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Sergliflozin etabonate, a selective SGLT2 inhibitor, improves glycemic control in streptozotocin-induced diabetic rats and Zucker fatty rats

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ABSTRACT

The low-affinity sodium glucose cotransporter (SGLT2) is responsible for most of the glucose reabsorption in the kidney and has been highlighted as a novel therapeutic target for the treatment of diabetes. We discovered sergliflozin etabonate, a novel selective SGLT2 inhibitor, and found that selective inhibition of SGLT2 increased urinary glucose excretion and consequently decreased plasma glucose levels. In this report, we examined the antihyperglycemic effects of sergliflozin etabonate in normal and diabetic rats in comparison with those of a sulfonylurea (gliclazide) and an α-glucosidase inhibitor (voglibose). Sergliflozin etabonate increased urinary glucose excretion in a dose-dependent manner, and inhibited the increase in plasma glucose after sucrose loading independently of insulin secretion in normal rats. Sergliflozin etabonate also improved postprandial hyperglycemia in neonatal streptozotocin-induced diabetic rats; whereas gliclazide did not improve it. In rats with mild or moderate streptozotocin-induced diabetes, the degree of the antihyperglycemic effects of sergliflozin etabonate correlated with the severity of the diabetic condition. Sergliflozin etabonate did not affect the plasma glucose level of normal rats as seen with gliclazide. Chronic treatment with sergliflozin etabonate reduced the levels of glycated hemoglobin and fasting plasma glucose, and improved the glycemic response after glucose loading in Zucker fatty rats. In addition, sergliflozin etabonate did not affect the body weight or food intake. These data indicate that sergliflozin etabonate could improve glycemic control without its use resulting in insulin secretion, hypoglycemia, and body weight gain, and may provide a unique approach to the treatment of diabetes.

1. Introduction

The low-affinity sodium glucose cotransporter (SGLT2) (Wells et al., 1992; Kanai et al., 1994), which is expressed specifically in the kidney tubules, plays a major role in renal glucose reabsorption, with high-affinity sodium glucose cotransporter (SGLT1) (Pajor and Wright, 1992; Wright, 2001), having a supporting role. To date, several drug companies are evaluating SGLT2 inhibitors as a potential new class of antidiabetic drugs (Ashiya and Smith, 2007; Isaji, 2007). In a previous study, we discovered sergliflozin etabonate, a selective SGLT2 inhibitor, which is a prodrug based on benzylphenol glucoside, and validated the critical role of SGLT2 for modulation of the plasma glucose level (Katsuno et al., 2007). Sergliflozin etabonate causes excess glucose to be discarded in the urine by inhibiting renal glucose reabsorption, and controls energy balance in a negative direction (Isaji, 2007; Katsuno et al., 2007).

Type 2 diabetes has increased worldwide in incidence with excessive calorie intake and sedentary lifestyles. The basic management of type 2 diabetes is achieved by lifestyle interventions such as dietary changes and exercise (Nathan et al., 2006). From the point of view of energy balance, sergliflozin etabonate may be a new antidiabetic drug that depends on the same principle as lifestyle intervention (Isaji, 2007). To maintain good glycemic control in diabetic patients, several antidiabetic drugs have been used as treatments; however, these drugs carry some adverse effects. Sulfonylureas stimulate insulin secretion from pancreatic β-cells (Proks et al., 2002), but have the risk of causing hypoglycemia and body weight gain (Salas and Caro, 2002; Hermansen and Mortensen, 2007). α-Glucosidase inhibitors are effective at improving postprandial hyperglycemia by delaying carbohydrate digestion (Baron, 1998), and thus gastrointestinal symptoms are their side effects (Vichayanrat et al., 2002). Thiazolidinediones promote adipocyte differentiation and improve insulin sensitivity (Ferre, 2004), but body weight control may be compromised because glucose is accumulated as fat (Nesto et al., 2004; Hermansen and Mortensen, 2007).

In this report, focusing on the profile of sergliflozin etabonate compared with that of gliclazide, a sulfonylurea, or voglibose, an α-

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glucosidase inhibitor, we examined the potency and safety of sergliflozin etabonate in normal and streptozotocin-induced diabetic rats. Furthermore, we evaluated the effects of acute and chronic treatment with sergliflozin etabonate on hyperglycemia and body weight in Zucker fatty rats, which display hyperinsulinemia and obesity.

2. Materials and methods

2.1. Chemicals

Sergliflozin etabonate (2-[(4-methoxyphenyl)methyl]phenyl 6-*O*-ethoxycarbonyl-β-D-glucopyranoside), sergliflozin (2-[(4-methoxyphenyl)methyl]phenyl β-D-glucopyranoside), gliclazide, and voglibose were synthesized by Kissei Pharmaceutical Co., Ltd. Phlorizin dihydrate and methyl-α-D-glucopyranoside (AMG) were purchased from Sigma-Aldrich (St. Louis, MO). Methyl-α-D-[U-^{14}C]glucopyranoside was obtained from GE Healthcare Bio-Sciences (Little Chalfont, Buckinghamshire, UK).

2.2. Inhibitory effects on rat SGLTs

Rat SGLT1 and SGLT2 expression plasmids were constructed as described previously (Fujimori et al., 2008). Cell culture, transfection procedure and the AMG uptake experiment were performed as described previously (Katsuno et al., 2007; Fujimori et al., 2008).

2.3. Animals

Male Sprague–Dawley (SD) rats and Wistar rats were purchased from Japan SLC, Inc. (Hamamatsu, Japan). Male Zucker fatty rats were obtained from Charles River Japan, Inc. (Yokohama, Japan). These rodents were housed under a 12-h/12-h light cycle (light on 8:00 AM to 8:00 PM) under controlled conditions (room temperature, 20–26 °C; humidity, 35–65%) and fed a laboratory chow diet (CE-2 pellets; CLEA Japan, Inc.) and water *ad libitum*. All animal experiments were performed in accordance with the guidelines approved by the Laboratory Animal Committee of Kissei Pharmaceutical Co., Ltd.

2.4. Urinary glucose excretion in normal and diabetic rats

Male SD rats (5 weeks of age) were intravenously injected with streptozotocin (35 mg/kg, Wako Pure Chemicals, Osaka, Japan) to make them mildly diabetic. Sergliflozin etabonate was suspended (5 ml/kg) in 0.5% sodium carboxymethylcellulose and orally administered to SD rats and mildly diabetic rats (7 weeks of age). Urine was collected for 24 h after administration while the animals were kept in metabolic cages. After the urine volume had been measured, the glucose concentration in the urine was determined using a Glucose B-test Wako (Wako Pure Chemicals), and then the urinary glucose excretion was calculated.

2.5. Oral sucrose tolerance test in normal and diabetic rats

Male SD rats were intraperitoneally injected with streptozotocin (50 mg/kg, Wako Pure Chemicals) 1 day after birth to make neonatal streptozotocin-induced diabetic rats. Male Wistar rats and neonatal streptozotocin-induced diabetic rats (12 weeks of age) were fasted for 16 h. Sergliflozin etabonate, gliclazide or voglibose (5 ml/kg, in 0.1% methylcellulose) and sucrose solution (500 g/l, 5 ml/kg) were administered orally. Blood was obtained in heparinized and aprotinin-treated tubes from a tail vein at each sampling point. Plasma glucose concentrations were determined using a Glucose CII-test Wako (Wako Pure Chemicals). Plasma insulin was determined using an enzyme-linked immunosorbent assay kit (Morinaga Institute of Biological Science, Inc., Yokohama, Japan).

2.6. Acute administration in normal and diabetic rats

Male SD rats (5 weeks of age) were intravenously injected with streptozotocin (35 or 40 mg/kg, Wako Pure Chemicals) to prepare mildly diabetic or moderately diabetic rats, respectively. Sergliflozin etabonate was orally administered to male Wistar rats (12 weeks of age) and to mildly and moderately diabetic rats (7 weeks of age) in the fed condition. Blood was obtained from a tail vein at each sampling point. Blood glucose concentrations were measured with a glucose analyzer, ANTSENSE II (Bayer Medical Ltd., Tokyo, Japan).

2.7. Effects on plasma glucose level in fasted normal rats

Sergliflozin etabonate or gliclazide was orally administered to male Wistar rats (12 weeks of age) after 16-h fasting. Plasma glucose concentrations were measured as described above.

2.8. Acute administration in Zucker fatty rats

Sergliflozin etabonate was orally administered to Zucker fatty rats (18 weeks of age) in the fed condition. Blood glucose concentrations were measured as described above. The area under the curve (AUC) $_{0-6\ h}$ for blood glucose was calculated from the blood glucose concentration.

2.9. Chronic administration in Zucker fatty rats

Sergliflozin etabonate was orally administered to Zucker fatty rats (18 weeks of age) twice daily for 2 weeks. Body weight and food intake were measured per week. At the end of the administration period, glycated hemoglobin was determined using a TOTAL GLYCATED HEMOGLOBIN kit (Sigma-Aldrich). After 2 weeks of administration, the oral glucose tolerance test (400 g/l, 5 ml/kg) was performed. Plasma glucose concentrations were determined as described above. The $AUC_{0-4\ h}$ for plasma glucose was calculated from the plasma glucose concentration during the oral glucose tolerance test.

2.10. Statistical analysis

Data were presented as means ± S.E.M. for each group. Statistical analysis was performed by using SAS Systems Version 8.2 (SAS Institute Inc. Cary, NC). Statistical significance was determined with univariate repeated-measures analysis as a split-plot design and multiple comparisons by each time period or Dunnett's test as appropriate.

3. Results

3.1. Inhibitory effects on rat SGLTs

Orally administered sergliflozin etabonate is metabolized to its active form, sergliflozin, in the body. The inhibitory effects of sergliflozin etabonate, sergliflozin, and phlorizin, a nonselective SGLT inhibitor, on AMG uptake into COS-7 cells transiently transfected with the rat SGLT expression plasmid are shown in Fig. 1. Dose-dependent inhibition was observed with each of these drugs. The Ki values for sergliflozin etabonate, sergliflozin, and phlorizin toward rat SGLTs are shown in Table 1. For rat SGLT2, the inhibitory effect of sergliflozin was twice greater than that of phlorizin, but for SGLT1, it was approximately one-third of that of phlorizin. The ratio of selectivity (Ki value of rat SGLT1/Ki value of rat SGLT2) of sergliflozin and phlorizin was 41 and approximately 7, respectively. These data suggest that sergliflozin, the active form of sergliflozin etabonate, is selective for rat SGLT2.

3.2. Effects on urinary glucose excretion in normal and diabetic rats

Sergliflozin etabonate was orally administered to normal and mildly diabetic rats. In these rats, urinary glucose excretion was

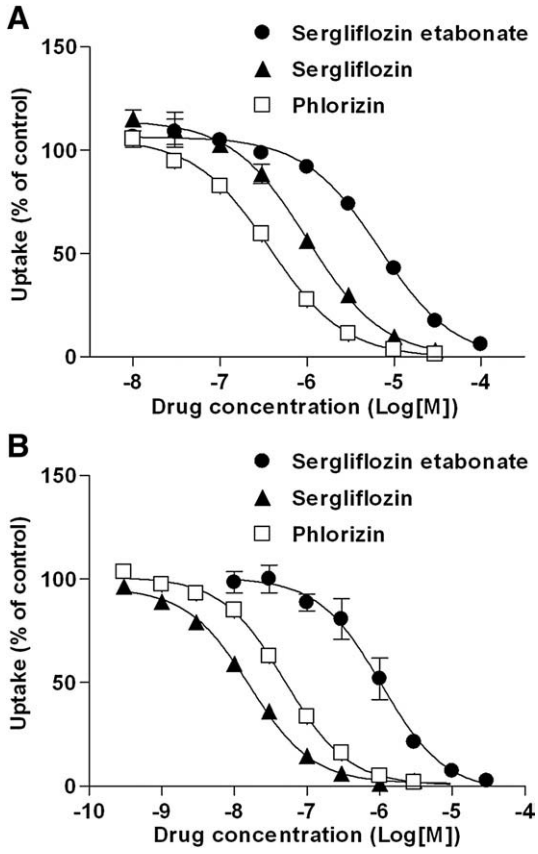

Fig. 1. Inhibitory effects of sergliflozin etabonate, sergliflozin, and phlorizin on rat SGLT1 (A) and SGLT2 (B). The AMG concentration used was 0.3 mM in the uptake buffer. Data are presented as means ± S.E.M. from 3 experiments.

increased by sergliflozin etabonate in a dose-dependent manner (Fig. 2). In the normal rats, no significant changes in urine volume were observed at either dose (10.5 ± 1.9, 9.9 ± 0.8, 9.9 ± 0.7, 11.1 ± 0.6 and 13.2 ± 0.4 ml for 0 (vehicle), 1, 3, 10, and 30 mg/kg group, respectively). In diabetic rats, a diuretic effect was observed at 30 mg/kg (12.6 ± 1.0, 13.4 ± 1.2, 15.5 ± 1.1, 15.3 ± 1.2 and 19.7 ± 2.3 ml for 0 (vehicle), 1, 3, 10, and 30 mg/kg group, respectively). The excretion of glucose into the urine by sergliflozin etabonate was thus enhanced in the diabetic state.

3.3. Effects on postprandial hyperglycemia in the oral sucrose tolerance test

In the oral sucrose tolerance test, the effects of sergliflozin etabonate on postprandial hyperglycemia were compared with those of gliclazide and voglibose. Sergliflozin etabonate, gliclazide, and voglibose dose-dependently inhibited the increase in plasma glucose after sucrose loading in normal rats (Fig. 3A, B, and C). Sergliflozin etabonate and voglibose had a tendency to decrease the plasma insulin level corresponding to the reduction in the plasma glucose level (Fig. 3D and F). On the other hand, gliclazide stimulated the insulin secretion (Fig. 3E). In neonatal streptozotocin-induced diabetic rats, postprandial hyperglycemia was improved by sergliflozin etabonate (1–10 mg/kg) as well as by voglibose (0.01–0.03 mg/kg; Fig. 4A and C); in contrast, gliclazide did not improve the postprandial hyperglycemia in these diabetic rats (Fig. 4B).

Table 1
Ki values of sergliflozin etabonate, sergliflozin, and phlorizin for rat SGLTs.

	Ki value (nM)	
	Rat SGLT1	Rat SGLT2
Sergliflozin etabonate	3350 ± 110	651 ± 149
Sergliflozin	704 ± 254	17.1 ± 2.6
Phlorizin	275 ± 153	41.8 ± 11.4

Data are presented as means ± S.E.M. from 3 experiments. An AMG uptake experiment was performed with COS-7 cells transiently transfected with rat SGLT1 or SGLT2, and the Ki values for each SGLT were calculated.

3.4. Effects of acute administration on blood glucose level in normal and diabetic rats

Next, sergliflozin etabonate was orally administered to normal, mildly diabetic, and moderately diabetic rats in the fed condition. Blood glucose levels in the normal rats were not significantly changed by sergliflozin etabonate (Fig. 5A). In the mildly diabetic and moderately diabetic rats, however, the blood glucose levels were significantly reduced at doses of 3 and 10 mg/kg of sergliflozin etabonate (Fig. 5B and C). The glucose-lowering effect of sergliflozin etabonate persisted for 6 h at the dose of 10 mg/kg in the moderately diabetic

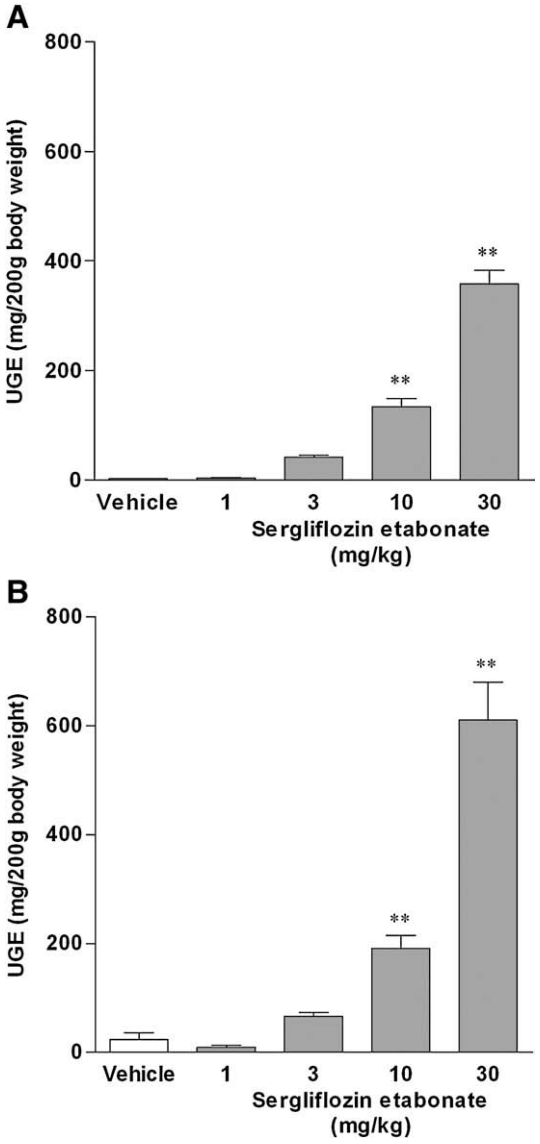

Fig. 2. Sergliflozin etabonate increased urinary glucose excretion (UGE) in normal (A) and mildly diabetic (B) rats. Sergliflozin etabonate was orally administered to normal and mildly diabetic rats. Urine was collected for 24 h after administration of sergliflozin etabonate, and UGE was determined. Data are presented as means ± S.E.M. ($n = 8$). $^{**}P < 0.01$ vs. vehicle group.

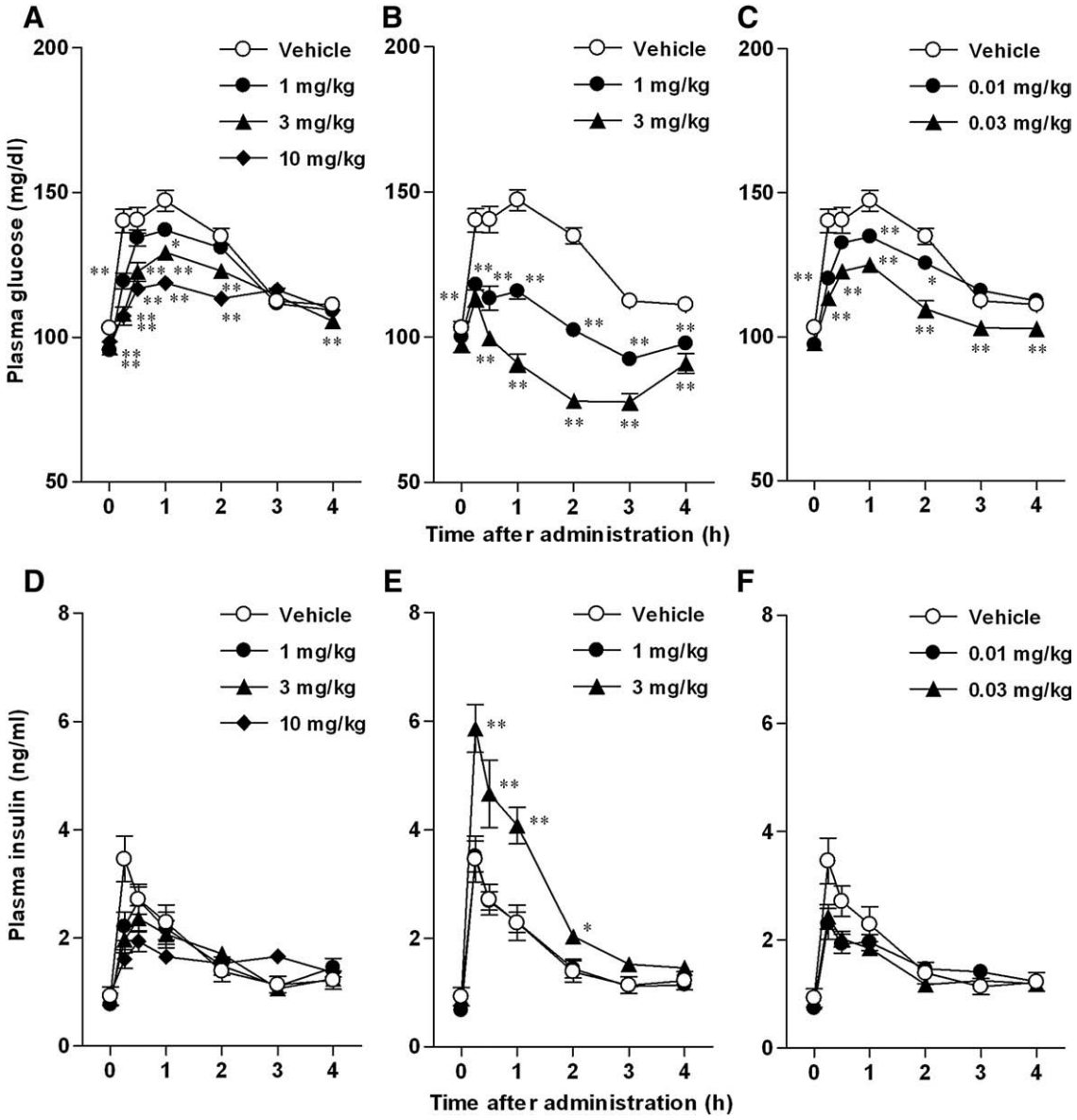

Fig. 3. Effects of sergliflozin etabonate, gliclazide, and voglibose on postprandial hyperglycemia (A, B and C) and insulin secretion (D, E and F) in normal rats during the oral sucrose tolerance test. A and D: sergliflozin etabonate. B and E: gliclazide. C and F: voglibose. Sergliflozin etabonate, gliclazide or voglibose and sucrose solution (2.5 g/kg) were orally administered to normal rats after 16-h fasting. Data are presented as means ± S.E.M. ($n = 8$). $^{*}P<0.05$, $^{**}P<0.01$ vs. vehicle group.

rats (Fig. 5C). The degree of the antihyperglycemic effects of sergliflozin etabonate correlated with the severity of the diabetic condition.

3.5. Effects on plasma glucose level in fasted normal rats

Sergliflozin etabonate did not alter the plasma glucose level in 16-h fasted normal rats (Fig. 6A), but gliclazide caused a hypoglycemia of approximately 60 mg/dl plasma glucose (Fig. 6B). These data suggest that sergliflozin etabonate has a less risk of causing hypoglycemia than gliclazide.

3.6. Antihyperglycemic effects of acute and chronic administration in Zucker fatty rats

In Zucker fatty rats with hyperinsulinemia and obesity, acute administration of sergliflozin etabonate also showed its antihyperglycemic effects at the doses of 3 and 10 mg/kg (Fig. 7A) and reduced the $AUC_{0-6\ h}$ for blood glucose in a dose-dependent manner (Fig. 7B). To examine the effects of chronic administration, we orally administered vehicle or sergliflozin etabonate (10 or 30 mg/kg) to Zucker fatty rats twice daily for 2 weeks. Sergliflozin etabonate affected neither the body weight (622.6 ± 12.4, 614.7 ± 23.2, and 615.8 ± 15.6 g for vehicle, 10 mg/kg group, and 30 mg/kg group, respectively) nor the food intake (30.6 ± 2.0, 29.5 ± 2.5, and 32.1 ± 1.3 g for vehicle, 10 mg/kg group, and 30 mg/kg group, respectively) at the end of the treatment. Sergliflozin etabonate reduced both glycated hemoglobin (Fig. 8A) and the fasting plasma glucose (Fig. 8B) levels in a dose-dependent manner. After 2 weeks of administration, the oral glucose tolerance test was performed. Chronic treatment with sergliflozin etabonate also reduced the value for plasma glucose (Fig. 8B) and the AUC for plasma glucose (Fig. 8C) in a dose-dependent manner during the oral glucose tolerance test.

4. Discussion

We had earlier discovered sergliflozin etabonate (prodrug) and sergliflozin (active form) by means of a screening system using CHO-

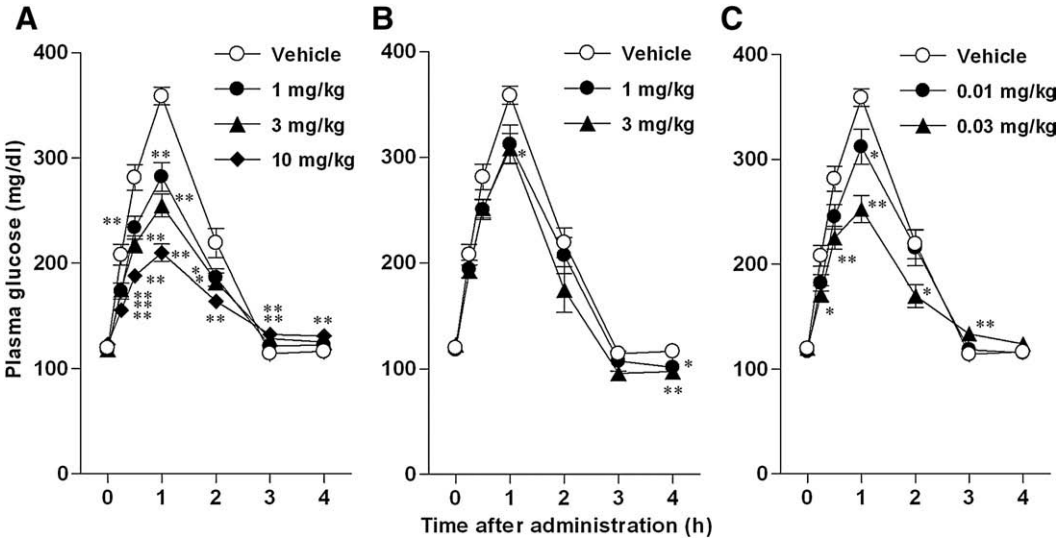

Fig. 4. Effects on postprandial hyperglycemia in neonatal streptozotocin-induced diabetic rats during the oral sucrose tolerance test. A: sergliflozin etabonate. B: gliclazide. C: voglibose. Sergliflozin etabonate, gliclazide or voglibose and sucrose solution (2.5 g/kg) were orally administered to neonatal streptozotocin-induced diabetic rats after 16-h fasting. Data are presented as means ± S.E.M. ($n = 10$). $^{*}P<0.05$, $^{**}P<0.01$ vs. vehicle group.

K1 cells stably expressing human SGLT (Katsuno et al., 2007). In this present study, we evaluated the potency of sergliflozin etabonate and sergliflozin toward rat SGLTs in transiently transfected COS-7 cells, and observed dose-dependent inhibitions by each of these drugs (Fig. 1). Based on the Ki values, we confirmed sergliflozin to be potent and selective for rat SGLT2, with a selectivity ratio of 41 (Table 1). Based on results obtained with a transient expression system similar to ours, Pajor et al. (2008) reported Ki values of sergliflozin for human SGLT1 and SGLT2 of 960 nM and 18 nM, respectively. These data indicate that sergliflozin is potent and selective for human SGLT2, as we showed for rat SGLT2. Thus, there appears to be little species difference in SGLT2 inhibition.

Urinary glucose excretion was increased in a dose-dependent manner by oral administration of sergliflozin etabonate in the normal and mildly diabetic rats. The excretion of glucose into the urine by sergliflozin etabonate was enhanced in the diabetic state. As was shown in Fig. 5, the blood glucose level in normal and mildly diabetic rats was approximately 110 and 200 mg/dl, respectively. Thus, sergliflozin etabonate promoted excretion of glucose in urine depending on the blood glucose level. The increase in urinary glucose excretion by sergliflozin etabonate may be of concern regarding its effects on urine volume and urinary excretion of electrolytes. In a previous study, we reported that sergliflozin etabonate had no obvious effect on urinary electrolyte excretion, though a temporary osmotic diuresis was observed at 30 mg/kg of it (Katsuno et al., 2007). Additionally, in normal rats, repeated administration of sergliflozin etabonate (300 and 1000 mg/kg for 3 weeks) increased the urine volume, but had little effect on urinary electrolyte excretion and plasma electrolyte levels (data not shown). We suppose that sergliflozin etabonate increased urinary glucose excretion without inducing either a marked osmotic diuresis or an electrolyte imbalance at pharmacological doses.

We evaluated the potency of and risk of hypoglycemia with sergliflozin etabonate under normoglycemic and hyperglycemic conditions. In the oral sucrose tolerance test, sergliflozin etabonate suppressed postprandial hyperglycemia in normal and neonatal streptozotocin-induced diabetic rats (Figs. 3A and 4A). Rapid- and

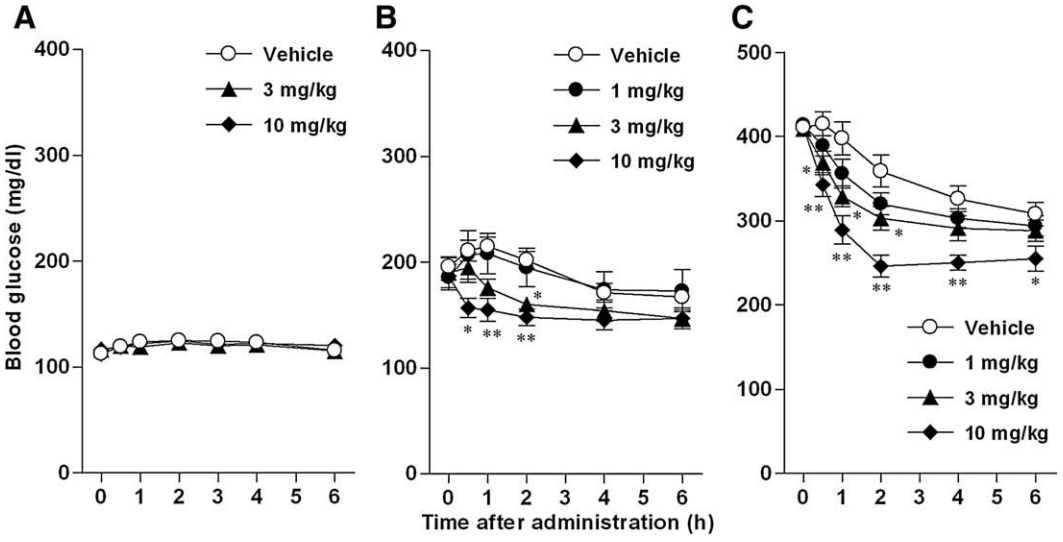

Fig. 5. Effects of sergliflozin etabonate on blood glucose level in normal and diabetic rats. Sergliflozin etabonate was orally administered to fed normal (A), mildly diabetic (B), and moderately diabetic (C) rats. Data are presented as means ± S.E.M. ($n = 6$ for normal rats, $n = 8$ for mildly diabetic rats, and $n = 12$ for moderately diabetic rats). $^{*}P<0.05$, $^{**}P<0.01$ vs. vehicle group.

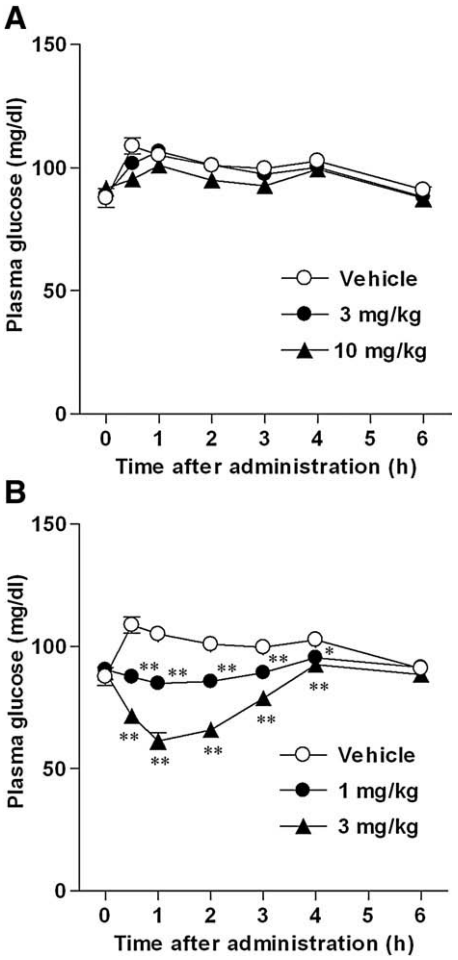

Fig. 6. Effects on plasma glucose level in fasted normal rats. Sergliflozin etabonate (A) or gliclazide (B) was orally administered to normal rats after 16-h fasting. Data are presented as means ± S.E.M. ($n = 6$). *$P<0.05$, **$P<0.01$ vs. vehicle group.

short-acting insulin secretagogues or α-glucosidase inhibitors have often been evaluated in neonatal streptozotocin-induced diabetic rats (Ikenoue et al., 1997; Ichikawa et al., 2002). Sergliflozin etabonate provided a parallel to these antidiabetic drugs as a way of improving postprandial hyperglycemia in these diabetic rats. Gliclazide did not ameliorate the postprandial hyperglycemia in these diabetic rats with impaired insulin secretion, which lack of effect may have been due to the delayed onset of insulin secretion stimulated by gliclazide. In addition, sergliflozin etabonate showed antihyperglycemic effects in rats with either mildly and moderately streptozotocin-induced diabetes in the fed condition; whereas the blood glucose levels in normal rats were not significantly changed (Fig. 5). The reduction in the blood glucose level was increased by sergliflozin etabonate to a greater degree in the hyperglycemic state than in the normoglycemic state. The antihyperglycemic effect of sergliflozin etabonate or voglibose did not depend on increased insulin secretion (Fig. 3, D or F, respectively). In addition, in 16-h fasted normal rats, sergliflozin etabonate did not induce hypoglycemia (Fig. 6), which is a major side effect of sulfonylureas (Salas and Caro, 2002). The lowering of blood glucose without stimulating insulin secretion is a considerable advantage of sergliflozin etabonate for clinical use. In addition, at the time of combination with sulfonylurea, sergliflozin etabonate may reduce the required dose of sulfonylurea. This may preserve the insulin secretion from β-cells and diminish the promotion of weight gain by insulin.

Next, we evaluated the antihyperglycemic effects of sergliflozin etabonate in Zucker fatty rats with hyperinsulinemia and obesity. Sulfonylureas may not be effective in these rats because of hyperinsulinemia. But acute treatment with sergliflozin etabonate showed the antihyperglycemic effects in these rats (Fig. 7), which effect was due to an antihyperglycemic mechanism not dependent on insulin secretion (Fig. 3D). Thiazolidinediones can ameliorate the diabetic condition by improving insulin resistance in this model (Ikeda et al., 1990; Buckingham et al., 1998). Chronic treatment with sergliflozin etabonate reduced both glycated hemoglobin and fasting plasma glucose levels, and improved the glycemic response after glucose loading in Zucker fatty rats (Fig. 8) as well as thiazolidinediones (Minoura et al., 2005, 2007). Additionally, no gastrointestinal side effects such as diarrhea or soft feces as a consequence of inhibition of intestinal SGLT1 were observed in chronically treated Zucker fatty rats. Thus, excretion of excess plasma glucose via urine can contribute to the normalization of glucose metabolism through suppressing glucose toxicity different from the mechanism of thiazolidinediones. Although increases in body weight and food intake have been reported in thiazolidinedione-treated Zucker fatty rats (Wang et al., 1997; de Souza et al., 2001), sergliflozin etabonate affected neither the body weight nor the food intake in these rats. An increase in urinary glucose excretion by sergliflozin etabonate leads to a negative energy

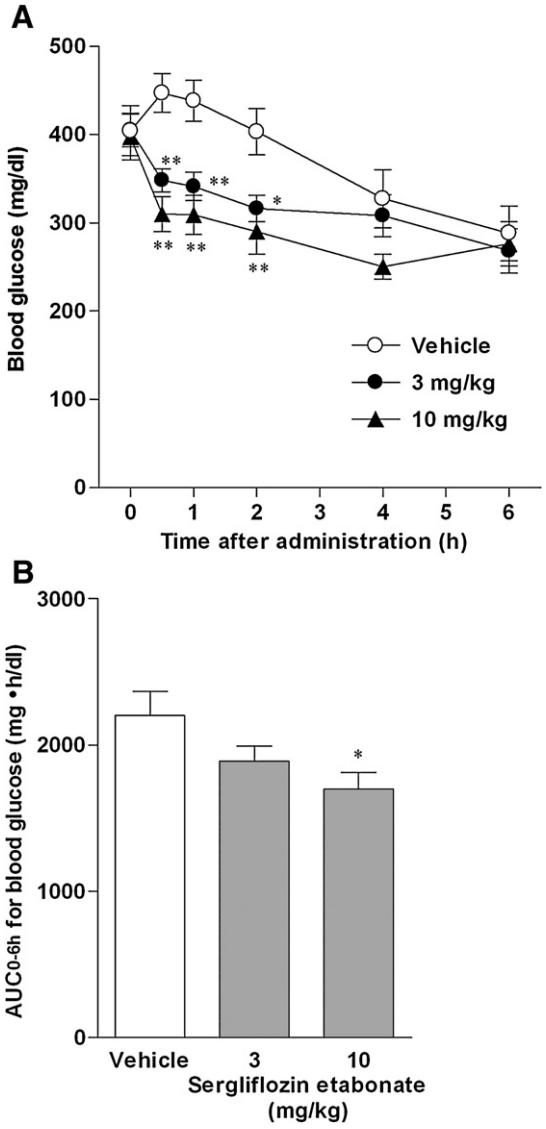

Fig. 7. Acute effects of sergliflozin etabonate in Zucker fatty rats. Sergliflozin etabonate was orally administered to fed Zucker fatty rats. Blood glucose concentrations (A) were measured, and the $AUC_{0-6\ h}$ for blood glucose (B) was calculated. Data are presented as means ± S.E.M. ($n = 7–8$). *$P<0.05$, **$P<0.01$ vs. vehicle group.

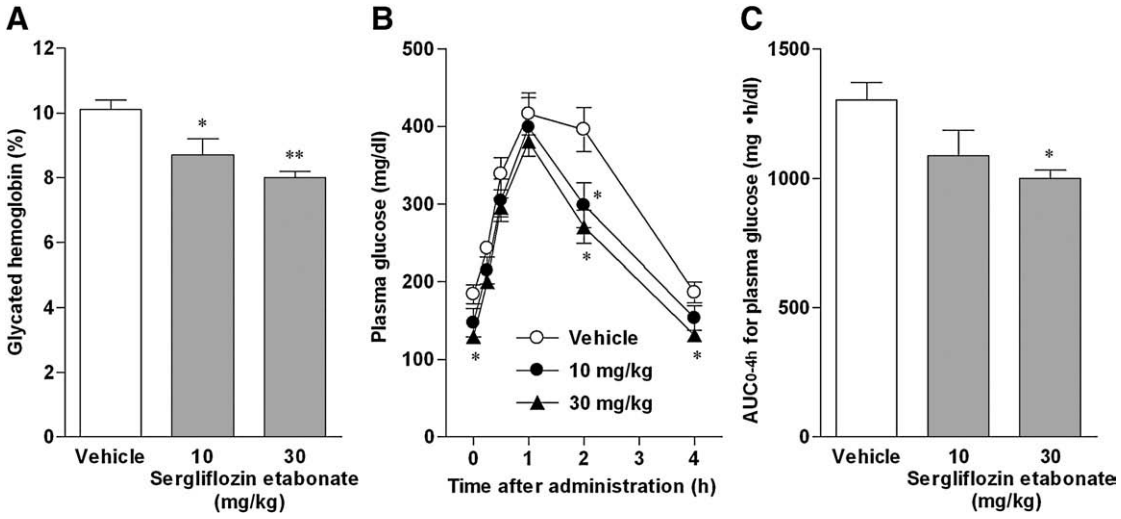

Fig. 8. Chronic effects of sergliflozin etabonate in Zucker fatty rats. Sergliflozin etabonate was orally administered to Zucker fatty rats twice daily for 2 weeks. At the end of the administration period, glycated hemoglobin (A) was determined; and the oral glucose tolerance test (2 g/kg) was performed. Plasma glucose concentrations (B) were measured, and the $AUC_{0-4\ h}$ for plasma glucose (C) was calculated from the plasma glucose concentration during the oral glucose tolerance test. Data are presented as means ± S.E.M. ($n = 4–5$). $^{*}P<0.05$, $^{**}P<0.01$ vs. vehicle group.

balance. Thus chronic treatment with sergliflozin etabonate was beneficial for suppressing body weight gain in addition to improving the glycemic control.

Several drug companies are developing SGLT2 inhibitors for the treatment of diabetes, and have confirmed the therapeutic potency and safety of SGLT2 inhibitors compared with those of other antidiabetic drugs. In this study, we demonstrated that sergliflozin etabonate increased urinary glucose excretion, and consequently improved hyperglycemia in correlation with the blood glucose level. Sergliflozin etabonate did not induce hypoglycemia or excessive insulin secretion. Chronic treatment with sergliflozin etabonate reduced the levels of glycated hemoglobin and fasting plasma glucose without inducing any gain in body weight. These properties of sergliflozin etabonate enable it to be suitable for blood glucose control with body weight control and prevention of exhaustion of the pancreatic β-cells. In this sense, sergliflozin etabonate has several advantages compared with sulfonylureas and thiazolidinediones. We suggest that sergliflozin etabonate may have a unique profile as an antidiabetic drug by improving glycemic control without its use resulting in insulin secretion, hypoglycemia or body weight gain.

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