SGK1 inhibitor reverses hyperglycemia partly through decreasing glucose absorption

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Abstract

This study investigates the effectiveness and mechanisms of a serum- and glucocorticoid-inducible kinase 1 (SGK1) inhibitor in counteracting hyperglycemia. In an in vivo experiment, we demonstrated that after an 8-week treatment with an SGK1 inhibitor, the fasting blood glucose and HbA1c level significantly decreased in db/db mice. RT-PCR and western blot analyses revealed that intestinal SGK1 and sodium glucose co-transporter 1 (SGLT1) expression were enhanced in db/db mice. Treatment with an SGK1 inhibitor decreased excessive SGLT1 expression in the intestine of db/db mice. In vitro experiments with intestinal IEC-6 cells showed that the co-administration of an SGK1 inhibitor partly reversed the SGLT1 expression and glucose absorption that were induced by dexamethasone. In conclusion, this study revealed that the favorable effect of an SGK1 inhibitor on hyperglycemia is partly due to decreased glucose absorption through SGLT1 in the small intestine. These data collectively suggest that SGK1 may be a potent target for the treatment of diabetes and other metabolic disorders.

Introduction

The serum- and glucocorticoid-inducible protein kinase 1 (SGK1) is the newest member of the AGC kinases, initially characterized in rat mammary tumor cells as an immediate early gene induced by serum and glucocorticoids (Webster et al. 1993). SGK1 is ubiquitously expressed and participates in the regulation of transport, hormone release, neuroexcitability, cell proliferation, and apoptosis (Lang et al. 2006). The expression of SGK1 is usually low; however, it dramatically increases under certain pathophysiological conditions, such as glucocorticoid or mineralocorticoid excess, hyperglycemia, cell shrinkage, and ischemia (Lang & Voelkl 2013).

Various functions of SGK1 have been identified (Salker et al. 2011, Borst et al. 2012, Das et al. 2012, Hall et al. 2012). Compelling evidence indicates a role for SGK1 in the development of metabolic syndrome (Lang et al. 2009, Lang & Voelkl 2013). SGK1 upregulates blood pressure, fosters the development of obesity and type 2 diabetes, and augments platelet activation, all key features of metabolic syndrome (Lang & Voelkl 2013). A certain variant of the SGK1 gene (the combined presence of distinct polymorphisms in intron 6 (I6CC) and exon 8 (E8CC/CT)) has been shown to be associated with increased blood pressure (Busjahn et al. 2002, von Wowern et al. 2005), obesity, and type 2 diabetes mellitus (Dieter et al. 2004, Schwab et al. 2008).

The mechanism linking SGK1 with hypertension is well documented. SGK1 stimulates renal tubular salt reabsorption and salt appetite; thus, it impacts blood pressure (Lang et al. 2006). SGK1 inhibitors have been developed and shown to reduce blood pressure in hyperinsulinemic mice but not in Sgk1-knockout mice (Ackermann et al. 2011). The relationship between SGK1 and diabetes is based on the evidence that SGK1
contributes to the development of obesity (Lang et al. 2009). A previous study on Xenopus oocytes demonstrated that heterologously expressed over-activity of SGK1 enhanced the activity of the sodium glucose co-transporter 1 (SGLT1), which serves to absorb intestinal glucose (Dieter et al. 2004). The accelerated glucose absorption could, at least in theory, lead to a more rapid increase in the plasma glucose concentration, an excessive release of insulin, and a subsequent stimulation of lipid deposition in fat tissue (Lang et al. 2009). This process could eventually potentiate the development of hyperglycemia and diabetes. Conversely, inhibitors of SGLT1 have been shown to counteract obesity (Wagman & Nuss 2001).

Currently, nothing is known about how these in vitro observations translate into the physiological and pathological regulation of intestinal function. There is no direct evidence to confirm the role of intestinal SGK1-SGLT1 in the development of obesity and hyperglycemia. Our previous study demonstrated enhanced SGK1 expression in the kidney, intestine, and adipose tissue of subjects with obesity and diabetes (Li et al. 2013). This study was performed to explore the effect of SGK1 inhibitors on metabolic disorders in obese and diabetic mice. Furthermore, we focused on intestinal tissue to determine whether the favorable effect of an SGK1 inhibitor on hyperglycemia is partly due to decreased glucose absorption through SGLT1 in the small intestine.

Materials and methods
Materials
Insulin, dexamethasone, and 3-isobutyl-1-methylxanthine were purchased from Sigma. EMD638683 was provided by Wuxi App Tec Co., Ltd. (Tianjin, China). The inhibitory effect of EMD638683 on SGK1 was tested in vitro by Shang Hai Chempartner Co., Ltd. (Shanghai, China). The rabbit monoclonal antibody against SGK1 was obtained from Cell Signaling Technology. The rabbit polyclonal antibody against SGLT1 was purchased from Merck Millipore. 2-NBDG (2-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxyglucose) was obtained from Invitrogen.

Animal procedures
Male obese 8-week-old db/db (BKS.Cg-m+/-Leprdb/NJU-/-) mice and their lean control male db/m heterozygous littersmates were purchased from the Model Animal Research Center of Nanjing University (Nanjing, China). The mice were maintained on a 12 h light:12h darkness cycle and were fed a standard laboratory diet and water in a room that was controlled for temperature (23 ± 3°C) and humidity (55 ± 15%). db/db mice received either no drug treatment (n=8) or the SGK1 inhibitor (n=8) EMD638683 via chow (4.46 mg EMD638683/g chow) for 8 weeks starting at 10 weeks of age. The dosage of EMD638683 was determined by referring several reports (Ackermann et al. 2011, Towhid et al. 2013). Age-matched db/m mice (n=8) were used as controls in all the experiments.

Body weight was obtained every week from 10 to 18 weeks of age. Food intake and fasting blood glucose were monitored every 2 weeks. HbA1c level was checked at 4 and 8 weeks after intervention using glycosylated hemoglobin analyzer A1CNow+ monitor (Bayer Healthcare LLC, Sunnyvale, CA, USA). Systolic blood pressure was measured in conscious animals using a tail-cuff blood pressure analyzer (BP-98A; Softron Corporation, Japan) every 2 weeks. To estimate glucose tolerance, at 17 weeks of age, mice were fasted for 16 h, and a basal blood sample was collected, followed by an intraperitoneal injection of D(+)glucose (0.5 mg/g of body weight). Blood samples were collected from the tail vein at 30, 60, and 120 min after injection. For the insulin tolerance test, mice were fasted for 12 h, and a basal blood sample was taken, followed by an intraperitoneal injection of human regular insulin (1.5 units/kg of body weight, Novolin R; Novo Nordisk). The blood samples were collected from the tail vein at 30, 60, 120, 150, and 180 min after injection.

Finally, the mice were killed at 18 weeks of age. Blood was collected from the left ventricle and centrifuged, and plasma was stored at −80°C for subsequent analyses. Total cholesterol and triglyceride concentrations were measured by an autoanalyzer (Wako). The proximal intestinal segments (from the pylorus to 14–15 cm above the ileocecal junction) were harvested. Specific tissue samples were either processed for brush-border membrane vesicles (BBMV) preparation, as described later, or rapidly frozen in liquid nitrogen. The tissue samples were stored at −80°C for subsequent RNA and western blot analyses. The Institutional Animal Care and Use Committee of Nanjing University approved our experimental procedures.

IEC-6 cell culture
Rat intestinal epithelial (IEC-6) cells were obtained from the Cell Resource Center of Peking Union medical school.
Research

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DOI: 10.1530/JME-15-0285

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IEC-6 cells were maintained in Dulbecco’s modified Eagle’s medium (containing 4.5 g/L glucose) with 10% fetal calf serum, 5% heat-inactivated fetal bovine serum (FBS; Gibco), 10 IU/mL penicillin G, 100 μg/mL streptomycin sulfate, and 10 mg/L of insulin. Before 24 h of treatment, the IEC-6 cells were incubated in a standard medium containing 1% heat-inactivated FBS. At the time of treatment, the cells were incubated with dexamethasone (10 µM) or dexamethasone (10 µM) plus the SGK1 inhibitor EMD638683 (50 µM). The cells were harvested for RNA and protein analyses after different incubation time points.

Quantitative real-time PCR

The total RNA was extracted from whole tissue samples and IEC-6 cells using Trizol reagent according to the manufacturer’s instructions. Briefly, 2 µg of total RNA was reverse transcribed into cDNA using random primers and SuperScript II reverse transcriptase (Invitrogen). The gene expression was analyzed using relative quantification with the

Figure 1

Effects of an SGK1 inhibitor on hyperglycemia in db/db mice. Db/db mice were fed chow containing either no compound (db/db group, db/db) or EMD638683 at 4.46 mg/g of chow (db/db+EMD group, db/db+EMD) from 10 weeks of age. Db/m mice served as the control (db/m group, db/m). The body weight was obtained every week from 10 to 18 weeks of age. The food intake, fasting blood glucose, and systolic blood pressure were measured every 2 weeks. The HbA1c level was checked at 4 and 8 weeks after intervention. Glucose and insulin tolerance tests were performed at 17 and 18 weeks of age respectively. (A) Body weight. (B) Food intake. (C) Fasting blood glucose. (D) HbA1c. (E) Plasma glucose curves under the glucose tolerance tests. (F) Plasma glucose curves under the insulin tolerance tests. The data are presented as the mean ± s.d., n = 8 mice per group. ### P < 0.001 vs control group of db/m mice. * P < 0.05; ** P < 0.01 vs control group in db/db mice.

Table 1

Effects of the SGK1 inhibitor EMD638683 on metabolic and physiologic parameters in db/db mice.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>db/m</th>
<th>db/db</th>
<th>db/db+EMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>21.8 ± 0.8</td>
<td>40.6 ± 2.1</td>
<td>34.5 ± 1.7</td>
</tr>
<tr>
<td>Food intake (g)</td>
<td>2.9 ± 0.3</td>
<td>4.6 ± 0.5</td>
<td>5.1 ± 0.8</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>118.1 ± 6.0</td>
<td>124.1 ± 6.5</td>
<td>115.4 ± 4.6</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>5.3 ± 1.9</td>
<td>29.3 ± 7.6</td>
<td>17.6 ± 7.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.6 ± 0.1</td>
<td>10.4 ± 1.5</td>
<td>8.9 ± 1.0</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>0.8 ± 0.18</td>
<td>1.5 ± 0.4</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>1.8 ± 0.2</td>
<td>3.9 ± 0.5</td>
<td>2.9 ± 0.1</td>
</tr>
</tbody>
</table>

# P < 0.05, ## P < 0.01 vs db/m mice, * P < 0.05 vs db/db mice. SBP, systolic BP.
2−△△Ct method using real-time PCR with an ABI Prism 7300 instrument (Applied Biosystems). Real-time PCR was performed in 96-well plates using SYBR Premix Ex Taq (Takara, Shiga, Japan) according to the supplier's instructions. All the samples were normalized to values of β-actin, and the results are expressed as fold-changes of the threshold cycle (Ct) value relative to the controls. The cycling parameters were 95°C for 10 s, 40 cycles of 95°C for 5 s, and 60°C for 31 s. The quantifications were performed in quadruplicate, and the experiments were independently repeated three times. The following primers were used: rat β-actin: FP, 5′-TCACCAACTGGGACGATA-3′; and RP, 5′-AGGCCATACAGGAGCAACA-3′; rat Sgk1: FP, 5′-CAGAATTGGGGAATTGTAGC-3′ and RP, 5′-AGAGGGACTTGAGGAGGGTG-3′; rat Sglt1: FP, 5′-GCCCTTTACACCATCACA-3′ and RP, 5′-GCCTCATAACCCTCCTACTCTC-3′; mouse β-actin: FP, 5′-TGTGACGTTGACATCGTAAAGAC-3′; and RP, 5′-TCTCTTGCTCCTACGGCCTG-3′; mouse Sglt1: FP, 5′-TGAGATGCTCTACGGCCTGC-3′ and RP, 5′-GCCCTTTACACCATCACA-3′; and mouse Sglt2: FP, 5′-GTGGCTTTCCCTACGGCCTGC-3′ and RP, 5′-CAGAATGGGGAATTGTAGC-3′.

Preparation of mouse intestinal brush-border membrane vesicles

Crude BBMV were obtained according to the method described by Kessler et al. (1978), with some modifications. BBMV were prepared from IEC-6 cells and a piece of small intestine taken from every animal in each group. The mucosa was re-suspended in a buffer consisting of 300 mM mannitol adjusted to pH 7.1 with Tris. The suspension was then homogenized at 10,000 rpm at 4°C for 1 min. Next, 1 M MgCl2 was added to a final concentration of 10 mM, and the mixture was incubated on ice with continuous ice-cold shaking for 20 min. The mixture was then centrifuged at 3000 × g for 15 min, and the supernatant was collected. After letting the supernatant stand for 15 min, it was finally centrifuged at 30,000 × g for 30 min. The supernatant was discarded, the pellet was re-suspended in the same buffer consisting of 300 mM mannitol, and the centrifugation at 30,000 × g for 30 min was repeated. The final pellet, containing the purified BBMV, was homogenized by passing the suspension through 25-gauge needles and was solubilized in a buffer consisting of 50 mM mannitol. All the steps were carried out at 4°C. After the final suspension, the samples were frozen at 80°C for later use.

Western blot analysis

The expression of transporters SGLT1 in BBMV and SGK1 from mouse small intestinal tissue and rat IEC-6 cell lysates were detected using western blot, as described previously (Li et al. 2013). The protein samples were loaded onto 12% SDS–PAGE gels and transferred onto nitrocellulose membranes following standard procedures.

Figure 2

Effects of an SGK1 inhibitor on intestinal SGLT1 expression in db/db mice. Mice were fed chow containing either no compound (db/m group, db/db group, or db/db + EMD group) or EMD638683 at 4.46 mg/g of chow (db/db + EMD group) from 10 weeks of age, and intestinal tissue was excised at 18 weeks of age and analyzed. (A and B) SGK1 mRNA (A) and protein (B) levels in intestinal tissue from db/m and control db/m mice. (C and D) SGLT1 mRNA (C) and protein (D) levels in intestinal tissue from db/m, db/db, and db/db + EMD mice. The total RNA was isolated from intestinal tissue, and first-strand cDNA was synthesized as described in the Methods section. Real-time quantitative PCR was performed, and the values were normalized to the level of β-actin mRNA. Protein was extracted from the intestinal tissue and subjected to western blot analysis. The relative protein levels were normalized to the GAPDH or β-actin protein level. The bands were quantified through densitometry using the Quantity One system. The results (means ± s.d.) are expressed as the fold change relative to the levels of the db/m group (Con, 100% or 1). *P<0.05 vs control group of db/m mice. **P<0.05 vs control group in db/db mice.
The membranes were incubated with a rabbit anti-SGK1 primary antibody (1:500) or an anti-SGLT1 primary antibody (1:500) overnight at 4–8°C, followed by incubation with horseradish peroxidase-conjugated secondary antibodies for at least 1 h at room temperature. Detection was carried out using enhanced chemiluminescence reagents according to the manufacturer’s protocol (Amersham Pharmacia).

**Glucose uptake measurement using flow cytometry**

The glucose uptake assay using the 2-NBDG screening system was performed as described previously (Zhang et al. 2010). Briefly, IEC-6 cells were seeded at 1×10⁴ cells/well into 96-well plates for 24 h and then treated with or without a given concentration of dexamethasone and 50 µM of the SGK1 inhibitor EMD638683 in the absence or presence of 100 µM 2-NBDG for 1 h. The fluorescence intensity of 2-NBDG was recorded in the FL1 channel using a FACSScano TM flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). To rule out false-positives, drug treatment in the absence of 2-NBDG was measured and considered as the background. The relative fluorescence intensities minus the background levels were used for the data analysis.

**Statistical analysis**

The results were reproduced in at least three independent experiments. The results are presented as the means±s.d. Significance was determined by Student’s t-test or one-way ANOVA. In all the statistical comparisons, a P value<0.05 was considered statistically significant.

**Results**

**Effects of an SGK1 inhibitor on hyperglycemia in db/db mice**

The body weight of db/db mice dramatically increased throughout the entire period of the experiment compared with that of nondiabetic db/m mice (P<0.001, Fig. 1A). A significant decrease was detected in the body weights of db/db mice after 5 weeks of treatment with the SGK1 inhibitor EMD638683 until the end of the experiment (P<0.01; Table 1 and Fig. 1A). There was no difference in

![Figure 3](http://jme.endocrinology-journals.org)

**Figure 3** Effects of an SGK1 inhibitor on SGLT1 expression in IEC-6 cells. IEC-6 cells were serum deprived overnight before dexamethasone and/or the SGK1 inhibitor (EMD638683, EMD) was added. (A and B) SGK1 mRNA (A) and protein (B) expression in dexamethasone (Dex)-treated IEC-6 cells. (C and D) Sglt1 mRNA (C) and protein (D) expression in Dex-treated IEC-6 cells. (E and F) Sglt1 mRNA (E) and protein (F) expression in Dex- and EMD-treated IEC-6 cells. The total RNA was extracted, and real-time quantitative PCR was performed. The relative mRNA levels were normalized to β-actin mRNA expression. The protein was extracted from IEC-6 cells and subjected to western blot analysis. The bands were quantified by densitometry using the Quantity One system. The results (means±s.d.) are expressed as the fold change relative to the levels of the control group (Con, 100% or 1). *P<0.05; **P<0.01; ***P<0.001 vs untreated control cells; ‘’P<0.05 vs Dex-treated cells.
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Diabetic db/db mice exhibited dramatically increased fasting blood glucose and HbA1c levels compared with those of the nondiabetic db/m mice (P<0.001; Table 1, Fig. 1C and D). The fasting blood glucose was decreased and became significant at 2 and 8 weeks after EMD638683 treatment compared with the control db/db mice (P<0.01 and P<0.05, respectively; Fig. 1C). The HbA1c levels were reduced at 4 weeks and were significantly lower at the end of the experiment than in the control db/db mice (P<0.05; Table 1 and Fig. 1D).

The glucose tolerance test demonstrated that EMD638683 treatment significantly suppressed an elevation in plasma glucose after glucose infusion in db/db mice (P<0.01 and P<0.05, respectively; Fig. 1D and E). In the insulin tolerance test, the plasma glucose level of the EMD638683 group tended to be reduced at 15 min and was significantly lower at 120, 150, and 180 min after insulin injection than those of the control group (P<0.05, Fig. 1F).

The treatment of db/db mice for 8 weeks with EMD638683 also significantly reduced the systolic blood pressure and the plasma triglyceride and cholesterol levels compared with the db/db control group (P<0.05, respectively; Table 1).

Effects of an SGK1 inhibitor on intestinal SGLT1 expression in db/db mice

Sgk1 mRNA expression in the intestinal tissue of db/db mice was higher than in the db/m mice (Fig. 2A). We further confirmed excessive intestinal SGK1 expression at the protein level in db/db mice (Fig. 2B).

SGLT1 is highly expressed on the brush-border membrane of villus enterocytes in the proximal part of the small intestine and is responsible for dietary glucose absorption. We examined intestinal SGLT1 mRNA and protein expression in db/db mice. Compared with db/m mice, db/db mice exhibited enhanced intestinal SGLT1 mRNA and protein expression (Fig. 2C and D). Treatment with the SGK1 inhibitor for 8 weeks significantly reduced intestinal SGLT1 mRNA and protein expression in db/db mice (Fig. 2C and D).

Effects of SGK1 inhibitor on SGLT1 expression and glucose absorption in IEC-6 cells

Dexamethasone treatment resulted in a time-dependent increase in SGK1 mRNA and protein expression in rat small intestinal cell lines (IEC-6 cells) (Fig. 3A and B). Simultaneously, dexamethasone enhanced Sglt1 mRNA and protein expression in a time-dependent manner.
(Fig. 3C and D). We additionally performed glucose uptake assays using the 2-NBDG screening system. As suspected, dexamethasone also promoted glucose uptake in IEC-6 cells (Fig. 4A). Co-administration of SGK1 inhibitor decreased the Sglt1 expression and glucose absorption that was induced by dexamethasone (Figs 3E, F and B). In addition, SGK1 inhibitor alone decreased Sglt1 expression but did not affect glucose absorption in IEC-6 cells (Figs 3E, F and B).

Discussion

The role of SGK1 in the development of metabolic syndrome is an interesting and vital topic that has not been fully elucidated. This study clearly showed that (1) an SGK1 inhibitor ameliorated obesity and hyperglycemia in db/db mice; (2) intestinal SGK1 and SGLT1 expression are enhanced in obese and diabetic db/db mice. Treatment with an SGK1 inhibitor decreased excessive intestinal SGLT1 expression in db/db mice; (3) in intestinal IEC-6 cells, the co-administration of an SGK1 inhibitor partly reverses the SGLT1 expression and glucose absorption induced by dexamethasone. This study reveals that an SGK1 inhibitor reverses hyperglycemia in db/db mice partly through decreasing glucose absorption in the small intestine.

This study is the first to demonstrate that the pharmacological inhibition of SGK1 counteracts hyperglycemia in vivo. Of note, both the fasting blood glucose and the HbA1c confirmed the hypoglycemic effect of an SGK1 inhibitor in db/db mice. The effect of weight loss due to an SGK1 inhibitor was observed in a previous study after a 4-day treatment, in which the SGK1 inhibitor decreased the blood pressure in fructose/saline-treated mice (Ackermann et al. 2011). This study confirmed the antihypertensive and weight loss effect of an SGK1 inhibitor in db/db mice during the long term. The food intake of the intervention group remained stable throughout the experiment, which ruled out weight loss owing to a decreased appetite. The fasting blood glucose significantly decreased after 1 week of SGK1 inhibitor treatment. However, the body weight of db/db mice did not change at that time point, which suggests that the hypoglycemic effect is not completely dependent on weight loss. Furthermore, we detected that the triglyceride and total cholesterol levels also decreased in db/db mice after the intervention of SGK1 inhibitor.

SGK1 expression is particularly abundant in the intestine, suggesting a role for the kinase in intestinal transport regulation (Lang et al. 2006). Our group first described that intestinal SGK1 expression is enhanced in obese and diabetic mice (Li et al. 2013). SGLT1 is an intestinal glucose sensor and electrogenic coupler of sodium ions and glucose uptake (Tahran et al. 2013). Fujita et al. (1998) reported that intestinal glucose absorption through SGLT1 was increased in 6-week-old OLETF rats before the onset of insulin resistance and hyperinsulinemia. An SGLT1 inhibitor has been shown to counteract hyperglycemia and obesity (Wagman & Nuss 2001). In accordance with previous studies, this study also detected enhanced intestinal SGLT1 expression in db/db mice. An excessive expression of SGK1 in Xenopus oocytes described the regulatory effect of SGK1 on SGLT1 (Dieter et al. 2004). SGK1 is a mediator of glucocorticoid-initiated signals in different cells (Ullrich et al. 2005, Di Pietro et al. 2010). Previous studies using Sgk1-knockout mice determined that intestinal SGK1 expression was upregulated by dexamethasone, and the effects of glucocorticoids on SGLT1 were fully dependent on SGK1 (Grahammer et al. 2006). Our study confirmed the regulatory effect of SGK1 on SGLT1 and its role as a mediator of glucocorticoids in rat intestinal IEC-6 cells.

This study reveals the effectiveness of an SGK1 inhibitor in decreasing intestinal SGLT1 expression and glucose absorption in vivo and in vitro. This effect may be one of the mechanisms by which the SGK1 inhibitor reverses hyperglycemia in db/db mice. The SGK1 inhibitor may also transiently inhibit SGLT1 and thereby defer and delay glucose absorption along the distal intestine (Oguma et al. 2015). This effect in itself would help reduce the prandial glucose excursion and might increase GLP1 and peptide YY secretion from intestinal L cells (Oguma et al. 2015). Further study is needed to investigate the effect of SGK1 inhibitors on the secretion of incretin.

Excessive glucocorticoids result in whole-body insulin resistance, obesity, and hyperglycemia (Geer et al. 2014). Metabolic syndrome shares many clinical features with excess glucocorticoid or Cushing’s syndrome (Lang et al. 2009). There is speculation that, at least in some individuals, increased glucocorticoid-independent SGK1 expression accounts for metabolic disorders (Lang et al. 2009). SGK1 expression is low in normal tissue, and SGK1-sensitive functions are in large regulated by its isoforms (Lang et al. 2006). Accordingly, the phenotype of the Sgk1-knockout mouse is mild (Lang et al. 2006). Thus, specific inhibition of SGK1 expected to have modest side effects and not abrogate housekeeping functions (Lang & Voelkl 2013). Targeting SGK1 may be a therapeutic option to counteract metabolic disorders.
Until now, several SGK1 inhibitors have been developed, including GSK650394, LY294002, Si113, and EMD638683 (Towhid et al. 2013, D’Antona et al. 2015). Compared with others, EMD638683 is the most selective SGK1 inhibitor (Towhid et al. 2013). Moreover, EMD638683 is readily soluble in water and is the first SGK inhibitor shown to be effective in vivo (Ackermann et al. 2011). A newly published study showed that EMD638683 can decrease the number of colonic tumors following chemical carcinogenesis (Towhid et al. 2013). Our study adds new evidence of the effectiveness of EMD638683 in vivo. Additionally, the 12-week treatment with EMD638683 in this study suggests the long-term safety of this inhibitor in mice.

In conclusion, our results add new evidence of the effectiveness of an SGK1 inhibitor in counteracting hyperglycemia and provide novel insights into targeting SGK1 for the treatment of diabetes and other metabolic disorders. Further study is ongoing in our laboratory to investigate non-intestinal tissues that may be involved in the pathological role of SGK1 in hyperglycemia and obesity.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This work was supported by the National Natural Science Foundation of China (grant numbers 81000350), Jiangsu Province’s Key Discipline of Medicine (XX201105), and Science Fund for Distinguished Young Scholars of Nanjing, China (JQX13010).

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Received in final form 15 February 2016
Accepted 23 February 2016
Accepted Preprint published online 23 February 2016