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Role of Sgk1 in salt and potassium homeostasis

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Role of Sgk1 in salt and potassium homeostasis. Am J Physiol Regul Integr Comp Physiol 288: R4–R10, 2004; doi:10.1152/ajpregu.00369.2004.—Aldosterone plays a pivotal role in NaCl and K+ homeostasis by stimulation of Na+ reabsorption and K+ secretion in the aldosterone-sensitive distal nephron (ASDN). Recent studies demonstrated that the serum- and glucocorticoid-regulated kinase 1 (Sgk1) is induced by aldosterone in the ASDN and that polymorphisms of the kinase associate with arterial blood pressure in normotensive subjects. This review discusses the role of Sgk1 in NaCl and K+ homeostasis as evidenced by in vivo studies, including those in Sgk1-deficient mice. The studies indicate that Sgk1 is not absolutely required for Na+ reabsorption and K+ secretion in the ASDN. On a standard NaCl and K+ diet, modestly enhanced plasma aldosterone concentrations appear sufficient to establish a compensated phenotype in the absence of Sgk1. The kinase is necessary, however, for upregulation of transcellular Na+ reabsorption in the ASDN. This may involve Sgk1-mediated stimulation of basolateral Na+-K+-ATPase as well as retention of epithelial Na+ channel, ENaC, in the apical membrane. Such an upregulation is a prerequisite for adequate adaptation of 1) renal NaCl reabsorption during restricted dietary NaCl intake, as well as 2) K+ secretion in response to enhanced K+ intake. Thus gain-of-function mutations of Sgk1 are expected to result in renal NaCl retention and enhanced K+ secretion. Further studies are required to elucidate renal and nonrenal aldosterone-induced effects of Sgk1, the role of other Sgk1 activators, as well as the link of Sgk1 polymorphisms to arterial hypertension in humans.

sodium reabsorption; potassium excretion; aldosterone; protein kinases; kidney

NA+ AND CL− are the most abundant ions in extracellular fluid, making body NaCl content a primary determinant of extracellular fluid volume. The homeostasis of body NaCl depends on an adequate adaptation of renal NaCl excretion to NaCl intake. An impaired ability to increase renal NaCl excretion in response to enhanced intake increases body NaCl content. The latter can enhance blood pressure. The subsequent increase of renal NaCl excretion through pressure natriuresis normalizes body NaCl. Thus as originally proposed by Guyton (24), arterial hypertension can serve to overcome an otherwise impaired renal NaCl excretion. Fine tuning of renal NaCl reabsorption and thus excretion involves the aldosterone-sensitive, epithelial Na+ channel (ENaC)-expressing distal nephron (ASDN). This nephron segment begins with the late distal convoluted tubule (DCT) and includes the connecting tubule (CNT) and the cortical and medullary collecting duct. The importance of ENaC is illustrated by loss-of-function mutations of ENaC subunits (12, 56) or the mineralocorticoid receptor (23) that in humans cause pseudohypaldosteronism type 1, characterized by NaCl wasting and hypotension despite elevated levels of aldosterone. Conversely, gain-of-function mutations of ENaC (Liddle’s syndrome) (54) or of the mineralocorticoid receptor (22) lead to severe hypertension. These causes of arterial hypertension, however, are very rare. Therefore, a better understanding of the molecular regulation of renal NaCl reabsorption is required. This is likely to provide the basis for further identification of candidate genes involved in arterial hypertension as well as new targets for antihypertensive therapy. Evidence has now emerged pointing to a significant role of the serum- and glucocorticoid-regulated kinase (Sgk1) in the regulation of ENaC by mineralocorticoids. In this review, recent studies on the role of Sgk1 in NaCl and K+ homeostasis are discussed, including experiments in mice deficient for Sgk1.

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ALDOSTERONE-INDUCED RENAL EXPRESSION AND IN VITRO ASSESSMENT OF SGK1 FUNCTION

The Sgk1 gene encodes a protein of 50 kDa that is a member of the “AGC” family of serine/threonine protein kinases. Its catalytic domain is ~45–60% homologous to the catalytic domains of other serine/threonine protein kinases, such as Akt/protein kinase B, protein kinase A, and protein kinase C-zeta (71). Sgk1 was originally cloned as a glucocorticoid-sensitive gene (20, 71), and renal expression of Sgk1 was indeed shown to be sensitive to glucocorticoids (2, 10, 53). The mineralocorticoid aldosterone plays a major role in the maintenance of NaCl homeostasis during alterations in NaCl intake or extracellular fluid volume, and Sgk1 was shown to be upregulated by aldosterone (for review, see Refs. 20, 49, 63). With regard to in vivo observations, aldosterone treatment of rats was found to increase Sgk1 mRNA in whole kidney (10, 53). Furthermore, feeding a low-NaCl diet for 2 wk markedly increased renal Sgk1 mRNA, which was reversed by 24-h resalination (53). Vice versa, a high-NaCl diet reduced renal Sgk1 mRNA and protein by half (19). A more detailed analysis revealed that aldosterone increases the expression of Sgk1 mRNA (6, 13, 29) and protein (42) along the entire ASDN (summarized in Table 1). With acute single application, the increase in mRNA is seen within 30 min and the Sgk1 protein expression already decreases between 2 and 4 h, indicating a short half-life of Sgk1 (6, 42). In adrenalectomized rats, up-regulation of Sgk1 protein precedes the aldosterone-induced apical translocation of ENaC into the membrane, consistent with a role of Sgk1 in ENaC activation (42). Notably, the rapid in vivo accumulation of Sgk1 and α-ENaC after aldosterone injection takes place along the entire ASDN, whereas the translocation of α-, β-, γ-ENaC to the apical plasma membrane was restricted to its proximal portions, indicating that other factors that follow an axial gradient along the ASDN are, in addition, required for ENaC expression in the cell membrane (42). A similar and persistent effect on Sgk1 mRNA in the ASDN was seen in response to a low-NaCl diet (29).

In vitro studies provided insights as to how activation of Sgk1 could be effective in the ASDN. In Xenopus oocytes expressing the α-, β-, γ-subunits of ENaC, coexpression of Sgk1 leads to a marked upregulation of Na\textsuperscript{+}-channel activity, which results at least in part from increasing ENaC protein abundance in the cell membrane (33, 38, 44, 49, 63). Additional increases of channel activity may be due to Sgk1-mediated increases of ENaC open probability (64). Upregulation of Na\textsuperscript{+}-channel activity was also demonstrated by over-expression of Sgk1 in the A6 model renal cell line (3, 18). Importantly, coexpression of Sgk1 in Xenopus oocytes also stimulates Na\textsuperscript{+}-K\textsuperscript{+}-ATPase (26, 51, 77), and thus Sgk1 may activate both apical and basolateral transport pathways required for transcellular Na\textsuperscript{+} reabsorption in the ASDN with Cl\textsuperscript{−} following through paracellular pathways. These findings are highly suggestive, but do not allow the estimation of the quantitative contribution of Sgk1 to renal NaCl reabsorption and extracellular fluid homeostasis. To address the functional significance of Sgk1 in vivo, mice deficient for Sgk1 were generated (72).

ROLE OF SGK1 IN NaCl HOMEOSTASIS

Targeted disruption of α-ENaC (31, 32), β-ENaC (43), γ-ENaC (4), or the mineralocorticoid receptor (5) in mice was reported to be either not compatible with survival or leading to severe NaCl wasting, demonstrating their essential role for NaCl homeostasis. In comparison, on a standard NaCl diet, mice deficient for Sgk1 (sgk1\textminus/\textminus) developed normally, did not display any gross functional abnormalities, and histology was normal in all organs analyzed, including the kidney (72). Furthermore, no significant difference in blood pressure, glomerular filtration rate (GFR), or renal NaCl excretion have been detected between sgk1\textminus/\textplus and littermate wild-type mice (sgk1\textplus/\textplus). A hint for a renal defect on standard NaCl diet, however, was provided by the observation that sgk1\textminus/\textminus/mice displayed modestly higher plasma aldosterone concentrations (72). Furthermore, plasma K\textsuperscript{+} concentrations under standard NaCl (and K\textsuperscript{+}) diet, as determined in two separate studies, were either not significantly different between genotypes (30) or modestly increased in sgk1\textminus/\textminus vs. sgk1\textplus/\textplus mice (4.7 vs. 4.1 mmol/l) (72). Thus, in the absence of Sgk1, normal NaCl reabsorption was achieved only by enhanced aldosterone release and/or enhanced aldosterone release served to stabilize plasma K\textsuperscript{+} concentrations reflecting an impaired renal ability to excrete K\textsuperscript{+} (see below).

In rats and mice on standard NaCl diet, expression of Sgk1 mRNA was localized to glomeruli, proximal tubule, the ASDN

### Table 1. Expression of Sgk1 in the kidney

<table>
<thead>
<tr>
<th>Expression Under Basal Conditions</th>
<th>Response to Aldo or Low-Na\textsuperscript{+} Diet</th>
</tr>
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<tbody>
<tr>
<td>Glomeruli</td>
<td>Insensitive to Aldo relative to DCT-OMCD in rat and mouse (6, 13, 29)</td>
</tr>
<tr>
<td>Proximal tubule</td>
<td>Insensitive to Aldo in rat (42)</td>
</tr>
<tr>
<td>TALH</td>
<td>Increase of mRNA 30 min after Aldo (1 μg/kg) in distal tubular elements and collecting ducts in both cortex and medulla in rat (6)</td>
</tr>
<tr>
<td>DCT-OMCD</td>
<td>Increase of protein 2 h after Aldo (500 μg/kg sc) in all segment-specific cells of the ASDN in adrenalectomized rats (42)</td>
</tr>
<tr>
<td>IMCD/papilla</td>
<td>Increase of mRNA 3 h after Aldo (150 μg/kg) from DCT to OMCD in mouse (29)</td>
</tr>
<tr>
<td></td>
<td>Increase of mRNA 4 h after Aldo (500 μg/kg sc) in cortical and medullary distal nephron/collecting duct in rat (13)</td>
</tr>
<tr>
<td></td>
<td>Progressive induction of mRNA to low-Na\textsuperscript{+} diet (0.03%) or Aldo for 6 days (50–750 μg/kg/days sc) with highly stimulated tubules first appearing in cortex and continuing downward until strong stimulation throughout outer medulla in mouse (29)</td>
</tr>
</tbody>
</table>

ASDN, aldosterone (Aldo) sensitive distal nephron; DCT, distal convoluted tubule; IMCD, inner medullary collecting duct; MCD, medullary collecting duct; OMCD, outer medullary collecting duct; TALH, thick ascending limb of Henle’s loop.
and very strongly to inner medullary collecting ducts (6, 13, 29, 42, 53). In comparison, no Sgk1 or very low levels of Sgk1 protein expression were detected under basal conditions in glomeruli, proximal tubule, or medullary collecting ducts, including the papilla in rat kidney (2). This dissociation between Sgk1 mRNA and protein expression may indicate some regulation on the translational level. Sgk1 is a cell volume-regulated gene transcriptionally upregulated by cell shrinkage (67), and a more recent study showed Sgk1-mediated osmotic induction of type A natriuretic peptide receptor (NPR-A) gene promoter in cultured cells from rat inner medullary collecting duct (14). Thus Sgk1 may contribute to cell volume regulation in the inner medulla during osmotic challenges, although its protein expression is low under basal conditions. Absence of Sgk1 in mice, however, was found not to impair basal or maximal urinary concentrating ability (72), and thus the role of Sgk1 in the inner medulla remains to be determined. The latter observation further indicated that NaCl transport in the thick ascending limb as well as water transport in the collecting duct, which are both required for maximum urine concentration, are not significantly impaired in the absence of Sgk1.

In sharp contrast to the very mild renal phenotype under normal NaCl diet, restriction of dietary NaCl disclosed that the ability to upregulate renal NaCl reabsorption is significantly impaired in mice lacking Sgk1. This resulted in a significant net NaCl and body weight loss and occurred despite decreased blood pressure and GFR, which are system responses to a NaCl-losing kidney. Micropuncture experiments on the 3rd day of dietary NaCl restriction confirmed a decline of single nephron GFR in sgk1−/− mice and revealed a marked compensating increase of Na+ reabsorption in the proximal tubule (72). The nephron segment most susceptible to induction of ENaC expression and translocation to the apical membrane in response to a low-NaCl diet or aldosterone is the early ASDN, i.e., the late DCT and the CNT (41). Adult mice in general have no superficial glomeruli and therefore distal tubular loops on the kidney surface accessible to micropuncture mostly represent late DCT and CNT (27). Thus at least part of the aldosterone-sensitive segment is upstream to distal micropuncture sites in a normal mouse. This is of interest because fractional reabsorption of Na+ was enhanced in sgk1−/− mice in proximal tubule but was not different up to distal tubular sites, consistent with an Na+ transport defect in a segment including the early ASDN (72).

Electrophysiological analysis of isolated perfused cortical collecting duct on the 3rd day of dietary NaCl restriction revealed an amiloride-sensitive transepithelial potential difference in both sgk1+/+ and sgk1−/− mice; the potential difference, however, was significantly reduced in the absence of Sgk1. In accordance, in both sgk1+/+ and sgk1−/− mice, the α-ENaC subunit was detected by immunohistochemistry in the luminal membrane of the ASDN, predominantly of the early ASDN (72). A blinded semiquantitative analysis, however, indicated that α-ENaC abundance is significantly reduced in the luminal membrane of the early ASDN in mice lacking Sgk1. These studies demonstrate that Sgk1 participates in the upregulation of ENaC in the ASDN but that the kinase is not absolutely required for the insertion of ENaC into the apical membrane. Recent in vitro studies have shown that Sgk1 phosphorylates and presumably thereby inactivates the ubiquitin-ligase Nedd4–2 (15, 55). Consequently, Sgk1 may retard ubiquitination and subsequent degradation of ENaC (15, 55), resulting in an increase in ENaC protein abundance within the cell membrane. The observed increase in aldosterone plasma concentrations in the sgk1−/− mouse is expected to stimulate ENaC insertion into the cell membrane that might, at least partially, compensate for enhanced retrieval. Owing to the residual abundance of ENaC in the cell membrane of sgk1−/− mice, the defect in these mice is relatively mild under normal NaCl diet compared with that of α-ENaC (31, 32), β-ENaC (43), γ-ENaC (4)−, mineralocorticoid receptor-knockout mice (5). In response to dietary NaCl restriction, however, an Sgk1-dependent increase of ENaC in the apical membrane and likely an upregulation of basolateral Na+K+−ATPase are required for an adequate increase of distal NaCl reabsorption and thus maintenance of NaCl homeostasis (Fig. 1).

The above data demonstrate a role of renal Sgk1 in the control of NaCl homeostasis (Fig. 2). Aldosterone, however, affects NaCl homeostasis also by stimulating NaCl uptake through effects on NaCl appetite and NaCl reabsorption in the other epithelia such as the colon. A role for Sgk1 in these

![Fig. 1. Proposed interaction between Sgk1, epithelial Na+ channel (ENaC), and renal outer medullary K+ channel (ROMK) in aldosterone-sensitive distal nephron.](http://ajpregu.physiology.org)
aldosterone-induced effects remains to be established (Fig. 2). Preliminary studies, however, provided evidence that the increase in NaCl appetite in response to the mineralocorticoid DOCA is attenuated in mice lacking Sgk1 (60), indicating that Sgk1 may play at least a dual role in mineralocorticoid-regulated NaCl homeostasis. Sgk1 dependence of both NaCl intake and renal NaCl reabsorption would make the kinase an attractive candidate gene for arterial hypertension, with gain of function mutations stimulating NaCl intake in the presence of aldosterone and a resulting enhanced NaCl appetite and/or NaCl transport in other epithelia such as the colon remains to be established.

**ROLE OF SGK1 IN K\(^+\) HOMEOSTASIS**

In addition to its role for NaCl homeostasis, aldosterone is a major regulator of renal excretion of K\(^+\) and thus of K\(^+\) homeostasis. The key transport molecule in this regard is the renal outer medullary K\(^+\) channel ROMK (66, 70), which is coexpressed with ENaC in the ASDN (41, 65, 73). Luminal ENaC and basolateral Na\(^+-\)K\(^+-\)ATPase are the two transport systems that establish the electrochemical basis for apical K\(^+\) secretion through ROMK. Through its effects on these two transport systems (see above) Sgk1 would be expected to influence renal K\(^+\) excretion. Furthermore, Sgk1 has recently been shown to upregulate ROMK1 activity in vitro (46, 47, 74, 76). Similar to what has been shown for ENaC (1, 42, 68), Sgk1 enhances the abundance of ROMK1 in the cell membrane of Xenopus oocytes (47, 74, 76). Whereas Sgk1 may interact with Nedd4-2 to stimulate ENaC, effects of Sgk1 on cell membrane expression of ROMK could involve interactions with the Na\(^+-\)H\(^+\) exchanger-regulating factor 2 (NHERF2) (76). Beyond that, evidence points to a more direct effect of Sgk1 on ROMK1, as the coexpression of the kinase leads to a small but significant shift of the pH sensitivity of the channel (46, 76).

To test the importance of Sgk1 in vivo, renal excretion of K\(^+\) has been studied in mice lacking Sgk1 (30). These experiments demonstrated an impaired upregulation of renal K\(^+\) excretion in Sgk1-deficient mice in response to both acute and chronic K\(^+\) loading. The actual phenotypes observed, however, were strikingly different. In response to acute K\(^+\) loading, the defect became apparent as an attenuated increase in renal K\(^+\) excretion in sgk1\(^{+/−}\) mice. In comparison, impaired upregulation of renal K\(^+\) excretion in response to chronic K\(^+\) loading was revealed by a renal K\(^+\) excretion in sgk1\(^{−/−}\) mice that was not different from sgk1\(^{+/+}\) mice despite markedly increased plasma concentrations of both K\(^+\) and aldosterone in sgk1\(^{−/−}\) mice, which are the major stimuli of renal K\(^+\) excretion.

A defect in ENaC and/or Na\(^+-\)K\(^+-\)ATPase rather than in ROMK as the dominant cause for the impaired upregulation of K\(^+\) excretion in Sgk1-deficient mice was indicated by the following two observations made under chronic K\(^+\) loading (30). First, immunohistochemistry did not show decreased but enhanced abundance of ROMK channel protein in the apical membrane of the ASDN of Sgk1-deficient mice during high K\(^+\) diet. This observation demonstrated that as for ENaC, Sgk1 is not required for insertion of ROMK into the apical membrane. The findings do not rule out an in vivo stimulating effect of Sgk1 on ROMK channel trafficking to the cell membrane because the lacking influence of Sgk1 could be more than compensated for by the observed hyperkalemia and/or enhanced aldosterone plasma concentrations if these influences enhance apical ROMK abundance partially independent of Sgk1 (Fig. 1). The observation nevertheless suggests that the impaired regulation of renal K\(^+\) elimination in Sgk1-deficient mice is the result of mechanisms other than impaired ROMK expression and ROMK channel trafficking to the cell membrane. Second, and supporting this assumption, electrophysiological experiments in the isolated perfused cortical collecting duct revealed a lower absolute and amiloride-sensitive trans-epithelial potential difference in mice deficient for Sgk1 in response to a high-K\(^+\) diet. This is consistent with a decreased activity of apical ENaC and/or basolateral Na\(^+-\)K\(^+-\)ATPase as the dominant cause for impaired upregulation of renal K\(^+\) elimination in Sgk1-deficient mice. A dominant defect in the apical K\(^+\) channel would be expected to increase rather than decrease the transepithelial potential difference in the collecting duct. The observation that renal K\(^+\) excretion in Sgk1-deficient mice on high-K\(^+\) diet reached similar values as K\(^+\) excretion in wild-type mice indicates that increases in plasma concentrations of K\(^+\) and aldosterone and a resulting enhanced apical abundance of ROMK compensate for the defect in apical ENaC and/or basolateral Na\(^+-\)K\(^+-\)ATPase (Fig. 2).

**Perspectives**

Data obtained in Sgk1-deficient mice demonstrate that the regulation of NaCl and K\(^+\) homeostasis involve Sgk1. More recently, the two isoforms, Sgk2 and Sgk3, have been cloned (35). The renal expression of these two isoforms appears l) significantly lower than Sgk1 (2) and 2) unresponsive to
cortisol or aldosterone (2), but both have been shown to stimulate ENaC activity in Xenopus oocytes (21). It remains to be determined whether they partly compensate for a lack in Sgk1. In addition to the ASDN, the kidney constitutively expresses Sgk1 in glomeruli, thick ascending limb, and possibly early distal convoluted tubule (Table 1), i.e., sites that are not typically considered aldosterone sensitive, although evidence for aldosterone-induced expression of the Na\(^+/\)Cl\(^-\) cotransporter NCC in the early distal convoluted tubule has been reported in rat (45). The functions of Sgk1 at these sites remain to be determined.

Expression studies in Xenopus oocytes demonstrated that Sgk1 could activate a K\(^+\) channel that is formed by KCNQ1 and its regulatory subunit KCNE1 (17). In the S2 and S3 segments of proximal tubule of the kidney, this K\(^+\) channel serves to prevent membrane depolarization during electrogenic reabsorption of Na\(^+\) with glucose (58). Normally, filtered glucose is almost completely reabsorbed in the proximal tubule. Apical entry is accomplished by electrogenic low-affinity Na\(^+\)-glucose cotransporter SGLT2 in the S1 segment and higher affinity SGLT1 in the later S2 and S3 segments. Recent coexpression studies in Xenopus oocytes showed that Sgk1 can activate SGLT1 (16) (whether Sgk1 similarly affects SGLT2 is not known). Similar to what was described for the regulation of ENaC, SGLT1 is regulated by the ubiquitin ligase Nedd4–2 (16). Activation of Sgk1 leads to phosphorylation and thus inhibition of Nedd4–2 binding to its target protein, leading to impaired clearance of SGLT1 protein from the cell membrane. Thus stimulation of Sgk1 enhanced glucose transport by increasing SGLT1 protein abundance in the cell membrane in vitro (16). Whether Sgk1 regulates and coordinates KCNQ1/KCNE1 and SGLT1 in vivo is unclear, and as noted above, Sgk1 mRNA, but not Sgk1 protein, was detected in proximal tubule under basal conditions (2, 42). Clearly, it is possible that under certain conditions the expression of Sgk1 can be stimulated in nephron segments that do not express Sgk1 protein under basal conditions, or the Sgk1 protein level is too low for detection. Similar thoughts apply to a proposed role of Sgk1 in proximal tubule regulation of both the Na\(^+/\)H\(^+\) exchanger NHE3 (75), which controls about 30% of Na\(^+\) and fluid reabsorption at this site (62), as well as the electrogenic Na\(^+\)-coupled dicarboxylate transporter NaDC-1 (9). The proposed regulation of these two transporters by Sgk1 through a mechanism involving NHERF-2 is based on in vitro expression studies and its relevance remains to be confirmed in vivo.

Whereas aldosterone can stimulate the expression of Sgk1, the latter has to be phosphorylated for activation (Fig. 1). Phosphorylation of Sgk1 involves signaling cascades, including phosphatidylinositol 3-kinase and the 3-phosphoinositide-dependent kinases PDK1 and PDK2 (7, 34, 48). Furthermore, aldosterone itself may promote Sgk1 activation by directly increasing the cellular concentrations of phosphatidylinositol [3,4,5]-triphosphate, but the involved mechanisms are not known (8). Other pathways independent of phosphatidylinositol [3,4,5]-triphosphate such as cell–cell and matrix interactions and phosphorylation by protein kinase A (PKA) have also been found to activate Sgk1 (37, 50, 52). Reported PKD-dependent activators of Sgk1 include insulin and growth factors such as insulin-like growth factor (25, 34, 50). Further studies demonstrated a role of Sgk1 in the stimulating effects of insulin and the PKA-activator AVP on Na\(^+\) transport in the A6 model renal cell line (3, 18, 69). Thus Sgk1 may integrate the influences of aldosterone and factors such as insulin, other growth factors, or AVP on renal NaCl reabsorption (18, 69) (see Fig. 1). Considering that insulin can increase renal NaCl reabsorption in the distal nephron and that hyperinsulinemia and enhanced growth hormone levels can be associated with hypertension, it seems possible that Sgk1 mediates these effects on the kidney and thus on blood pressure. Likewise, a possible role of Sgk1 in glucocorticoid-induced renal NaCl retention and arterial hypertension awaits support by functional studies. This also applies to the observation that peroxisome proliferators-activated receptor gamma (PPAR\(\gamma\)) activation enhances cell surface expression of ENaC via upregulation of Sgk1 in human collecting duct cells (28). Activators of PPAR\(\gamma\) are used as antidiabetic drugs, and adverse side effects include volume retention that may involve Sgk1. Furthermore, enhanced expression of Sgk1 was associated with diabetic nephropathy and fibrosis (36, 39). High glucose concentrations can induce the expression of Sgk1 (39), and a hot spot in the early diabetic kidney exposed to and responding to high glucose as well as the site of major changes in NaCl transport and NaCl transport regulation in early diabetes is the proximal tubule (57, 59, 61). Clearly, the roles of Sgk1 in the early diabetic kidney, diabetic nephropathy, and fibrosis remain to be established, and, as for the above aspects, studies in Sgk1-deficient mice are expected to provide significant insights.

A potential role for impaired regulation of Sgk1 in NaCl-sensitive hypertension was suggested from studies in Dahl rats: whereas a high-NaCl diet lowered renal expression of Sgk1 and did not affect blood pressure in Sprague-Dawley rats, the NaCl-sensitive Dahl rats showed an increased renal expression of Sgk1 associated with the increase in blood pressure (19). Unfortunately, the nephron site of enhanced Sgk1 expression was not determined. A significance of Sgk1 for regulation of arterial blood pressure in humans was indicated by the fact that certain polymorphisms of the Sgk1 gene correlate with enhanced blood pressure in twin studies (11). Moreover, the same polymorphisms are associated with increased body mass index (16), which may result from the potential stimulation by Sgk1 of the Na\(^+\)-glucose transporter SGLT1 in the intestine (16). However, at present it is not clear how the polymorphisms influence the expression or function of Sgk1. Further studies are required to establish the functional consequences of these polymorphisms for NaCl, K\(^+\), or glucose transport or induction of NaCl appetite and, most importantly, whether polymorphisms of the Sgk1 gene and/or enhanced activities of Sgk1 correlate with the occurrence of arterial hypertension in humans, which would underline the potential of Sgk1 as an attractive target for novel therapeutic strategies.

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