) fusion protein. Biochem Biophys Res Commun 2006;346:306–313. [PubMed: 16756948]

36. Waldegger S, Erdel M, Nagl UO, et al. Genomic organization and chromosomal localization of the human SGK protein kinase gene. Genomics 1998;51:299–302. [PubMed: 9722955]
37. Arteaga MF, Alvarez dlR, Alvarez JA, et al. Multiple translational isoforms give functional specificity to serum- and glucocorticoid-induced kinase 1. Mol Biol Cell 2007;18:2072–2080. [PubMed: 17377066]
38. Raikwar NS, Snyder PM, Thomas CP. An evolutionarily conserved N-terminal Sgk1 variant with enhanced stability and improved function. Am J Physiol Renal Physiol 2008;295:F1440–F1448. [PubMed: 18753299] ** A 5′ variant alternate transcript of human SGK1 was identified that is widely expressed, is conserved from rodent to humans, and is predicted to encode an SGK1 isoform, SGK1_i2, with a different NH2 terminus. This variant shows improved stability, enhanced membrane association, and greater stimulation of epithelial Na^+ transport in a heterologous expression system.
39. Simon P, Schneck M, Hochstetter T, et al. Differential regulation of serum- and glucocorticoid-inducible kinase 1 (SGK1) splice variants based on alternative initiation of transcription. Cell Physiol Biochem 2007;20:715–728. [PubMed: 17982254]
40. Zhao B, Lehr R, Smallwood AM, et al. Crystal structure of the kinase domain of serum and glucocorticoid-regulated kinase 1 in complex with AMP PNP. Protein Sci 2007;16:2761–2769. [PubMed: 17965184]
41. Keller-Wood M, Powers MJ, Gersting JA, et al. Genomic analysis of neuroendocrine development of fetal brain-pituitary-adrenal axis in late gestation. Physiol Genomics 2006;24:218–224. [PubMed: 16352695]
42. Stichel CC, Schoenebeck B, Foguet M, et al. sgk1, a member of an RNA cluster associated with cell death in a model of Parkinson's disease. Eur J Neurosci 2005;21:301–316. [PubMed: 15673431]
43. Zhong SX, Liu ZH. Expression patterns of Nedd4 isoforms and SGK1 in the rat cochlea. Acta Otolaryngol 2008:1–5. [PubMed: 19051070]
44. Aoi W, Niisato N, Sawabe Y, et al. Aldosterone-induced abnormal regulation of ENaC and SGK1 in Dahl salt-sensitive rat. Biochem Biophys Res Commun 2006;341:376–381. [PubMed: 16426574]
45. Brown SG, Gallacher M, Olver RE, et al. The regulation of selective and nonselective Na+ conductances in H441 human airway epithelial cells. Am J Physiol Lung Cell Mol Physiol 2008;294:L942–L954. [PubMed: 18310228]
46. Inglis SK, Gallacher M, Brown SG, et al. SGK1 activity in Na(+) absorbing airway epithelial cells monitored by assaying NDRG1-Thr(346/356/366) phosphorylation. Pflugers Arch. 2008
47. Keller-Wood M, Wood CE, Hua Y, et al. Mineralocorticoid receptor expression in late-gestation ovine fetal lung. J Soc Gynecol Investig 2005;12:84–1.
48. Wirbelauer J, Schmidt B, Klingel K, et al. Serum and glucocorticoid-inducible kinase in pulmonary tissue of preterm fetuses exposed to chorioamnionitis. Neonatology 2008;93:257–262. [PubMed: 18032912]
49. Uawithya P, Pisitkun T, Ruttenberg BE, et al. Transcriptional profiling of native inner medullary collecting duct cells from rat kidney. Physiol Genomics 2008;32:229–253. [PubMed: 17956998]
50. Cobb J, Duboule D. Comparative analysis of genes downstream of the Hoxd cluster in developing digits and external genitalia. Development 2005;132:3055–3067. [PubMed: 15944189]
51. Huber SM, Friedrich B, Klingel K, et al. Protein and mRNA expression of serum and glucocorticoid-dependent kinase 1 in metanephrogenesis. Dev Dyn 2001;221:464–469. [PubMed: 11500984]
52. Lee E, Lein ES, Firestone GL. Tissue-specific expression of the transcriptionally regulated serum and glucocorticoid-inducible protein kinase (Sgk) during mouse embryogenesis. Mech Dev 2001;103:177–181. [PubMed: 11335130]
53. Cordas E, Naray-Fejes-Toth A, Fejes-Toth G. Subcellular location of serum- and glucocorticoid-induced kinase-1 in renal and mammary epithelial cells. Am J Physiol Cell Physiol 2007;292:C1971–C1981. [PubMed: 17202226]
54. Engelsberg A, Kobelt F, Kuhl D. The N-terminus of the serum- and glucocorticoid-inducible kinase Sgk1 specifies mitochondrial localization and rapid turnover. Biochem J 2006;399:69–76. [PubMed: 16776652]
55. Lian Z, Di Cristofano A. Class reunion: PTEN joins the nuclear crew. Oncogene 2005;24:7394–7400. [PubMed: 16288286]

56. Dunlop EA, Tee AR. Mammalian target of rapamycin complex 1: Signaling inputs, substrates and feedback mechanisms. Cell Signal. 2009 in press.
57. Garcia-Martinez JM, Alessi DR. mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). Biochem J 2008;416:375–385. [PubMed: 18925875] ** The identity of the protein kinase(s) responsible for phosphorylation of SGK1 at Ser^{422} (the so-called hydrophobic motif) that promotes activation of the kinase by PDK1, was unclear. This study revealed the identity of a 'PDK2′ kinase that catalyses Ser^{422} phosphorylation as mTORC2 (mammalian target of rapamycin complex 2), a multiprotein kinase that phosphorylates a similar site in PKB.
58. Hong F, Larrea MD, Doughty C, et al. mTOR-raptor binds and activates SGK1 to regulate p27 phosphorylation. Mol Cell 2008;30:701–711. [PubMed: 18570873]
59. Yan L, Mieulet V, Lamb RF. mTORC2 is the hydrophobic motif kinase for SGK1. Biochem J 2008;416:e19–e21. [PubMed: 19025518]
60. Chen W, Chen Y, Xu BE, et al. Regulation of a Third Conserved Phosphorylation Site in SGK1. J Biol Chem 2009;284:3453–3460. [PubMed: 19068477] ** This study identified two new phosphorylation sites, Ser397 and Ser401, that both are required for maximum SGK1 activity induced by extracellular agents or by coexpression with other protein kinases, with the largest loss of activity from mutation of Ser397. Coexpression with active Akt1 increased the phosphorylation of Ser397 and thereby SGK1 kinase activity, revealing further complexity underlying the regulation of SGK1 activity.
61. Xu BE, Stippec S, Chu PY, et al. WNK1 activates SGK1 to regulate the epithelial sodium channel. Proc Natl Acad Sci U S A 2005;102:10315–10320. [PubMed: 16006511]
62. Xu BE, Stippec S, Lazrak A, et al. WNK1 activates SGK1 by a phosphatidylinositol 3-kinase-dependent and non-catalytic mechanism. J Biol Chem 2005;280:34218–34223. [PubMed: 16081417]
63. Bayascas JR, Wullschleger S, Sakamoto K, et al. Mutation of the PDK1 PH domain inhibits protein kinase B/Akt, leading to small size and insulin resistance. Mol Cell Biol 2008;28:3258–3272. [PubMed: 18347057]
64. Arteaga MF, Wang L, Ravid T, et al. An amphipathic helix targets serum and glucocorticoid-induced kinase 1 to the endoplasmic reticulum-associated ubiquitin-conjugation machinery. Proc Natl Acad Sci U S A 2006;103:11178–1113. [PubMed: 16847254]
65. Bogusz AM, Brickley DR, Pew T, et al. A novel N-terminal hydrophobic motif mediates constitutive degradation of serum- and glucocorticoid-induced kinase-1 by the ubiquitin-proteasome pathway. FEBS J 2006;273:2913–2928. [PubMed: 16817852]
66. Zhou R, Snyder PM. Nedd4-2 phosphorylation induces serum and glucocorticoid-regulated kinase (SGK) ubiquitination and degradation. J Biol Chem 2005;280:4518–4523. [PubMed: 15576372]
67. Murray JT, Cummings LA, Bloomberg GB, et al. Identification of different specificity requirements between SGK1 and PKBalpha. FEBS Lett 2005;579:991–994. [PubMed: 15710380]
68. De Seigneux S, Leroy V, Ghzili H, et al. NF-kappaB inhibits sodium transport via down-regulation of SGK1 in renal collecting duct principal cells. J Biol Chem 2008;283:25671–25681. [PubMed: 18586672]
69. Edinger RS, Lebowitz J, Li H, et al. Functional regulation of the epithelial Na+ channel by IkappaB kinase-beta occurs via phosphorylation of the ubiquitin ligase Nedd4-2. J Biol Chem 2009;284:150–157. [PubMed: 18981174]
70. Hills CE, Squires PE, Bland R. Serum and glucocorticoid regulated kinase and disturbed renal sodium transport in diabetes. J Endocrinol 2008;199:343–349. [PubMed: 18653620]
71. Lee IH, Dinudom A, Sanchez-Perez A, et al. Akt mediates the effect of insulin on epithelial sodium channels by inhibiting Nedd4-2. J Biol Chem 2007;282:29866–29873. [PubMed: 17715136]
72. Lee IH, Campbell CR, Cook DI, et al. Regulation of epithelial Na+ channels by aldosterone: role of Sgk1. Clin Exp Pharmacol Physiol 2008;35:235–241. [PubMed: 18197893]
73. Naray-Fejes-Toth A, Boyd C, Fejes-Toth G. Regulation of epithelial sodium transport by promyelocytic leukemia zinc finger protein. Am J Physiol Renal Physiol 2008;295:F18–F26. [PubMed: 18448589]

74. Pao AC, McCormick JA, Li H, et al. NH2 terminus of serum and glucocorticoid-regulated kinase 1 binds to phosphoinositides and is essential for isoform-specific physiological functions. Am J Physiol Renal Physiol 2007;292:F1741–F1750. [PubMed: 17356130]
75. Vasquez MM, Castro R, Seidner SR, et al. Induction of serum- and glucocorticoid-induced kinase-1 (SGK1) by cAMP regulates increases in alpha-ENaC. J Cell Physiol 2008;217:632–642. [PubMed: 18615584]
76. Wang J, Knight ZA, Fiedler D, et al. Activity of the p110-alpha subunit of phosphatidylinositol-3-kinase is required for activation of epithelial sodium transport. Am J Physiol Renal Physiol 2008;295:F843–F850. [PubMed: 18653476]
77. Wielputz MO, Lee IH, Dinudom A, et al. (NDRG2) stimulates amiloride-sensitive Na+ currents in Xenopus laevis oocytes and fisher rat thyroid cells. J Biol Chem 2007;282:28264–28273. [PubMed: 17652085]
78. Bohmer C, Palmada M, Kenngott C, et al. Regulation of the epithelial calcium channel TRPV6 by the serum and glucocorticoid-inducible kinase isoforms SGK1 and SGK3. FEBS Lett 2007;581:5586–5590. [PubMed: 18005662]
79. Bergler T, Stoelcker B, Jeblick R, et al. High osmolality induces the kidney-specific chloride channel CLC-K1 by a serum and glucocorticoid-inducible kinase 1 MAPK pathway. Kidney Int 2008;74:1170–1177. [PubMed: 18614997] ** This study indicates a link between high osmolality and the induction of SGK1 and the subsequent increase of CLC-K1/barttin expression in distal renal tubular cells in vivo and in vitro, which may relate to a role of the kinase in urinary concentration and dilution.
80. Sato JD, Chapline MC, Thibodeau R, et al. Regulation of human cystic fibrosis transmembrane conductance regulator (CFTR) by serum- and glucocorticoid-inducible kinase (SGK1). Cell Physiol Biochem 2007;20:91–8. [PubMed: 17595519]
81. Shaw JR, Sato JD, VanderHeide J, et al. The role of SGK and CFTR in acute adaptation to seawater in Fundulus heteroclitus. Cell Physiol Biochem 2008;22:69–78. [PubMed: 18769033]
82. Seebohm G, Strutz-Seebohm N, Ureche ON, et al. Long QT syndrome-associated mutations in KCNQ1 and KCNE1 subunits disrupt normal endosomal recycling of IKs channels. Circ Res 2008;103:1451–1457. [PubMed: 19008479]
83. Seebohm G, Strutz-Seebohm N, Baltaev R, et al. Regulation of KCNQ4 potassium channel prepulse dependence and current amplitude by SGK1 in Xenopus oocytes. Cell Physiol Biochem 2005;16:255–262. [PubMed: 16301825]
84. Shumilina E, Lampert A, Lupescu A, et al. Deranged Kv channel regulation in fibroblasts from mice lacking the serum and glucocorticoid inducible kinase SGK1. J Cell Physiol 2005;204:87–98. [PubMed: 15605386]
85. Boehmer C, Laufer J, Jeyaraj S, et al. Modulation of the voltage-gated potassium channel Kv1.5 by the SGK1 protein kinase involves inhibition of channel ubiquitination. Cell Physiol Biochem 2008;22:591–600. [PubMed: 19088441]
86. Ullrich S, Berchtold S, Ranta F, et al. Serum- and glucocorticoid-inducible kinase 1 (SGK1) mediates glucocorticoid-induced inhibition of insulin secretion. Diabetes 2005;54:1090–1099. [PubMed: 15793248]
87. Baltaev R, Strutz-Seebohm N, Korniychuk G, et al. Regulation of cardiac shal-related potassium channel Kv 4.3 by serum- and glucocorticoid-inducible kinase isoforms in Xenopus oocytes. Pflugers Arch 2005;450:26–33. [PubMed: 15578212]
88. Arteaga MF, Coric T, Straub C, et al. A brain-specific SGK1 splice isoform regulates expression of ASIC1 in neurons. Proc Natl Acad Sci U S A 2008;105:4459–4464. [PubMed: 18334630]
89. Strutz-Seebohm N, Seebohm G, Shumilina E, et al. Glucocorticoid adrenal steroids and glucocorticoid-inducible kinase isoforms in the regulation of GluR6 expression. J Physiol 2005;565:391–401. [PubMed: 15774535]
90. Fejes-Toth G, Frindt G, Naray-Fejes-Toth A, et al. Epithelial Na+ channel activation and processing in mice lacking SGK1. Am J Physiol Renal Physiol 2008;294:F1298–F1305. [PubMed: 18385268] ** This study implicates that SGK1 contributes to the regulation of the expression of the Na^+-Cl^- cotransporter under Na-depleted conditions and that the kinase is essential for optimal processing of ENaC.

91. Fuster DG, Bobulescu IA, Zhang J, et al. Characterization of the regulation of renal Na+/H+ exchanger NHE3 by insulin. Am J Physiol Renal Physiol 2007;292:F577–F585. [PubMed: 17018843]
92. Wang D, Zhang H, Lang F, et al. Acute activation of NHE3 by dexamethasone correlates with activation of SGK1 and requires a functional glucocorticoid receptor. Am J Physiol Cell Physiol 2007;292:C396–C404. [PubMed: 16971495]
93. Yun CC, Chen Y, Lang F. Glucocorticoid activation of Na(+)/H(+) exchanger isoform 3 revisited. The roles of SGK1 and NHERF2. J Biol Chem 2002;277:7676–7683. [PubMed: 11751930]
94. Grahammer, F.; Artunc, F.; Sandulache, D., et al. Renal function of gene targeted mice lacking both SGK1 and SGK3. 2006. in press
95. Shojaiefard M, Strutz-Seebohm N, Tavare JM, et al. Regulation of the Na(+), glucose cotransporter by PIKfyve and the serum and glucocorticoid inducible kinase SGK1. Biochem Biophys Res Commun 2007;359:843–847. [PubMed: 17570343]
96. Palmada M, Boehmer C, Akel A, et al. SGK1 kinase upregulates GLUT1 activity and plasma membrane expression. Diabetes 2006;55:421–47. [PubMed: 16443776]
97. Jeyaraj S, Boehmer C, Lang F, et al. Role of SGK1 kinase in regulating glucose transport via glucose transporter GLUT4. Biochem Biophys Res Commun 2007;356:629–635. [PubMed: 17382906]
98. Boehmer C, Palmada M, Rajamanickam J, et al. Post-translational regulation of EAAT2 function by co-expressed ubiquitin ligase Nedd4-2 is impacted by SGK kinases. J Neurochem 2006;97:911–921. [PubMed: 16573659]
99. Rajamanickam J, Palmada M, Lang F, et al. EAAT4 phosphorylation at the SGK1 consensus site is required for transport modulation by the kinase. J Neurochem 2007;102:858–866. [PubMed: 17442044]
100. Boehmer C, Rajamanickam J, Schniepp R, et al. Regulation of the excitatory amino acid transporter EAAT5 by the serum and glucocorticoid dependent kinases SGK1 and SGK3. Biochem Biophys Res Commun 2005;329:738–742. [PubMed: 15737648]
101. Boehmer C, Palmada M, Klaus F, et al. The peptide transporter PEPT2 is targeted by the protein kinase SGK1 and the scaffold protein NHERF2. Cell Physiol Biochem 2008;22:705–714. [PubMed: 19088452]
102. Shojaiefard M, Christie DL, Lang F. Stimulation of the creatine transporter SLC6A8 by the protein kinases SGK1 and SGK3. Biochem Biophys Res Commun 2005;334:742–746. [PubMed: 16036218]
103. Shojaiefard M, Christie DL, Lang F. Stimulation of the creatine transporter SLC6A8 by the protein kinase mTOR. Biochem Biophys Res Commun 2006;341:945–949. [PubMed: 16466692]
104. Klaus F, Palmada M, Lindner R, et al. Up-regulation of hypertonicity-activated myo-inositol transporter SMIT1 by the cell volume-sensitive protein kinase SGK1. J Physiol 2008;586:1539–1547. [PubMed: 18202099]
105. Palmada M, Dieter M, Speil A, et al. Regulation of intestinal phosphate cotransporter NaPi IIb by ubiquitin ligase Nedd4-2 and by serum- and glucocorticoid-dependent kinase 1. Am J Physiol Gastrointest Liver Physiol 2004;287:G143–G150. [PubMed: 15044175]
106. Shojaiefard M, Lang F. Stimulation of the intestinal phosphate transporter SLC34A2 by the protein kinase mTOR. Biochem Biophys Res Commun 2006;345:1611–1614. [PubMed: 16730658]
107. Ullrich S, Zhang Y, Avram D, et al. Dexamethasone increases Na+/K+ ATPase activity in insulin secreting cells through SGK1. Biochem Biophys Res Commun 2007;352:662–667. [PubMed: 17157265]
108. Bhalla V, Daidie D, Li H, et al. Serum- and glucocorticoid-regulated kinase 1 regulates ubiquitin ligase neural precursor cell-expressed, developmentally down-regulated protein 4-2 by inducing interaction with 14-3-3. Mol Endocrinol 2005;19:3073–3084. [PubMed: 16099816]
109. Ichimura T, Yamamura H, Sasamoto K, et al. 14-3-3 proteins modulate the expression of epithelial Na+ channels by phosphorylation-dependent interaction with Nedd4-2 ubiquitin ligase. J Biol Chem 2005;280:13187–13194. [PubMed: 15677482]
110. Liang X, Peters KW, Butterworth MB, et al. 14-3-3 isoforms are induced by aldosterone and participate in its regulation of epithelial sodium channels. J Biol Chem 2006;281:16323–16332. [PubMed: 16613846]

111. Nagaki K, Yamamura H, Shimada S, et al. 14-3-3 Mediates phosphorylation-dependent inhibition of the interaction between the ubiquitin E3 ligase Nedd4-2 and epithelial Na+ channels. Biochemistry 2006;45:6733–6740. [PubMed: 16716084]

112. Ring AM, Leng Q, Rinehart J, et al. An SGK1 site in WNK4 regulates Na+ channel and K+ channel activity and has implications for aldosterone signaling and K+ homeostasis. Proc Natl Acad Sci U S A 2007;104:4025–409. [PubMed: 17360471]

113. Zhang W, Xia X, Reisenauer MR, et al. Aldosterone-induced Sgk1 relieves Dot1a-Af9-mediated transcriptional repression of epithelial Na+ channel alpha. J Clin Invest 2007;117:773–783. [PubMed: 17332896]

114. Helms MN, Yu L, Malik B, et al. Role of SGK1 in nitric oxide inhibition of ENaC in Na+-transporting epithelia. Am J Physiol Cell Physiol 2005;289:C717–C726. [PubMed: 15843443]

115. Klaus F, Laufer J, Czarkowski K, et al. PIKfyve-dependent regulation of the Cl(−) channel ClC-2. Biochem Biophys Res Commun. 2009

116. Strutz-Seebohm N, Shojaiefard M, Christie D, et al. PIKfyve in the SGK1 mediated regulation of the creatine transporter SLC6A8. Cell Physiol Biochem 2007;20:729–734. [PubMed: 17982255]

117. Menniti M, Iuliano R, Amato R, et al. Serum and glucocorticoid-regulated kinase Sgk1 inhibits insulin-dependent activation of phosphomannomutase 2 in transfected COS-7 cells. Am J Physiol Cell Physiol 2005;288:C148–C155. [PubMed: 15342340]

118. Wyatt AW, Hussain A, Amann K, et al. DOCA-induced phosphorylation of glycogen synthase kinase 3beta. Cell Physiol Biochem 2006;17:137–144. [PubMed: 16543730]

119. David S, Kalb RG. Serum/glucocorticoid-inducible kinase can phosphorylate the cyclic AMP response element binding protein, CREB. FEBS Lett 2005;579:1534–1538. [PubMed: 15733869]

120. Leroy V, De Seigneux S, Agassiz V, et al. Aldosterone activates NF-kappaB in the collecting duct. J Am Soc Nephrol 2009;20:131–144. [PubMed: 18987305] * The studies performed in both cultured cells and freshly isolated rat cortical collecting ducts indicate that aldosterone activates the canonical NF-kappaB pathway in principal cells of the cortical collecting duct by activating the mineralocorticoid receptor and by inducing SGK1.

121. Tai DJ, Su CC, Ma YL, et al. SGK1 Phosphorylation of I{kappa}B Kinase {alpha} and p300 Up-regulates NF-{kappa}B Activity and Increases N-Methyl-D-aspartate Receptor NR2A and NR2B Expression. J Biol Chem 2009;284:4073–4089. [PubMed: 19088076]

122. Dehner M, Hadjihannas M, Weiske J, et al. Wnt signaling inhibits Forkhead box O3a-induced transcription and apoptosis through up-regulation of serum- and glucocorticoid-inducible kinase 1. J Biol Chem 2008;283:19201–19210. [PubMed: 18487207]

123. Auld GC, Campbell DG, Morrice N, et al. Identification of calcium-regulated heat-stable protein of 24 kDa (CRHSP24) as a physiological substrate for PKB and RSK using KESTREL. Biochem J 2005;389:775–783. [PubMed: 15910284]

124. Martel JA, Michael D, Fejes-Toth G, et al. Melanophilin, a novel aldosterone-induced gene in mouse cortical collecting duct cells. Am J Physiol Renal Physiol 2007;293:F904–F913. [PubMed: 17609287]

125. Yang YC, Lin CH, Lee EH. Serum- and glucocorticoid-inducible kinase 1 (SGK1) increases neurite formation through microtubule depolymerization by SGK1 and by SGK1 phosphorylation of tau. Mol Cell Biol 2006;26:8357–8370. [PubMed: 16982696]

126. Taruno A, Niisato N, Marunaka Y. Intracellular calcium plays a role as the second messenger of hypotonic stress in gene regulation of SGK1 and ENaC in renal epithelial A6 cells. Am J Physiol Renal Physiol 2008;294:F177–F186. [PubMed: 17959754]

127. Amato R, Menniti M, Agosti V, et al. IL-2 signals through Sgk1 and inhibits proliferation and apoptosis in kidney cancer cells. J Mol Med 2007;85:707–721. [PubMed: 17571248]

128. Shanmugam I, Cheng G, Terranova PF, et al. Serum/glucocorticoid-induced protein kinase-1 facilitates androgen receptor-dependent cell survival. Cell Death Differ 2007;14:2085–2094. [PubMed: 17932503]

129. Friedrich B, Weyrich P, Stancakova A, et al. Variance of the SGK1 gene is associated with insulin secretion in different European populations: results from the TUEF, EUGENE2, and METSIM studies. PLoS ONE 2008;3:e3506. [PubMed: 18985156]

130. Boini, KM.; Hennige, AM.; Huang, DY., et al. The serum and glucocorticoid inducible kinase SGK1 mediates salt sensitivity of glucose tolerance. 2006. submitted

131. Sandu C, Artunc F, Grahammer F, et al. Role of the serum and glucocorticoid inducible kinase SGK1 in glucocorticoid stimulation of gastric acid secretion. Pflugers Arch 2007;455:493–503. [PubMed: 17618452]

132. Sandulache D, Grahammer F, Artunc F, et al. Renal Ca2+ handling in sgk1 knockout mice. Pflugers Arch 2006;452:444–452. [PubMed: 16685564]

133. Artunc F, Amann K, Nasir O, et al. Blunted DOCA/high salt induced albuminuria and renal tubulointerstitial damage in gene-targeted mice lacking SGK1. J Mol Med 2006;84:737–746. [PubMed: 16924469]

134. Quinkler M, Zehnder D, Eardley KS, et al. Increased expression of mineralocorticoid effector mechanisms in kidney biopsies of patients with heavy proteinuria. Circulation 2005;112:1435–1443. [PubMed: 16145013]

135. Artunc F, Nasir O, Amann K, et al. Serum- and glucocorticoid-inducible kinase 1 in doxorubicin-induced nephrotic syndrome. Am J Physiol Renal Physiol 2008;295:F1624–F1634. [PubMed: 18768591]

136. Huang DY, Boini KM, Friedrich B, et al. Blunted hypertensive effect of combined fructose and high-salt diet in gene-targeted mice lacking functional serum- and glucocorticoid-inducible kinase SGK1. Am J Physiol Regul Integr Comp Physiol 2006;290:R935–R944. [PubMed: 16284089]

137. Huang DY, Boini KM, Osswald H, et al. Resistance of mice lacking the serum- and glucocorticoid-inducible kinase SGK1 against salt-sensitive hypertension induced by a high-fat diet. Am J Physiol Renal Physiol 2006;291:F1264–F1273. [PubMed: 17003223]

138. Busjahn A, Seebohm G, Maier G, et al. Association of the serum and glucocorticoid regulated kinase (sgk1) gene with QT interval. Cell Physiol Biochem 2004;14:135–142. [PubMed: 15107590]

139. Aoyama T, Matsui T, Novikov M, et al. Serum and glucocorticoid-responsive kinase-1 regulates cardiomyocyte survival and hypertrophic response. Circulation 2005;111:1652–1659. [PubMed: 15795328]

140. Lister K, Autelitano DJ, Jenkins A, et al. Cross talk between corticosteroids and alpha-adrenergic signalling augments cardiomyocyte hypertrophy: a possible role for SGK1. Cardiovasc Res 2006;70:555–565. [PubMed: 16533503]

141. Chao CC, Ma YL, Lee EH. Protein kinase CK2 impairs spatial memory formation through differential cross talk with PI-3 kinase signaling: activation of Akt and inactivation of SGK1. J Neurosci 2007;27:6243–6248. [PubMed: 17553997]

142. Tyan SW, Tsai MC, Lin CL, et al. Serum- and glucocorticoid-inducible kinase 1 enhances zif268 expression through the mediation of SRF and CREB1 associated with spatial memory formation. J Neurochem 2008;105:820–832. [PubMed: 18088355]

143. Geranton SM, Morenilla-Palao C, Hunt SP. A role for transcriptional repressor methyl-CpG-binding protein 2 and plasticity-related gene serum- and glucocorticoid-inducible kinase 1 in the induction of inflammatory pain states. J Neurosci 2007;27:6163–6173. [PubMed: 17553988]

144. Segditsas S, Sieber O, Deheragoda M, et al. Putative direct and indirect Wnt targets identified through consistent gene expression changes in APC-mutant intestinal adenomas from humans and mice. Hum Mol Genet 2008;17:3864–3875. [PubMed: 18782851]

145. Sherk AB, Frigo DE, Schnackenberg CG, et al. Development of a small-molecule serum- and glucocorticoid-regulated kinase-1 antagonist and its evaluation as a prostate cancer therapeutic. Cancer Res 2008;68:7475–7483. [PubMed: 18794135] ** To explore the utility of SGK1 as a therapeutic target, a small-molecule competitive inhibitor of this enzyme was developed, GSK650394. The study shows that the compound quantitatively blocks the effect of androgens on growth of a prostate cancer cell line.

146. Yoon JW, Gilbertson R, Iannaccone S, et al. Defining a role for Sonic hedgehog pathway activation in desmoplastic medulloblastoma by identifying GLI1 target genes. Int J Cancer 2009;124:109–119. [PubMed: 18924150]

147. Hussain A, Wyatt AW, Wang K, et al. SGK1-dependent upregulation of connective tissue growth factor by angiotensin II. Kidney Blood Press Res 2008;31:80–86. [PubMed: 18319604] ** Using human kidney fibroblasts and mouse lung fibroblasts from gene-targeted mice lacking SGK1,

evidence is provided that angiotensin II stimulates the expression of SGK1, which is in turn required for the stimulating effect of angiotensin II on the expression of CTGF. These studies implicate a role for SGK1 in the profibrotic effect of angiotensin II.

148. Nagase M, Matsui H, Shibata S, et al. Salt-induced nephropathy in obese spontaneously hypertensive rats via paradoxical activation of the mineralocorticoid receptor: role of oxidative stress. Hypertension 2007;50:877–883. [PubMed: 17875821]
149. Nishimura H, Ito Y, Mizuno M, et al. Mineralocorticoid receptor blockade ameliorates peritoneal fibrosis in new rat peritonitis model. Am J Physiol Renal Physiol 2008;294:F1084–F1093. [PubMed: 18353870]
150. Terada Y, Kuwana H, Kobayashi T, et al. Aldosterone-stimulated SGK1 activity mediates profibrotic signaling in the mesangium. J Am Soc Nephrol 2008;19:298–309. [PubMed: 18184857] ** Using primary cultures of rat mesangial cells and aldosterone-treatment of uninephrectomized rats, evidence is presented that aldosterone stimulates ICAM-1 and CTGF transcription via the activation of SGK1 and NF-kappaB, effects that may contribute to the progression of aldosterone-induced mesangial fibrosis and inflammation.
151. Loffing J, Flores SY, Staub O. Sgk kinases and their role in epithelial transport. Annu Rev Physiol 2006;68:461–490. [PubMed: 16460280]
152. Stockand JD. Preserving salt: in vivo studies with Sgk1-deficient mice define a modern role for this ancient protein. Am J Physiol Regul Integr Comp Physiol 2005;288:R1–R3. [PubMed: 15590990]
153. Vallon V, Lang F. New insights into the role of serum- and glucocorticoid-inducible kinase SGK1 in the regulation of renal function and blood pressure. Curr Opin Nephrol Hypertens 2005;14:59–66. [PubMed: 15586017]
154. Vallon V, Wulff P, Huang DY, et al. Role of Sgk1 in salt and potassium homeostasis. Am J Physiol Regul Integr Comp Physiol 2005;288:R4–10. [PubMed: 15590995]
155. Gonzalez-Rodriguez E, Gaeggeler HP, Rossier BC. IGF-1 vs insulin: respective roles in modulating sodium transport via the PI-3 kinase/Sgk1 pathway in a cortical collecting duct cell line. Kidney Int 2007;71:116–125. [PubMed: 17164836]
156. Arteaga MF, Canessa CM. Functional specificity of Sgk1 and Akt1 on ENaC activity. Am J Physiol Renal Physiol 2005;289:F90–F96. [PubMed: 15951481]
157. Rexhepaj R, Artunc F, Grahammer F, et al. SGK1 is not required for regulation of colonic ENaC activity. Pflugers Arch 2006;453:97–105. [PubMed: 16897044]
158. Artunc F, Ebrahim A, Siraskar B, et al. Responses to diuretic treatment in gene-targeted mice lacking serum- and glucocorticoid-inducible kinase 1 (SGK1). Kidney & Blood Press Res. 2009 in press.
159. Grahammer, F.; Henke, G.; Sandu, C., et al. Intestinal function of gene targeted mice lacking the Serum and Glucocorticoid inducible kinase SGK1. 2006. submitted
160. Boini KM, Graf D, Kuhl D, et al. SGK1 dependence of insulin induced hypokalemia. Pflugers Arch 2009;457:955–961. [PubMed: 18665390]
161. Stier CT Jr. Itskovitz HD. Renal calcium metabolism and diuretics. Annu Rev Pharmacol Toxicol 1986;26:101–116. [PubMed: 3521452]
162. Nijenhuis T, Vallon V, van der Kemp AW, et al. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest 2005;115:1651–1658. [PubMed: 15902302]
163. Ackermann TF, Boini KM, Volkl H, et al. SGK1-sensitive renal tubular glucose reabsorption in diabetes. Am J Physiol Renal Physiol. 2009 ** This study used crossbreeding of diabetic Akita mice with gene-targeted mice lacking SGK1 to provide the first evidence that SGK1 participates in the stimulation of renal tubular glucose transport in diabetic kidneys.
164. Vallon V, Grahammer F, Volkl H, et al. KCNQ1-dependent transport in renal and gastrointestinal epithelia. Proc Natl Acad Sci U S A 2005;102:17864–17869. [PubMed: 16314573]
165. Nagase M, Fujita T. Aldosterone and glomerular podocyte injury. Clin Exp Nephrol 2008;12:233–242. [PubMed: 18317876]
166. Artunc F, Sandulache D, Nasir O, et al. Lack of the serum and glucocorticoid-inducible kinase SGK1 attenuates the volume retention after treatment with the PPARgamma agonist pioglitazone. Pflugers Arch 2008;456:425–436. [PubMed: 18172605]

167. Ackermann D, Mordasini D, Cheval L, et al. Sodium retention and ascites formation in a cholestatic mice model: role of aldosterone and mineralocorticoid receptor? Hepatology 2007;46:173–179. [PubMed: 17596887]

168. Vallon V, Huang DY, Grahammer F, et al. SGK1 as a determinant of kidney function and salt intake in response to mineralocorticoid excess. Am J Physiol Regul Integr Comp Physiol 2005;289:R395–R401. [PubMed: 16014448]

169. von Wowern F, Berglund G, Carlson J, et al. Genetic variance of SGK-1 is associated with blood pressure, blood pressure change over time and strength of the insulin-diastolic blood pressure relationship. Kidney Int 2005;68:2164–2172. [PubMed: 16221215]

170. Boini KM, Nammi S, Grahammer F, et al. Role of serum- and glucocorticoid-inducible kinase SGK1 in glucocorticoid regulation of renal electrolyte excretion and blood pressure. Kidney Blood Press Res 2008;31:280–289. [PubMed: 18753797]

171. Shi PP, Cao XR, Sweezer EM, et al. Salt-sensitive hypertension and cardiac hypertrophy in mice deficient in the ubiquitin ligase Nedd4-2. Am J Physiol Renal Physiol 2008;295:F462–F470. [PubMed: 18524855]

172. Rexhepaj R, Boini KM, Huang DY, et al. Role of maternal glucocorticoid inducible kinase SGK1 in fetal programming of blood pressure in response to prenatal diet. Am J Physiol Regul Integr Comp Physiol 2008;294:R2008–R2013. [PubMed: 18367651] * In this study mice were mated with either the male or female being a SGK1 knockout mouse, resulting in both cases in heterozygotic offspring. First evidence is provided that maternal signals mediated by SGK1 may play a decisive role in fetal programming of hypertension induced by prenatal protein restriction.

173. Schwab M, Lupescu A, Mota M, et al. Association of SGK1 gene polymorphisms with type 2 diabetes. Cell Physiol Biochem 2008;21:151–160. [PubMed: 18209482]

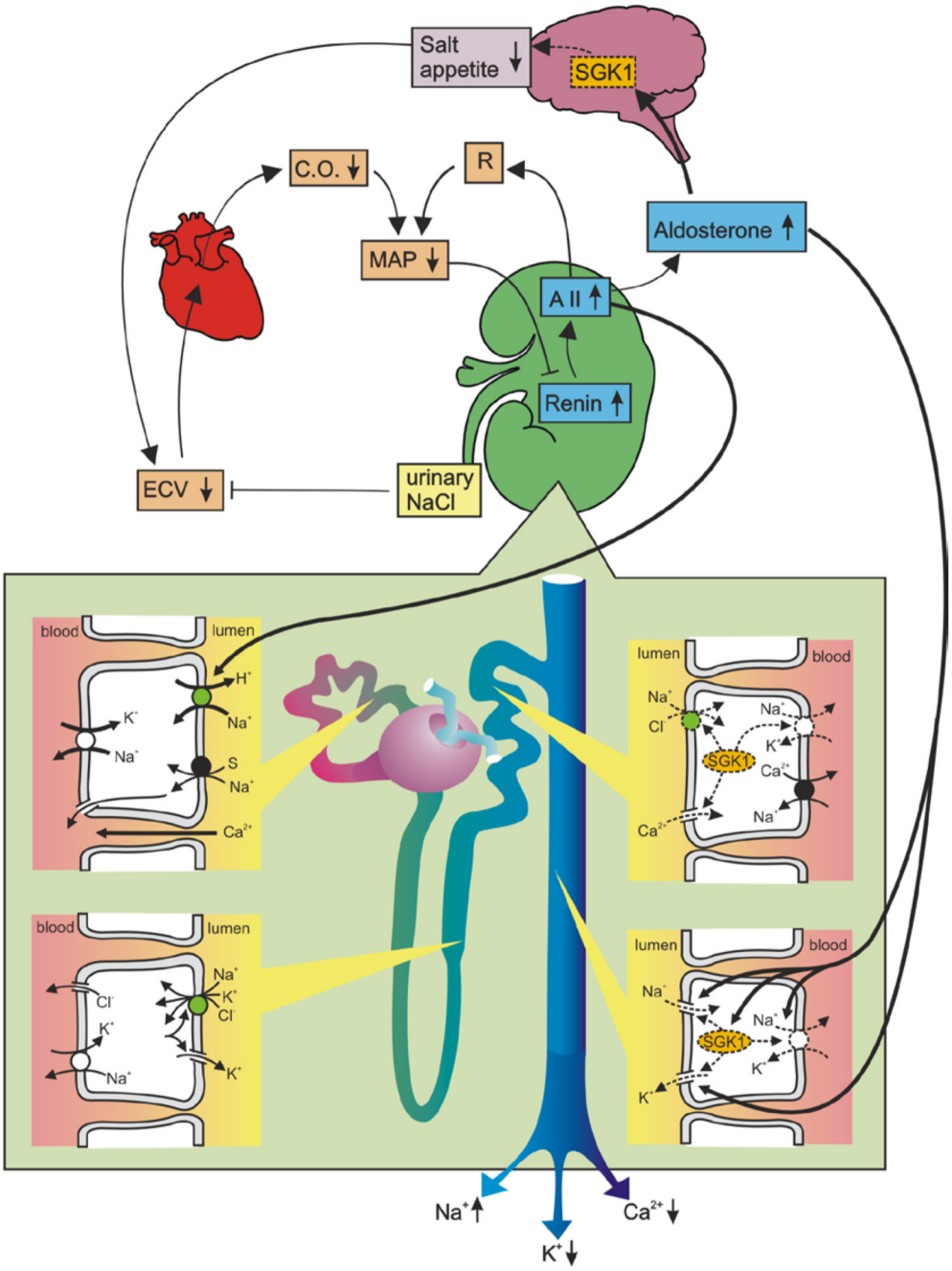

Fig. 1. Renal function in SGK1 deficient mice

SGK1 deficiency decreases NCC and ENaC activity and blunts the stimulation of renal Na^+ reabsorption by insulin and aldosterone as well as the stimulation of salt appetite by mineralocorticoids. The extracellular fluid volume (ECV) contraction decreases cardiac output (C.O.) thus compromising maintenance of mean arterial pressure (MAP) with subsequent stimulation of the renin-angiotensin and aldosterone system. The hyperaldosteronism at least partially reverses the decrease of ENaC, ROMK and Na^+/K^+ ATPase activity in principle cells. Nevertheless, SGK1 deficiency impairs stimulation of renal K^+ excretion during K^+ excess. Despite its stimulation of the distal tubular Ca^{2+} channel TRPV5, lack of SGK1 leads to

anticalciuria due compensatory stimulation of Na^+ (and Ca^{2+}) reabsorption in proximal tubules. (A II = angiotensin II; R= total peripheral vascular resistance).

Table 1

Regulation of SGK1 transcription (due to space limits, only recent original papers are cited, for previous citations see the cited reviews)

Stimulators	References
glucocorticoids	[1,3-7]
mineralocorticoids	[7-9]
gonadotropins	[7]
progestin	[10]
medroxyprogesterone	[11]
1,25-dyhydroxyvitamin D_3 ($1,25(OH)_2D_3$)	[7]
transforming growth factor β (TGFβ)	[7]
interleukin 6	[12]
fibroblast and platelet-derived growth factor	[7]
thrombin	[13]
endothelin	[14]
advanced glycation end products (AGE)	[15]
further cytokines	[7]
activation of peroxisome proliferator-activated receptor γ	[7]
cell shrinkage	[7,16]
chelation of Ca^{2+}	[17]
A6 cell swelling	[17]
excessive glucose concentrations	[7,18]
metabolic acidosis	[19]
salt loading of spontaneously hypertensive mice	[20]
heat shock, UV radiation and oxidative stress	[21,22]
DNA damage	[7]
ischemia	[23]
neuronal injury	[7]
neuronal excitotoxicity	[7]
neuronal challenge by exposure to microgravity	[24]
fear conditioning	[25]
plus maze exposure	[26]
enrichment training	[7]
amphetamine	[7]
lysergic acid dimethylamide LSD	[7]
electroconvulsive therapy	[27]
sleep deprivation	[27]
fluoxetine	[27]
Rett syndrome	[28]
organ rejection	[29]
dialysis	[30]
wound healing	[7]

Stimulators	**References**
diabetic nephropathy	[7,31]
glomerulonephritis	[7]
liver cirrhosis	[7]
fibrosing pancreatitis	[7]
Crohn's disease	[7]
lung fibrosis	[7]
cardiac fibrosis	[32]
Inhibitors	
heparin	[7]
mutations in the gene MECP2	[7,28]
dietary iron	[7]
nucleosides	[33]
Signaling molecules	
protein kinase C	[7]
protein kinase Raf	[7]
mitogen-activated protein kinase (BMK1)	[7]
mitogen-activated protein kinase (MKK1)	[7]
stress-activated protein kinase-2 (SAPK2, p38 kinase)	[7]
Nuclear factor of activated T cells (NFAT) 5	[16]
phosphatidylinositol-(PI)-3-kinase	[7]
cyclic AMP	[7,10]
extracellular signal-regulated kinase (ERK1/2)	[7]
P53	[7]
cytosolic Ca^{2+}	[7]
nitric oxide	[7,34]
EWS/NOR1(NR4A3) fusion protein	[35]

Table 2

Regulation of carriers and transporters by SGK1 (due to space limits, only recent original papers are cited, for previous citations see the cited reviews)

Channel	Function	References
ENaC	Epithelial Na^+ channel	[7,68-77]
ROMK1	Renal outer medullary K^+ channel	[7]
TRPV5	Ca^{2+} channel	[7]
TRPV6	Ca^{2+} channel	[78]
ClCKa/barttin	Cl^- channel	[7,79]
ClC2	Cl^- channel	[7]
CFTR	Cystic fibrosis transmembrane conductance regulator	[80,81]
VSOAC	volume-sensitive osmolyte and anion channel	[7]
SCN5A	Na^+ channel	[7]
KCNE1/KCNQ1	K^+ channel	[7,82]
KCNQ4	K^+ channel	[83]
Kv1.3	K^+ channel	[7,84]
Kv1.5	K^+ channel	[85,86]
Kv4.3	K^+ channel	[87]
ASIC1	acid sensing ion channel	[88]
GluR6	glutamate receptor	[89]
4F2/LAT	cation channel	[7]
NCC	NaCl cotransport	[90]
NKCC2	Na+,K+,2Cl- cotransport	[7]
NHE3	Na^+/H^+ exchanger	[7,91-93]
SGLT1	glucose transporters	[7,94,95]
GLUT1	glucose transporter	[96]
GLUT4	glucose transporter	[97]
ASCT2	amino acid transporter	[97]
SN1	glutamine transporter	[7]
EAAT1	glutamate transporter	[7]
EAAT2	glutamate transporter	[7,98]
EAAT3	glutamate transporter	[7]
EAAT4	glutamate transporter	[7,99]
EAAT5	glutamate transporter	[100]
PepT2	peptide transporter	[101]
NaDC-1	Na^+,dicarboxylate cotransporter	[7]
CreaT	creatine transporter	[102,103]
SMIT	Na^+, myoinositol cotransporter	[104]
NaPiIIb	phosphate carrier	[7,105,106]
Na^+/K^+-ATPase	Na^+/K^+-pump	[7,107]

Table 3

SGK1 sensitive functions (due to space limits, only recent original papers are cited, for previous citations see the cited reviews)

Function	References
Cell volume	[7,126]
Cell survival	[7,127,128]
Cell proliferation	[1,7]
Aldosterone release	[1,7]
Insulin release	[86,86,129]
Glucose metabolism	[130]
Function of decidualizing cells	[10,10]
Gastric acid secretion	[131]
Intestinal transport	[94]
Renal transport	[7,16,90,132]
Proteinuria & nephrotic syndrome	[133-135]
Blood pressure regulation	[7,136,137]
Coagulation	[13]
Pulmonary hypertension	[13]
Cardiac excitation	[7,82,138]
Cardiac hypertrophy	[139,140]
Memory consolidation	[7,24,25,125,141,142]
Pain perception	[143]
Tumor growth and metastasis	[7,39,144-146]
Inflammation and Fibrosis	[7,32,147-150]