

SGK1: A Rapid Aldosterone-Induced Regulator of Renal Sodium Reabsorption

James A. McCormick, Vivek Bhalla,
Alan C. Pao, and David Pearce

Departments of Medicine and
Cellular and Molecular Pharmacology,
University of California-San Francisco,
San Francisco, California
pearced@medicine.ucsf.edu

Recently, substantial progress has been made in understanding the mechanisms by which aldosterone rapidly stimulates sodium transport in the distal nephron and other tight epithelia. Serum- and glucocorticoid-regulated kinase 1 (SGK1) has been identified as an important mediator of this process. Its physiological relevance has been revealed through heterologous expression in cultured cells and generation of SGK1 knockout mice.

Although the majority of Na^+ reabsorption in the kidney tubules occurs in the proximal segments (>85%), most of the regulation takes place in the distal nephron. This is particularly true for the aldosterone-sensitive distal nephron (ASDN), which is comprised of the last third of the distal convoluted tubule, connecting segment, and cortical and medullary collecting ducts (CCD and MCD) (FIGURE 1). Na^+ reabsorption in the ASDN occurs through the epithelial sodium channel (ENaC). Sodium reabsorption along the whole nephron is driven by activity of the basolateral Na^+ - K^+ -ATPase, which generates a low intracellular Na^+ concentration and intracellular electronegativity, both of which provide an electrochemical gradient for Na^+ entry across the apical membrane of the cell. Although <10% of Na^+ reabsorption occurs in the distal nephron, this site plays a key role in fine-tuning plasma volume, as demonstrated by the development of abnormal blood pressure when distal Na^+ reabsorption is perturbed. Genetic defects of the ASDN, including Liddle's syndrome, apparent mineralocorticoid excess (AME), and pseudohypoaldosteronism type I (PHA1), best exemplify the

importance of Na^+ transport in the ASDN. These disorders have been extensively reviewed elsewhere (31, 33).

Na^+ reabsorption by the ENaC-expressing portion of the nephron is highly sensitive to regulation by the mineralocorticoid hormone aldosterone. Aldosterone effects on Na^+ transport are elicited in two stages: the early (1–4 h) and late (after 4 h) phases. The late phase of aldosterone action involves upregulation of ENaC and Na^+ - K^+ -ATPase expression levels (38), as well as alterations in enzymes of intermediary metabolism. However, until recently, little was known about the mechanistic basis of the early phase of aldosterone action. SGK1, a close relative of PKB/Akt, has now been identified as a key mediator of the early phase of aldosterone-dependent Na^+ reabsorption by renal epithelia. Expression of SGK1 overlaps with that of ENaC and mineralocorticoid receptor (MR) (FIGURE 1). SGK1 is also expressed at moderate levels in the glomerulus, and possibly at low levels in the proximal tubule, but is not regulated by aldosterone or glucocorticoids at these sites; the physiological significance of this expression is

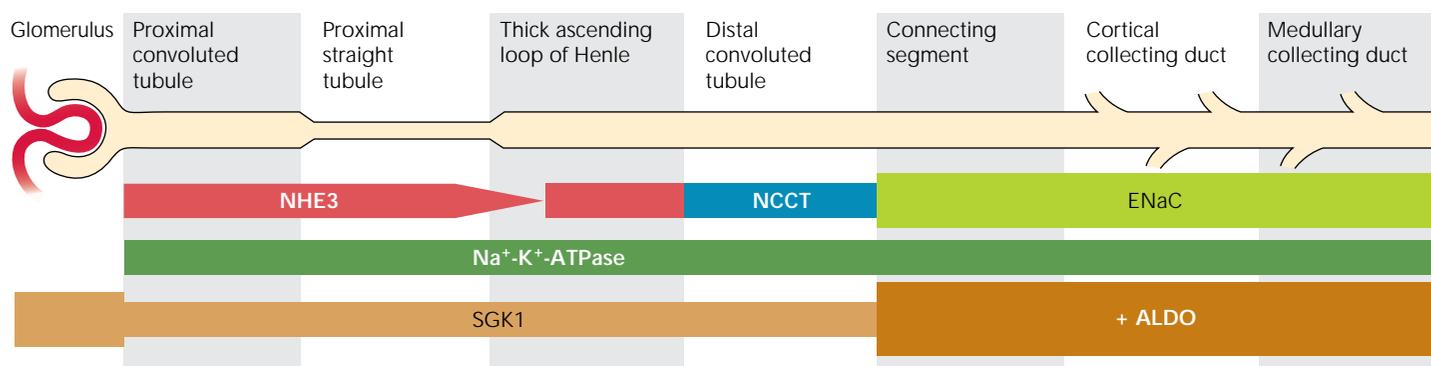


FIGURE 1. Segment-specific expression of renal sodium transporters and SGK1

Sodium transport from the lumen across epithelial cell apical membranes is mediated in the proximal convoluted and straight tubules and in the thick ascending loop of Henle through sodium/proton exchanger 3 (NHE3), in the distal convoluted tubule and connecting segment through the sodium-chloride cotransporter (NCCT), and in the cortical and medullary collecting ducts through the epithelial sodium channel (ENaC). The Na^+ - K^+ -ATPase transports sodium across the basolateral membrane into the blood. The aldosterone-sensitive distal nephron (ASDN) primarily overlaps sites of ENaC expression. Serum- and glucocorticoid-regulated kinase 1 (SGK1) is expressed along the nephron but is strongly induced by aldosterone in the ASDN.

unknown. Thus far, although SGK1 has not been linked to human forms of hypertension, human polymorphisms linking SGK1 to differences in blood pressure have been identified (6). Furthermore, mice lacking SGK1 display impaired Na⁺ homeostasis (see below).

SGK1: Induction by Aldosterone and Stimulation of ENaC in the Distal Nephron

Physiological doses of aldosterone selectively induce SGK1 mRNA expression in the distal nephron of rat kidney within 30 min (5) (FIGURE 1). Induction is likely to be mediated by the MR since it is inhibited by the MR antagonist spironolactone but not by RU-486, a glucocorticoid receptor antagonist. Following the rapid-induction phase, SGK1 levels return to near baseline by 24 h, even in the presence of constant hormone. This phenomenon has been described for both mRNA and protein in cultured cells (7) and in rat kidney (for mRNA only) (5) and may be relevant in limiting the extent of aldosterone action. Hence, defective deinduction of SGK1 expression might also play a role in the pathogenesis of salt-sensitive hypertension. Immunofluorescence has revealed that aldosterone upregulates SGK1 protein expression levels in the Na⁺-transporting principal cells of the collecting duct, but not in the proton-transporting intercalated cells, in a time course consistent with the observed changes in mRNA levels (25). Activation of another member of the nuclear receptor superfamily, peroxisome proliferator-activated receptor (PPAR- γ), also stimulates SGK1 expression and activity in human renal CCD cells, enhancing cell surface expression of ENaC (20). Nonhormonal pathways also induce SGK1 expression: among these, osmotic shock is greatest relevance to epithelial ion transport. Interestingly, both hyper- and hypo-osmotic stress can potentially stimulate SGK1 expression (30, 39) and ENaC-mediated Na⁺ transport (30).

SGK1 was first shown to strongly stimulate ENaC-mediated Na⁺ entry into *Xenopus laevis* oocytes (7, 28) and was subsequently shown to stimulate transepithelial Na⁺ current in A6 cells (2, 17), a widely used model of collecting duct. It is uncertain if the SGK1 effect on Na⁺ entry via ENaC is sufficient to stimulate transepithelial transport or if an additional effect on Na⁺-K⁺-ATPase is required (19). The phenotype of Liddle's syndrome suggests that increased apical entry might be sufficient to increase transepithelial Na⁺ transport.

SGK1 activity, like that of the related serine-threonine kinase PKB/Akt, is dependent on phosphorylation at two serine residues by an effector of phosphoinositol 3-kinase (PI3K) signaling, phospho-

inositide-dependent protein kinase (PDK1) (23). Insulin, an activator of the PI3K pathway, synergizes with aldosterone to stimulate ENaC-dependent sodium transport by A6 cells, and this synergy correlates with increased phosphorylation of SGK1 (40). Furthermore, LY-294002, a PI3K inhibitor, blocked both phosphorylation of SGK1 and ENaC-dependent sodium transport. Together, these data suggest that SGK1 integrates PI3K and mineralocorticoid regulation of epithelial sodium transport.

The mechanism by which SGK1 increases ENaC activity is at least partly due to its ability to increase apical membrane abundance of ENaC. It is unclear whether the greater abundance is the result of increased translocation to, or decreased removal from, the plasma membrane (3, 15). Nontrafficking effects of SGK1 on ENaC, such as an increase in channel open probability, cannot be ruled out either.

SGK1: From Cells to Animals

The physiological relevance of SGK1 in the regulation of Na⁺ transport is best illustrated by the phenotype of the SGK1 knockout mouse (41). On a normal-salt diet, SGK1 knockout mice are indistinguishable from their wild-type counterparts with respect to growth, blood pressure, glomerular filtration rate (GFR), and urinary Na⁺ excretion. Their only sign of aldosterone resistance is a significantly increased aldosterone level compared with wild-type littermates. However, when SGK1 knockout mice are placed on a low-salt diet, they develop more obvious signs of aldosterone resistance, including a decreased ability to retain Na⁺ (FIGURE 2A), low blood pressure (FIGURE 2B), weight loss, and a decline in GFR despite marked elevation of plasma aldosterone. In response to acute K⁺ infusion, SGK1 knockout mice display a less-robust increase in urinary K⁺ excretion than wild-type mice (21); consistent with this finding, chronic K⁺ loading resulted in hyperkalemia (FIGURE 3). Although no discrepancy in daily urinary K⁺ excretion was detectable under these chronic loading conditions, steady-state fractional excretion of K⁺ was reduced. Electrophysiological studies with isolated perfused collecting ducts from SGK1 knockout mice on a high-K⁺ diet demonstrated a decreased amiloride-sensitive transepithelial potential difference compared with that of wild-type mice, suggesting that a defect in Na⁺ reabsorption is ultimately responsible for impaired urinary K⁺ excretion. This is further supported by the observation that apical localization of the potassium channel ROMK in the connecting tubule is enhanced in SGK1 knockout mice compared with that of wild-type mice on a chronic high-K⁺ diet. Coexpression studies are conflicting on the issue of

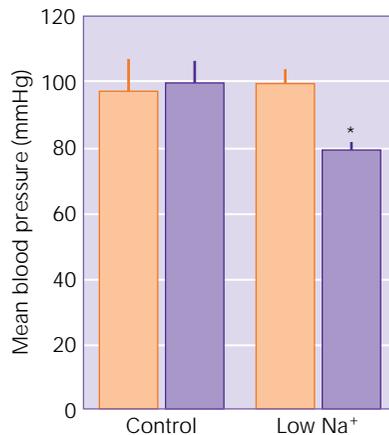
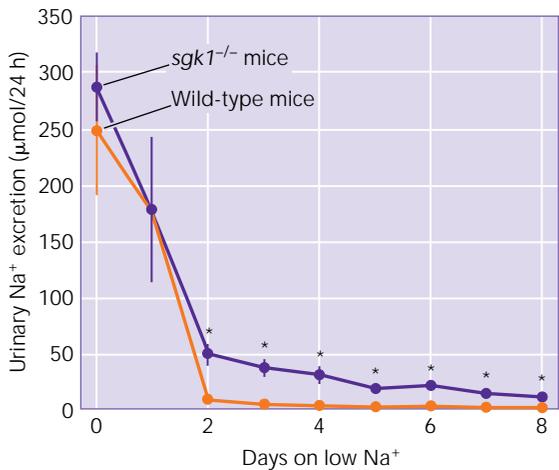


FIGURE 2. SGK1 knockout mice on a low-NaCl diet
SGK1 knockout mice display urinary Na⁺ wasting (A) and hypotension (B) when placed on a low-NaCl (0 g Na⁺/kg) diet (n = 6 each group). *P < 0.05 vs. wild-type mice. Data are from Ref. 41.

direct effects of SGK1 on ROMK. Chen et al. (7) suggested that SGK1 does not stimulate ROMK-mediated K⁺ transport. In contrast, the work of others (42, 43) suggests the opposite. In light of the congruent functional and immunocytochemical data from the SGK1 knockout study (21), we favor the idea that SGK1 most likely does not directly influence ROMK trafficking in the collecting duct and that its effect on renal K⁺ excretion is through its effects on transepithelial potential difference. Additional studies will be needed to resolve this issue.

This relatively mild phenotype is in contrast to mice with targeted disruption of MR (4), the α-ENaC subunit (22), or the β-ENaC subunit (27), which display severe renal salt wasting, hyperkalemia, and early death. This suggests that other compensatory mechanisms for salt reabsorption occur in SGK1 knockout mice that prevent renal salt wasting to the extent observed in MR knockout

mice. Indeed, micropuncture studies of the SGK1 knockout mouse revealed an increase in fractional Na⁺ reabsorption in the proximal tubule (41). These observations suggest that factors independent of SGK1 are involved in the maintenance of ENaC expression in the distal nephron and that SGK1 might only play a role in the acute regulation of perturbations in plasma Na⁺. Such compensatory factors may include other aldosterone-regulated gene products or closely related kinases, although there is no evidence at this time that other SGK isoforms play a role in aldosterone-regulated Na⁺ transport (see below).

Nedd4-2: A Link Between SGK1 and ENaC

In Liddle's syndrome, the PY motif, a COOH-terminal internalization signal, of the β- or γ-ENaC subunit is mutated or deleted, resulting in increased plasma membrane abundance of ENaC and hence gain of function (33). Nedd4 and Nedd4-2 are closely related E3 ubiquitin ligases identified as candidates for regulating ENaC plasma membrane levels. They consist of three or four PY motif-interacting WW domains and a HECT domain, responsible for ubiquitin transfer. When co-injected into *X. laevis* oocytes with ENaC, Nedd4 or Nedd4-2 reduces abundance and hence activity of the channel at the plasma membrane (1, 15), and ENaC subunits lacking PY motifs are unable to interact with either isoform (15, 37). Moreover, intact ENaC channels comprising all three subunits appear to undergo ubiquitinylation and/or endocytosis as well as degradation by the lysosome (15, 37), suggesting that Nedd4 and Nedd4-2 regulate ENaC degradation via ubiquitinylation.

Mounting evidence indicates that Nedd4-2, but not Nedd4, is phosphorylated and regulated by SGK1. Three SGK1 phosphorylation motifs (RXRXXS/T) are present in Nedd4-2 but not in

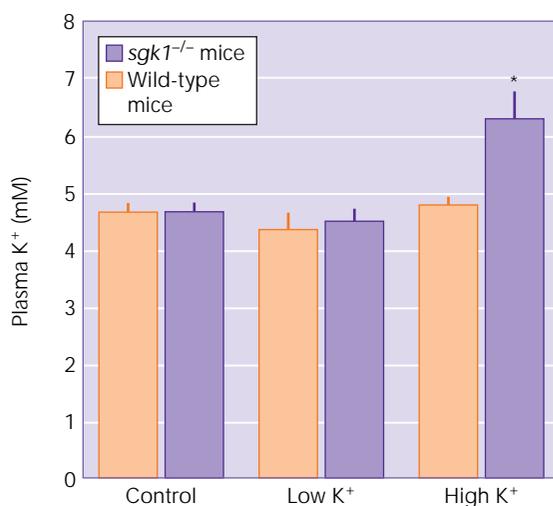


FIGURE 3. Chronic (6-day) dietary K⁺ loading leads to hyperkalemia in SGK1 knockout mice
*P < 0.05 vs. wild-type mice; n = 8. Data are from Ref. 21.

Nedd4, and indeed SGK1 phosphorylates Nedd4-2 but not Nedd4 both in vitro and in vivo (15, 35). In cell culture systems, phosphorylation of Nedd4-2 by SGK1 leads to a disruption of Nedd4-2's ability to interact with ENaC, thereby allowing accumulation of ENaC at the plasma membrane and increased sodium transport (15, 35, 36). The current view of this model is summarized in **FIGURE 4**. Knockdown of Nedd4-2, but not Nedd4, with RNA interference increases ENaC-mediated Na⁺ current in two nonrenal epithelial cell types (36). In these cells, overexpression of a Nedd4-2 mutant in which the SGK1 phosphorylation sites are mutated, preventing SGK1 inhibition, blocks corticosteroid activation of ENaC activity, showing that corticosteroid-dependent ENaC-mediated sodium transport requires phosphorylation of Nedd4-2 (36).

It should be noted that there is also evidence to support SGK1 actions that are independent of Nedd4-2. In particular, the role of the PY motifs of ENaC in SGK1-dependent regulation of ENaC is controversial. Although some studies have shown that SGK1 fails to activate PY motif-deficient ENaC (15, 35), others have found that it still can (3, 10). The action of SGK1 is probably not simply competition between SGK1 and ENaC for binding to Nedd4-2, because SGK kinase activity is required for full stimulation of ENaC and modulation of Nedd4-2 function (35). Alternatively, SGK1 might also stimulate ENaC through mechanisms independent of Nedd4-2. Indeed, SGK1 has been shown to directly interact with the COOH terminus of ENaC through its cat-

alytic domain (40), and this interaction may interfere with the Nedd4-2/ENaC interaction. Although several studies have suggested that SGK1 does not phosphorylate ENaC (3, 32, 40), one recent study identified a functionally important SGK1 phosphorylation site in the COOH terminus of α-ENaC (16).

Recently, two mediators of vasopressin action, cAMP and cAMP-dependent protein kinase (PKA), were found to regulate Na⁺ transport in part by phosphorylating and inhibiting the function of Nedd4-2 (34). Interestingly, the three Nedd4-2 residues phosphorylated by PKA are the same ones phosphorylated by SGK1. The data suggest that cAMP and SGK1 converge at Nedd4-2 in the activation of ENaC, further enhancing the concept of integration of multiple signaling pathways that impact Na⁺ transport: insulin, aldosterone and osmotic effects converging at SGK1, and integration of these signals with cAMP-dependent signals by Nedd4-2.

Multiple SGK/Akt Isoforms: Possible Compensatory Functions in Na⁺ Reabsorption

The sodium-wasting phenotype of SGK1 knockout mice is clearly milder than the severe sodium wasting observed in mice lacking MR (4), the α-ENaC subunit (22), or the β-ENaC subunit (27). Possible compensatory elements include two closely related kinases, SGK2 and 3 (the latter also termed CISK or SGKL), cloned by homology with SGK1 (14, 24),

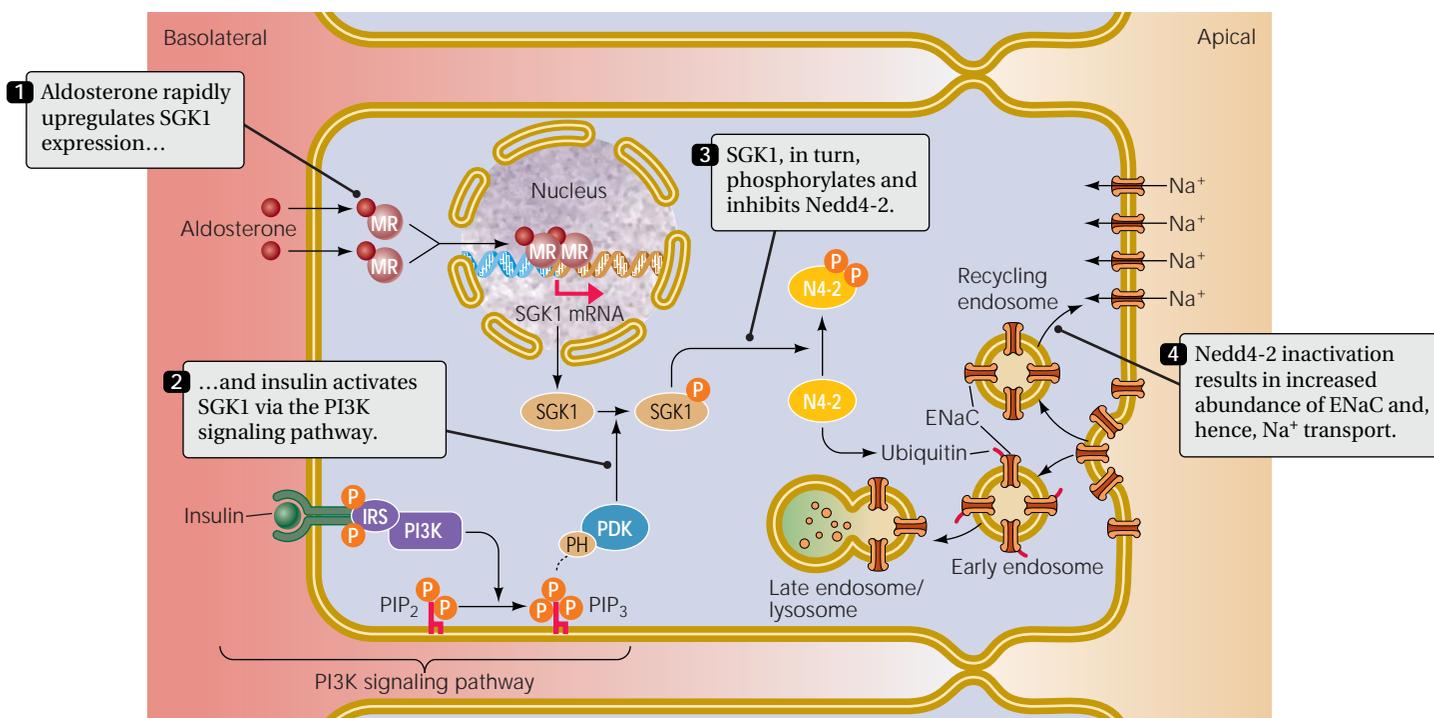


FIGURE 4. Aldosterone and insulin converge to stimulate Na⁺ transport in the principal cells of the mammalian collecting duct. IRS, insulin receptor substrate; PI3K, phosphoinositol 3-kinase; PIP₂, phosphoinositol bisphosphate; PIP₃, phosphoinositol trisphosphate.

that are 75% identical to SGK1 in their kinase domains. Both SGK2 and SGK3 are expressed in the kidney (14, 24), are activated through the PI3K signaling pathway (13, 24), and share in vitro substrates with SGK1 (13, 24), as do the three members of the Akt family. SGK2 and SGK3 both stimulate ENaC (18) and Na⁺-K⁺-ATPase (19) activity when overexpressed in *X. laevis* oocytes, suggesting a possible compensatory role in SGK1 knockout mice. Although SGK2 and 3 are not corticosteroid-regulated in cultured CCD cells (29), they might play a role in regulating basal sodium reabsorption in the distal nephron or become aldosterone-regulated in the context of SGK1 deletion.

Of the six SGK/Akt family members, four have been knocked out in mice: Akt1, Akt2, SGK1, and SGK3 (9, 11, 12, 26). Sodium balance studies have been performed on SGK1 (as described above) and SGK3 knockout mice. Unlike SGK1 knockout mice, mice lacking SGK3 display normal sodium balance when sodium restricted and do not display the aldosterone resistance observed in SGK1 knockout mice (26). SGK1 knockout mice do not show any defect in glucose homeostasis on a normal diet but display a striking and unexpected defect in postnatal hair follicle development. Akt1 and Akt2 knockout mice have not been characterized with regard to possible renal phenotypes. Generation of SGK2 and Akt3 knockout mice and interbreeding of the various knockout mice to generate compound knockouts will be required to fully elucidate the roles of SGK/Akt isoforms in regulating renal sodium reabsorption.

Conclusion

Since the identification of SGK1 as a key aldosterone-induced gene product in the distal nephron, much progress has been made toward understanding its role in regulating renal sodium transport both in vitro and in vivo. More recently, the molecular mechanisms by which it influences ENaC activity through inhibition of Nedd4-2 have taken center stage. Future work will include determining the precise mechanisms and intracellular location of SGK1-mediated ENaC trafficking. SGK1 knockout mice have mild aldosterone resistance that manifests as an inability to sustain adequate sodium balance under conditions of severe sodium restriction. Further use of knockout and transgenic models will help elucidate the full spectrum of SGK1's renal actions. ■

References

1. Abriel H, Loffing J, Rebhun JF, Pratt JH, Schild L, Horisberger JD, Rotin D, and Staub O. Defective regulation of the epithelial Na⁺ channel by Nedd4 in Liddle's syndrome. *J Clin Invest* 103: 667–673, 1999.

2. Alvarez de la Rosa D and Canessa CM. Role of SGK in hormonal regulation of epithelial sodium channel in A6 cells. *Am J Physiol Cell Physiol* 284: C404–C414, 2003.
3. Alvarez de la Rosa D, Zhang P, Naray-Fejes-Toth A, Fejes-Toth G, and Canessa CM. The serum and glucocorticoid kinase sgk increases the abundance of epithelial sodium channels in the plasma membrane of *Xenopus* oocytes. *J Biol Chem* 274: 37834–37839, 1999.
4. Asher C, Sinha I, and Garty H. Characterization of the interactions between Nedd4-2, ENaC, and sgk-1 using surface plasmon resonance. *Biochim Biophys Acta* 1612: 59–64, 2003.
5. Bhargava A, Fullerton MJ, Myles K, Purdy TM, Funder JW, Pearce D, and Cole TJ. The serum- and glucocorticoid-induced kinase is a physiological mediator of aldosterone action. *Endocrinology* 142: 1587–1594, 2001.
6. Busjahn A, Aydin A, Uhlmann R, Krasko C, Bähring S, Szelestei T, Feng Y, Dahm S, Sharma AM, Luft FC, and Lang F. Serum- and glucocorticoid-regulated kinase (SGK1) gene and blood pressure. *Hypertension* 40: 256–260, 2002.
7. Chen SY, Bhargava A, Mastroberardino L, Meijer OC, Wang J, Buse P, Firestone GL, Verrey F, and Pearce D. Epithelial sodium channel regulated by aldosterone-induced protein sgk. *Proc Natl Acad Sci USA* 96: 2514–2519, 1999.
9. Chen WS, Xu PZ, Gottlob K, Chen ML, Sokol K, Shiyanova T, Roninson I, Weng W, Suzuki R, Tobe K, Kadowaki T, and Hay N. Growth retardation and increased apoptosis in mice with homozygous disruption of the Akt1 gene. *Genes Dev* 15: 2203–2208, 2001.
10. Chigaev A, Lu G, Shi H, Asher C, Xu R, Latter H, Seger R, Garty H, and Reuveny E. In vitro phosphorylation of COOH termini of the epithelial Na⁺ channel and its effects on channel activity in *Xenopus* oocytes. *Am J Physiol Renal Physiol* 280: F1030–F1036, 2001.
11. Cho H, Mu J, Kim JK, Thorvaldsen JL, Chu Q, Crenshaw EB 3rd, Kaestner KH, Bartolomei MS, Shulman GI, and Birnbaum MJ. Insulin resistance and a diabetes mellitus-like syndrome in mice lacking the protein kinase Akt2 (PKBβ). *Science* 292: 1728–1731, 2001.
12. Cho H, Thorvaldsen JL, Chu Q, Feng F, and Birnbaum MJ. Akt1/PKBα is required for normal growth but dispensable for maintenance of glucose homeostasis in mice. *J Biol Chem* 276: 38349–38352, 2001.
13. Dai F, Yu L, He H, Chen Y, Yu J, Yang Y, Xu Y, Ling W, and Zhao S. Human serum and glucocorticoid-inducible kinase-like kinase (SGKL) phosphorylates glycogen synthase kinase 3β (GSK-3β) at serine-9 through direct interaction. *Biochem Biophys Res Commun* 293: 1191–1196, 2002.
14. Dai F, Yu L, He H, Zhao Y, Yang J, Zhang X, and Zhao S. Cloning and mapping of a novel human serum/glucocorticoid regulated kinase-like gene, SGK1, to chromosome 8q12.3-q13.1. *Genomics* 62: 95–97, 1999.
15. Debonneville C, Flores SY, Kamynina E, Plant PJ, Tauxe C, Thomas MA, Munster C, Chraïbi A, Pratt JH, Horisberger JD, Pearce D, Loffing J, and Staub O. Phosphorylation of Nedd4-2 by Sgk1 regulates epithelial Na⁺ channel cell surface expression. *EMBO J* 20: 7052–7059, 2001.
16. Diakov A and Korbmayer C. A novel pathway of ENaC activation involves an SGK1 consensus motif in the C-terminus of the channel's α-subunit. *J Biol Chem* 279: 38134–38142, 2004.
17. Faletti CJ, Perrotti N, Taylor SI, and Blazer-Yost BL. Sgk: an essential convergence point for peptide and steroid hormone regulation of ENaC-mediated Na⁺ transport. *Am J Physiol Cell Physiol* 282: C494–C500, 2002.
18. Friedrich B, Feng Y, Cohen P, Risler T, Vandewalle A, Broer S, Wang J, Pearce D, and Lang F. The serine/threonine kinases SGK2 and SGK3 are potent stimulators of the epithelial Na⁺ channel α,β,γ-ENaC. *Pflügers Arch* 445: 693–696, 2003.
19. Henke G, Setiawan I, Bohmer C, and Lang F. Activation of Na⁺/K⁺-ATPase by the serum and glucocorticoid-dependent kinase isoforms. *Kidney Blood Press Res* 25: 370–374, 2002.
20. Hong G, Lockhart A, Davis B, Rahmoune H, Baker S, Ye L, Thompson P, Shou Y, O'Shaughnessy K, Ronco P, and Brown J. PPARγ activation enhances cell surface ENaCα via up-regulation of SGK1 in human collecting duct cells. *FASEB J* 17: 1966–1968, 2003.

21. Huang DY, Wulff P, Volkl H, Loffing J, Richter K, Kuhl D, Lang F, and Vallon V. Impaired regulation of renal K⁺ elimination in the *sgk1*-knock-out mouse. *J Am Soc Nephrol* 15: 885–891, 2004.
22. Hummler E, Barker P, Talbot C, Wang Q, Verdumo C, Grubb B, Gatz J, Burnier M, Horisberger JD, Beermann F, Boucher R, and Rossier BC. A mouse model for the renal salt-wasting syndrome pseudohypoaldosteronism. *Proc Natl Acad Sci USA* 94: 11710–11715, 1997.
23. Kobayashi T and Cohen P. Activation of serum- and glucocorticoid-regulated protein kinase by agonists that activate phosphatidylinositol 3-kinase is mediated by 3-phosphoinositide-dependent protein kinase-1 (PDK1) and PDK2. *Biochem J* 339: 319–328, 1999.
24. Kobayashi T, Deak M, Morrice N, and Cohen P. Characterization of the structure and regulation of two novel isoforms of serum- and glucocorticoid-induced protein kinase. *Biochem J* 344: 189–197, 1999.
25. Loffing J, Zecevic M, Feraille E, Kaissling B, Asher C, Rossier BC, Firestone GL, Pearce D, and Verrey F. Aldosterone induces rapid apical translocation of ENaC in early portion of renal collecting system: possible role of SGK. *Am J Physiol Renal Physiol* 280: F675–F682, 2001.
26. McCormick JA, Feng Y, Dawson K, Behne MJ, Yu B, Wang J, Wyatt AW, Henke G, Grahammer F, Mauro TM, Lang F, and Pearce D. Targeted disruption of the protein kinase SGK3/CISK impairs postnatal hair follicle development. *Mol Biol Cell* 15: 4278–4288, 2004.
27. McDonald FJ, Yang B, Hrstka RF, Drummond HA, Tarr DE, McCray PB Jr, Stokes JB, Welsh MJ, and Williamson RA. Disruption of the β subunit of the epithelial Na⁺ channel in mice: hyperkalemia and neonatal death associated with a pseudohypoaldosteronism phenotype. *Proc Natl Acad Sci USA* 96: 1727–1731, 1999.
28. Naray-Fejes-Toth A, Canessa C, Cleaveland ES, Aldrich G, and Fejes-Toth G. Sgk is an aldosterone-induced kinase in the renal collecting duct. Effects on epithelial Na⁺ channels. *J Biol Chem* 274: 16973–16978, 1999.
29. Naray-Fejes-Toth A, Helms MN, Stokes JB, and Fejes-Toth G. Regulation of sodium transport in mammalian collecting duct cells by aldosterone-induced kinase, SGK1: structure/function studies. *Mol Cell Endocrinol* 217: 197–202, 2004.
30. Rozansky DJ, Wang J, Doan N, Purdy T, Faulk T, Bhargava A, Dawson K, and Pearce D. Hypotonic induction of SGK1 and Na⁺ transport in A6 cells. *Am J Physiol Renal Physiol* 283: F105–F113, 2002.
31. Sartorato P, Khaldi Y, Lapeyraque AL, Armanini D, Kuhnle U, Salomon R, Caprio M, Viengchareun S, Lombes M, and Zennaro MC. Inactivating mutations of the mineralocorticoid receptor in type I pseudohypoaldosteronism. *Mol Cell Endocrinol* 217: 119–125, 2004.
32. Shigaev A, Asher C, Latter H, Garty H, and Reuveny E. Regulation of *sgk* by aldosterone and its effects on the epithelial Na⁺ channel. *Am J Physiol Renal Physiol* 278: F613–F619, 2000.
33. Snyder PM. The epithelial Na⁺ channel: cell surface insertion and retrieval in Na⁺ homeostasis and hypertension. *Endocr Rev* 23: 258–275, 2002.
34. Snyder PM, Olson DR, Kabra R, Zhou R, and Steines JC. cAMP and SGK regulate ENaC through convergent phosphorylation of Nedd4-2. *J Biol Chem* 279: 45753–45758, 2004.
35. Snyder PM, Olson DR, and Thomas BC. Serum and glucocorticoid-regulated kinase modulates Nedd4-2-mediated inhibition of the epithelial Na⁺ channel. *J Biol Chem* 277: 5–8, 2002.
36. Snyder PM, Steines JC, and Olson DR. Relative contribution of Nedd4 and Nedd4-2 to ENaC regulation in epithelia determined by RNA interference. *J Biol Chem* 279: 5042–5046, 2004.
37. Staub O, Abriel H, Plant P, Ishikawa T, Kanelis V, Saleki R, Horisberger JD, Schild L, and Rotin D. Regulation of the epithelial Na⁺ channel by Nedd4 and ubiquitination. *Kidney Int* 57: 809–815, 2000.
38. Verrey F, Schaerer E, Zoerkler P, Paccolat MP, Geering K, Kraehenbuhl JP, and Rossier BC. Regulation by aldosterone of Na⁺,K⁺-ATPase mRNAs, protein synthesis, and sodium transport in cultured kidney cells. *J Cell Biol* 104: 1231–1237, 1987.
39. Waldegger S, Barth P, Forrest JN Jr, Greger R, and Lang F. Cloning of *sgk* serine-threonine protein kinase from shark rectal gland—a gene induced by hypertonicity and secretagogues. *Pflugers Arch* 436: 575–580, 1998.
40. Wang J, Barbry P, Maiyar AC, Rozansky DJ, Bhargava A, Leong M, Firestone GL, and Pearce D. SGK integrates insulin and mineralocorticoid regulation of epithelial sodium transport. *Am J Physiol Renal Physiol* 280: F303–F313, 2001.
41. Wulff P, Vallon V, Huang DY, Volkl H, Yu F, Richter K, Jansen M, Schlunz M, Klingel K, Loffing J, Kauselmann G, Bosl MR, Lang F, and Kuhl D. Impaired renal Na⁺ retention in the *sgk1*-knock-out mouse. *J Clin Invest* 110: 1263–1268, 2002.
42. Yoo D, Kim BY, Campo C, Nance L, King A, Maouyo D, and Welling PA. Cell surface expression of the ROMK (Kir 1.1) channel is regulated by the aldosterone-induced kinase, SGK-1, and protein kinase A. *J Biol Chem* 278: 23066–23075, 2003.
43. Yun CC, Palmada M, Embark HM, Fedorenko O, Feng Y, Henke G, Setiawan I, Boehmer C, Weinman EJ, Sandarasagra S, Korbmacher C, Cohen P, Pearce D, and Lang F. The serum and glucocorticoid-inducible kinase SGK1 and the Na⁺/H⁺ exchange regulating factor NHERF2 synergize to stimulate the renal outer medullary K⁺ channel ROMK1. *J Am Soc Nephrol* 13: 2823–2830, 2002.