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Full paper

Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects

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ABSTRACT

The sodium-glucose cotransporter (SGLT) 2 offer a novel approach to treating type 2 diabetes by reducing hyperglycaemia via increased urinary glucose excretion. In the present study, the pharmacokinetic, pharmacodynamic, and pharmacologic properties of all six SGLT2 inhibitors commercially available in Japan were investigated and compared. Based on findings in normal and diabetic mice, the six drugs were classified into two categories, long-acting: ipragliflozin and dapagliflozin, and intermediate-acting: tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin. Long-acting SGLT2 inhibitors exerted an antihyperglycemic effect with lower variability of blood glucose level via a long-lasting increase in urinary glucose excretion. In addition, ipragliflozin and luseogliflozin exhibited superiority over the others with respect to fast onset of pharmacological effect. Duration and onset of the pharmacologic effects seemed to be closely correlated with the pharmacokinetic properties of each SGLT2 inhibitor, particularly with respect to high distribution and long retention in the target organ, the kidney. While all six SGLT2 inhibitors were significantly effective in increasing urinary glucose excretion and reducing hyperglycemia, our findings suggest that variation in the quality of daily blood glucose control associated with duration and onset of pharmacologic effects of each SGLT2 inhibitor might cause slight differences in rates of improvement in type 2 diabetes.

1. Introduction

Due to increasing prevalence of obesity and physical inactivity, the number of patients with diabetes is dramatically increasing and is expected to rise to 366 million worldwide by 2030 (1). Approximately 90% of all patients with diabetes have type 2 diabetes, a progressive metabolic disease characterized by hyperglycemia and relative insulin deficiency as a result of impaired insulin secretion from pancreatic β-cells or insulin resistance. Chronic hyperglycemia leads to progressive impairment of insulin secretion, exacerbates insulin resistance, and worsens diabetes (2). However, while many antidiabetic drugs have been developed and used for treatment, most type 2 diabetic patients' therapeutic goals are still not achieved (3), highlighting the need for efficient new therapeutic strategies for treating type 2 diabetes, including combination therapy.

In recent years, inhibitors of sodium-glucose cotransporter (SGLT) 2, which can inhibit reabsorption of glucose by blocking SGLT2 and stimulate glucose excretion in the urine, have been proposed as novel drugs for treating type 2 diabetes (4), with several shown to improve hyperglycemia in this patient population (5). Although many studies have focused on nonclinical and clinical pharmacologic effects of SGLT2 inhibitors (6,7), most have examined these compounds on an individual basis, with only one study comparing several SGLT2 inhibitors in terms of *in vitro* inhibitory activity and selectivity for SGLT2 (8) and none comparing their *in vivo* effects.

Here, to clarify and compare the pharmacological properties of all six SGLT2 inhibitors commercially available in Japan (ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin), we conducted pharmacokinetic, pharmacodynamic, and pharmacologic experiments in normal and type 2 diabetic mice.

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2. Materials and methods

2.1. Materials

Ipragliflozin (9), dapagliflozin (10), tofogliflozin (11), canagliflozin (12), empagliflozin (8), and luseogliflozin (13) were synthesized at Astellas Pharma Inc. (Ibaraki, Japan) and suspended in 0.5% methylcellulose solution for oral administration. Drugs were administered around the beginning (19:00) of the active period of mice, which corresponds to the administration timing in clinical practice. Doses of drugs were expressed as the free base form.

2.2. Animals

Male ICR (normal) mice for investigating pharmacokinetic and pharmacodynamic properties were purchased from Japan SLC, Inc. (Shizuoka, Japan). Male C57BL/6 (normal) and KK/A^y type 2 diabetic mice for investigating pharmacologic effects were purchased from CLEA Japan (Kanagawa, Japan). The diabetic mice were uniformly grouped by blood glucose levels. All animals were housed under conventional conditions with controlled temperature, humidity, and light (12-h light–dark cycle) and were provided with standard commercial diet and water *ad libitum*. All animal experimental procedures were approved by the Institutional Animal Care and Use Committee of Astellas Pharma Inc. Astellas Pharma Inc., Tsukuba Research Center was awarded Accreditation Status by the AAALAC International.

2.3. Pharmacokinetics

After oral administration of each SGLT2 inhibitor (3 mg/kg) to nonfasting normal mice in the evening (19:00), blood was withdrawn from the abdominal vena cava, and tissues (kidney, liver, and brain) were isolated under isoflurane anesthesia at designated time points for up to 24 h. Isolated tissues were homogenized with phosphate-buffered saline. The plasma and tissue concentrations of the test drug were measured using high-performance liquid chromatography (HPLC). Acetonitrile (100 μL) and methyl tert-butyl ether (100 μL) were added to the plasma or tissue homogenate (100 μL), mixed, and centrifuged (15,000 rpm, 10 min). The supernatant was transferred to a tube and evaporated in a vacuum centrifugal concentrator, and the residue was dissolved in the mobile phase for use as the assay sample. Concentrations of drug in assay sample were analyzed using HPLC with an ultraviolet detector (ipragliflozin and tofogliflozin: 265 nm, dapagliflozin, canagliflozin, empagliflozin, and luseogliflozin: 280 nm) and a 4.6 × 250-mm reversed-phase ODS-80Ts column (Tosoh, Tokyo, Japan). The column temperature was maintained at 60 °C, the mobile phase used was acetonitrile/20 mM ammonium acetate solution (60/40 [v/v]), and the flow rate was 1 mL/min. The pharmacokinetic parameters, maximum plasma/tissue concentration (C_{max}), time to C_{max} (T_{max}), elimination half-life ($t_{1/2}$), and area under the plasma/tissue drug concentration–time curve (AUC) for 24 h, were calculated.

2.4. Pharmacodynamics

Each SGLT2 inhibitor (ipragliflozin and dapagliflozin: 0.3–3 mg/kg, tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin: 1–10 mg/kg) was administered orally in the evening (19:00) to the normal mice under nonfasting conditions. Spontaneously voided urine was collected every 6 h throughout the first 24 h after dosing while the animals were kept in metabolic cages under nonfasting conditions. After the urine volume was measured, the glucose concentration in the urine was measured using the Glucose CII test reagent (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

2.5. Effects of SGLT2 inhibitors on blood glucose and plasma insulin levels

Each SGLT2 inhibitor (ipragliflozin and dapagliflozin: 0.01–3 mg/kg, tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin: 0.03–10 mg/kg) was administered orally in the evening (19:00) to diabetic mice, and blood samples were obtained from a tail vein at each sampling point for up to 24 h under nonfasting conditions. Blood sampling during nighttime (dark period) was performed using a spotlight to minimize lighting, taking special care not to affect food consumption or related parameters. Blood glucose concentrations were measured as described above. Plasma insulin levels were measured using an ultra-high sensitive mouse insulin enzyme-linked immunosorbent assay (ELISA) kit (Morinaga Institute of Biological Science, Inc., Kanagawa, Japan).

2.6. Effects of SGLT2 inhibitors on glucose tolerance during the oral glucose tolerance tests

Durability experiment: Each SGLT2 inhibitor (3 mg/kg) was administered orally in the evening (19:00) to diabetic mice fasted for half a day, and glucose solution (2 g/kg) was orally loaded 0.5, 6, and 12 h after drug administration. Blood samples were obtained at each sampling point.

Rapid-onset experiment: Each SGLT2 inhibitor (3 mg/kg) was administered orally in the evening (19:00) to diabetic mice fasted for half a day at 30 min before, 5 min before, or 10 min after oral loading of glucose solution (2 g/kg). Blood samples were obtained at each sampling point.

2.7. Statistical analysis

The experimental results are expressed as the mean, mean ± standard deviation (SD), or mean ± standard error of means (SEM). The AUCs were calculated from blood glucose and plasma insulin concentrations measured over time. Significance of differences between normal and diabetic vehicle groups was assessed using Student's *t*-test, while that between the vehicle- and drug-treated groups was assessed using Dunnett's multiple comparison test. A value of $P < 0.05$ was considered to be significant. Statistical and data analyses were conducted using GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA).

3. Results

3.1. Pharmacokinetics

Following oral administration of each SGLT2 inhibitor (3 mg/kg) to normal mice, the maximum plasma concentration was reached at 0.5–1 h, followed by time-dependent elimination (Fig. 1 and Table 1). The drug concentrations in the kidney, liver, and brain also peaked at 0.5–1 h, followed by time-dependent elimination. Although distribution in the brain was low for all SGLT2 inhibitors, distribution in the kidney, the SGLT2-expressing site, varied widely among drugs. T_{max}, as determined from drug concentrations in plasma and kidney, was 0.5 h for ipragliflozin and luseogliflozin and 1 h for the other four drugs. The $t_{1/2}$ was longest in plasma in the descending order of canagliflozin > dapagliflozin > ipragliflozin > empagliflozin > tofogliflozin > luseogliflozin and longest in kidney in the descending order of dapagliflozin > ipragliflozin > canagliflozin > empagliflozin = tofogliflozin > luseogliflozin.

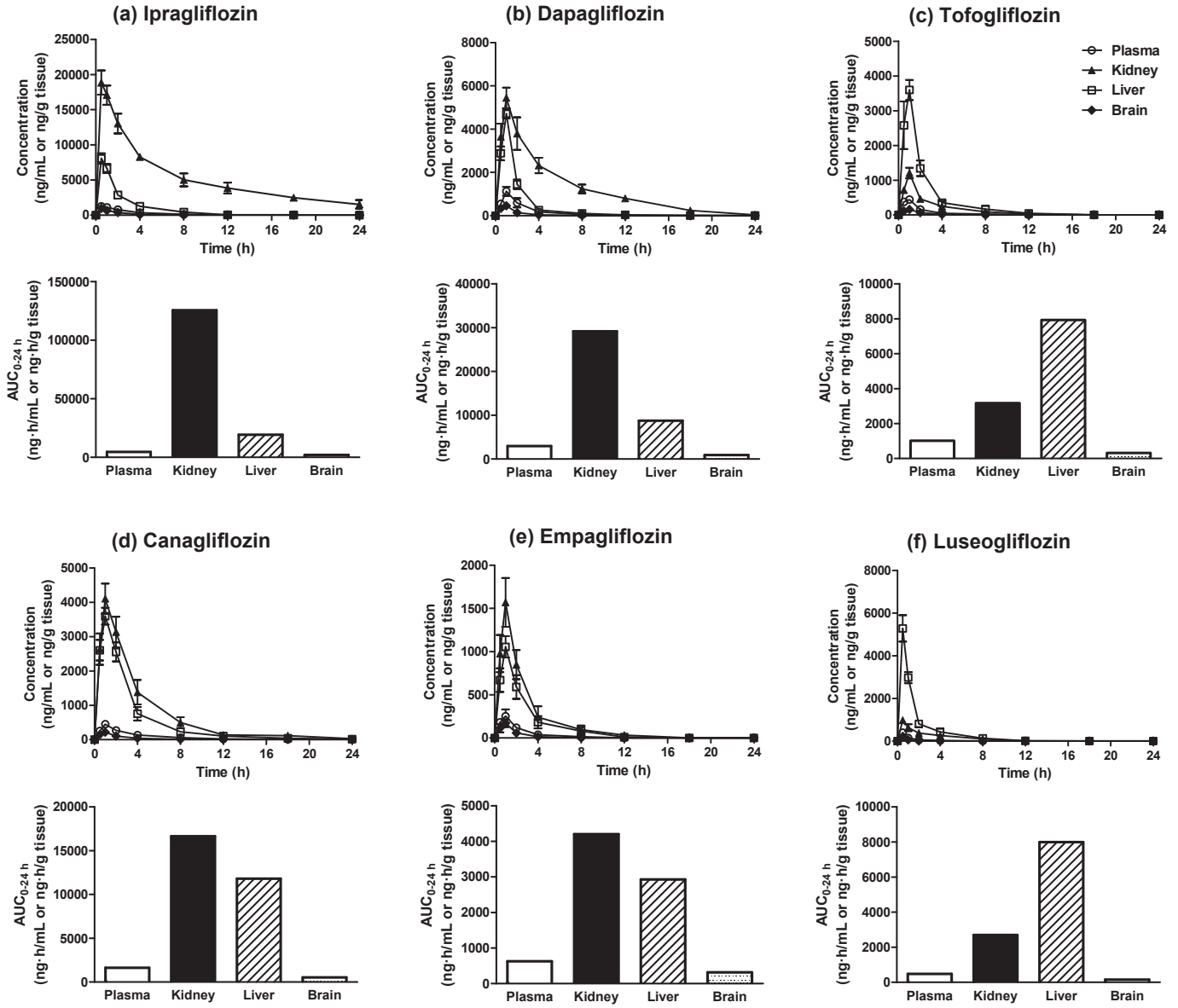

Fig. 1. Pharmacokinetics of SGLT2 inhibitors in normal mice. Time course of changes in plasma, renal, hepatic, and brain concentrations of drug, and plasma or tissue area under the drug concentration–time curve (AUC) for 24 h. Each SGLT2 inhibitor (3 mg/kg) was orally administered to normal mice. Each data point expresses mean or mean ± SD for three animals.

The kidney/plasma AUC ratio (distribution in the kidney) was highest in the descending order of ipragliflozin > dapagliflozin = canagliflozin > empagliflozin > luseogliflozin > tofogliflozin.

3.2. Pharmacodynamics

Following administration of each SGLT2 inhibitor (3 mg/kg) to normal mice, significantly increased urinary glucose excretion was noted in a dose-dependent manner (Fig. 2). These effects of tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin were markedly attenuated from 12 h post-dose, resulting in non-significant effects from 18 h post-dose. In contrast, the effects of ipragliflozin and dapagliflozin were longer-lasting than other SGLT2 inhibitors, with a significant increase in urinary glucose excretion noted even after 18 h post-dose. In addition, all drugs induced a slight increase in urine volume (data not shown).

3.3. Effects of SGLT2 inhibitors on blood glucose and plasma insulin levels

Following administration of each SGLT2 inhibitor (0.01–10 mg/kg) to diabetic mice, blood glucose and plasma insulin levels were significantly reduced in a dose-dependent manner (Fig. 3 and Fig. 4). The effects were comparable for all drugs until 8 h after dosing, although the effective doses varied, but were stronger with ipragliflozin and dapagliflozin than with the other four drugs until 24 h after dosing (Fig. 5). When compared at doses that produced comparable reductions in 24-h blood glucose and plasma insulin levels (ipragliflozin and dapagliflozin, 0.3 mg/kg; tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin, 10 mg/kg), standard deviations of blood glucose and plasma insulin levels for 24 h were smaller with ipragliflozin and dapagliflozin than with the other four drugs (Fig. 6).

Table 1
Pharmacokinetics of SGLT2 inhibitors in normal mice.

		C_{max} (ng/mL) (ng/g tissue)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-24\ h}$ (ng·h/mL) (ng·h/g tissue)	Tissue/plasma AUC ratio
Ipragliflozin	Plasma	1230	0.5	2.1	4520	1
	Kidney	18,871	0.5	4.1	126,000	28
	Liver	8074	0.5	1.2	19,300	4
	Brain	959	0.5	1.1	2090	0.5
Dapagliflozin	Plasma	1130	1	2.4	2970	1
	Kidney	5448	1	4.2	29,200	10
	Liver	4719	1	1.5	8750	3
	Brain	464	1	1.3	904	0.3
Tofogliflozin	Plasma	439	1	1.3	1010	1
	Kidney	1202	1	2.1	3170	3
	Liver	3597	1	1.5	7930	8
	Brain	157	1	1.6	315	0.3
Canagliflozin	Plasma	449	1	3.1	1620	1
	Kidney	4103	1	3.2	16,600	10
	Liver	3593	1	2.4	11,800	7
	Brain	214	1	1.9	532	0.3
Empagliflozin	Plasma	253	1	1.8	626	1
	Kidney	1570	1	2.1	4200	7
	Liver	1056	1	2.2	2930	5
	Brain	171	1	1.5	313	0.5
Luseogliflozin	Plasma	394	0.5	0.4	478	1
	Kidney	978	0.5	1.4	2690	6
	Liver	5288	0.5	0.6	7990	17
	Brain	188	0.5	0.3	157	0.3

Each mouse was treated with a single oral dose (3 mg/kg) of drug. Pharmacokinetic parameters are expressed as the mean for three animals at each time point.

3.4. Effects of SGLT2 inhibitors on glucose tolerance during the oral glucose tolerance test

The oral glucose tolerance test (OGTT) performed at 0.5 h after administration of each SGLT2 inhibitor (3 mg/kg) showed significant improvement in glucose tolerance with all drugs, which exerted comparable effects (Fig. 7A). The OGTT at 6 h after dosing also showed significant improvement in glucose tolerance with all drugs, although the effect strengthened with ipragliflozin and dapagliflozin and weakened with the other four drugs (Fig. 7B). At 12 h after dosing, glucose tolerance was significantly improved with ipragliflozin and dapagliflozin but not with the other four drugs (Fig. 7C).

Following administration of each SGLT2 inhibitor (3 mg/kg) at 30 min before oral glucose loading, significant improvements in glucose tolerance and reductions in plasma insulin level were noted with all SGLT2 inhibitors, which exerted comparable effects (Fig. 8 left). In contrast, following administration immediately before (5 min before) or after (10 min after) oral glucose loading, glucose tolerance was significantly improved with all drugs; however, the effect was stronger with ipragliflozin and luseogliflozin than with the other four drugs, and the associated reduction in plasma insulin level was significant only for ipragliflozin and luseogliflozin (Fig. 8 center and right).

4. Discussion

Given substantial recent evidence supporting their usefulness for reducing hyperglycemia in clinical settings, various SGLT2 inhibitors have been used as antidiabetic drugs. All of these drugs have selective inhibitory activity for SGLT2, with many studies reporting their effects in reducing hyperglycemia through increases in urinary glucose excretion, both in nonclinical animal models and in type 2 diabetic patients. Most of these studies, however, have focused on the pharmacologic effects of individual SGLT2 inhibitors, with no studies performed to compare pharmacologic properties across multiple SGLT2 inhibitors. The present study involved pharmacokinetic, pharmacodynamic, and pharmacologic experiments to compare the characteristics of all six SGLT2 inhibitors commercially available in Japan: ipragliflozin, dapagliflozin, tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin.

Pharmacokinetic experiments showed ipragliflozin and luseogliflozin to have the shortest T_{max} at 0.5 h, as determined from drug concentrations in plasma and the SGLT2-expressing tissue kidney. The $t_{1/2}$ was longest in plasma with canagliflozin, followed by dapagliflozin, ipragliflozin, empagliflozin, tofogliflozin, and luseogliflozin, and longest in kidney with dapagliflozin, followed by ipragliflozin, canagliflozin, empagliflozin and tofogliflozin (roughly the same), and luseogliflozin, showing different persistence of canagliflozin concentration between plasma and kidney. The kidney/plasma AUC ratio (distribution in the kidney) was highest with ipragliflozin, followed by dapagliflozin and canagliflozin (roughly the same), empagliflozin, luseogliflozin, and tofogliflozin, showing correlation with the persistence of drug concentration in the kidney. The large difference among the drugs in distribution in the kidney suggests that this characteristic might depends on a compound's chemical structure.

The pharmacodynamic experiments revealed that all SGLT2 inhibitors increased urinary glucose excretion dose-dependently and significantly, although the duration of action differed among the drugs. Ipragliflozin and dapagliflozin exhibited persistent action, with significant increase in urinary glucose excretion noted even after 18 h post-dose, whereas the effects of tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin were markedly attenuated from 12 h post-dose, resulting in non-significant effects from 18 h post-dose. Consistent with their long duration of action, ipragliflozin and dapagliflozin showed long $t_{1/2}$ in plasma. However, despite the long $t_{1/2}$ of its plasma concentration, the pharmacologic effect of canagliflozin was not persistent, in contrast to ipragliflozin and dapagliflozin.

The results suggested close correlation of duration of action of SGLT2 inhibitors with not only plasma drug concentration but also drug distribution and retention in the kidney. A similar report published previously noted discrepancies between the time course of plasma drug concentration and persistence of increase in urinary glucose excretion, proposing a close relationship between

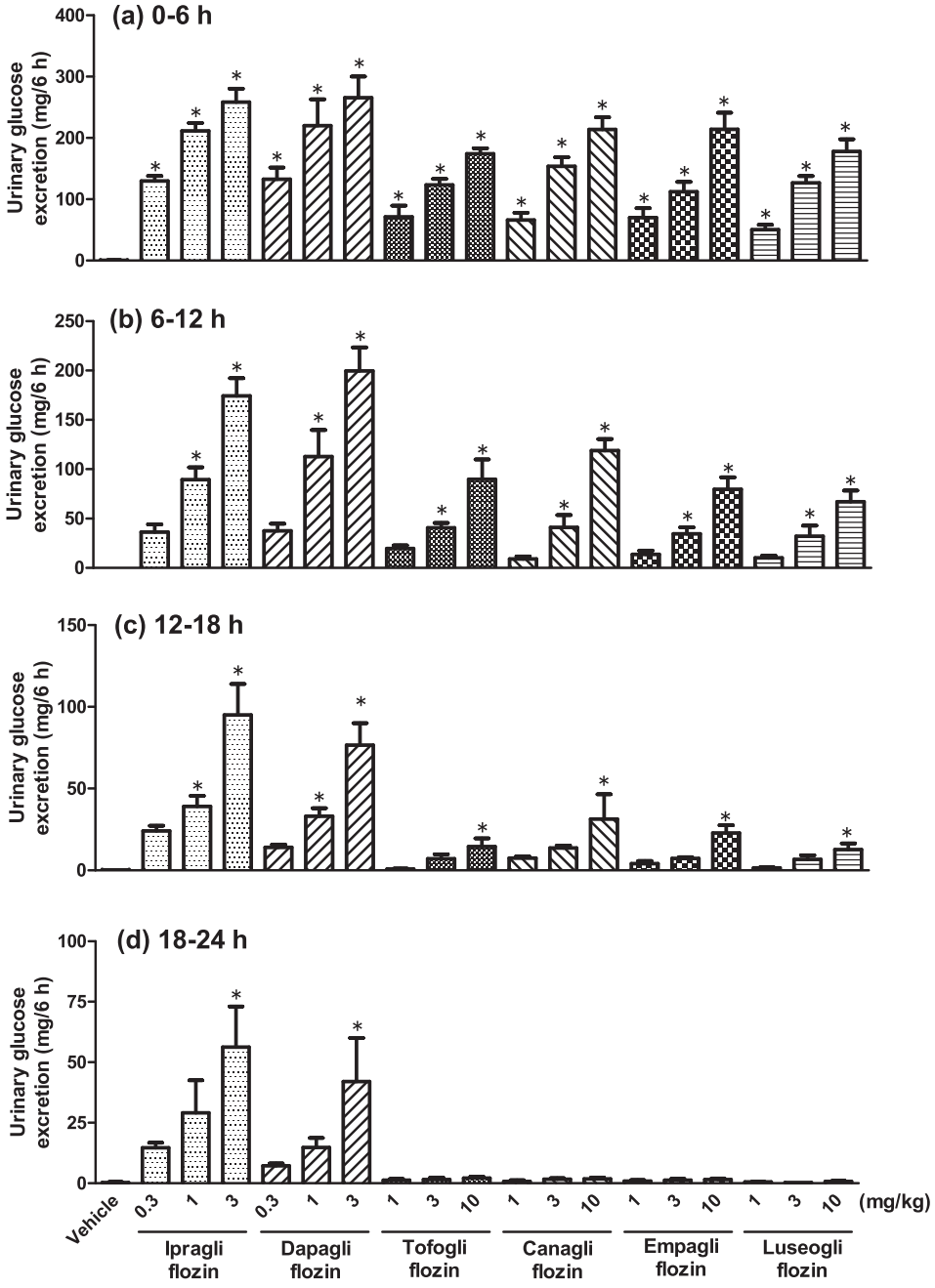

Fig. 2. Effect of SGLT2 inhibitors on urinary glucose excretion in normal mice. Each SGLT2 inhibitor was orally administered to mice, and spontaneously voided urine was collected every 6 h: (a) 0–6 h, (b) 6–12 h, (c) 12–18 h, and (d) 18–24 h, for 24 h. The values are the mean ± SEM for five animals in each group. $^{*}P < 0.05$ vs. vehicle group.

durability of pharmacologic effect and local drug concentration in the renal proximal tubule, the SGLT2-expressing site (14). While SGLT2 inhibitors are converted to various metabolites through the metabolic process in the body, only tofogliflozin and luseogliflozin produce pharmacologically active metabolites, and the proportion of these active metabolites is only a small fraction of the concentrations of their respective parent drugs, showing that none of the active metabolites contribute to the durability of pharmacologic effect (15–20). Further, the results of *in vitro* binding experiments have suggested that the difference in the rate of dissociation of a drug from SGLT2 may be associated with duration of action (21). The present study was limited to investigation of drug concentration in the whole kidney and did not examine renal local drug concentrations or rate of drug dissociation from SGLT2. As such, further investigation is warranted.

The 24-h blood glucose and plasma insulin measurements revealed dose-dependent, significant reductions in blood glucose and plasma insulin levels with all drugs. The effects were comparable for all drugs until 8 h after dosing but were stronger with ipragliflozin and dapagliflozin than with the other four drugs on observation until 24 h after dosing. The OGTT also produced similar results: ipragliflozin and dapagliflozin significantly improved glucose tolerance even at 12 h after dosing, whereas the effects of the other four drugs on improvement in glucose tolerance were markedly attenuated at 6 h after dosing, resulting in non-significant effects at 12 h after dosing. These results indicate the superiority of

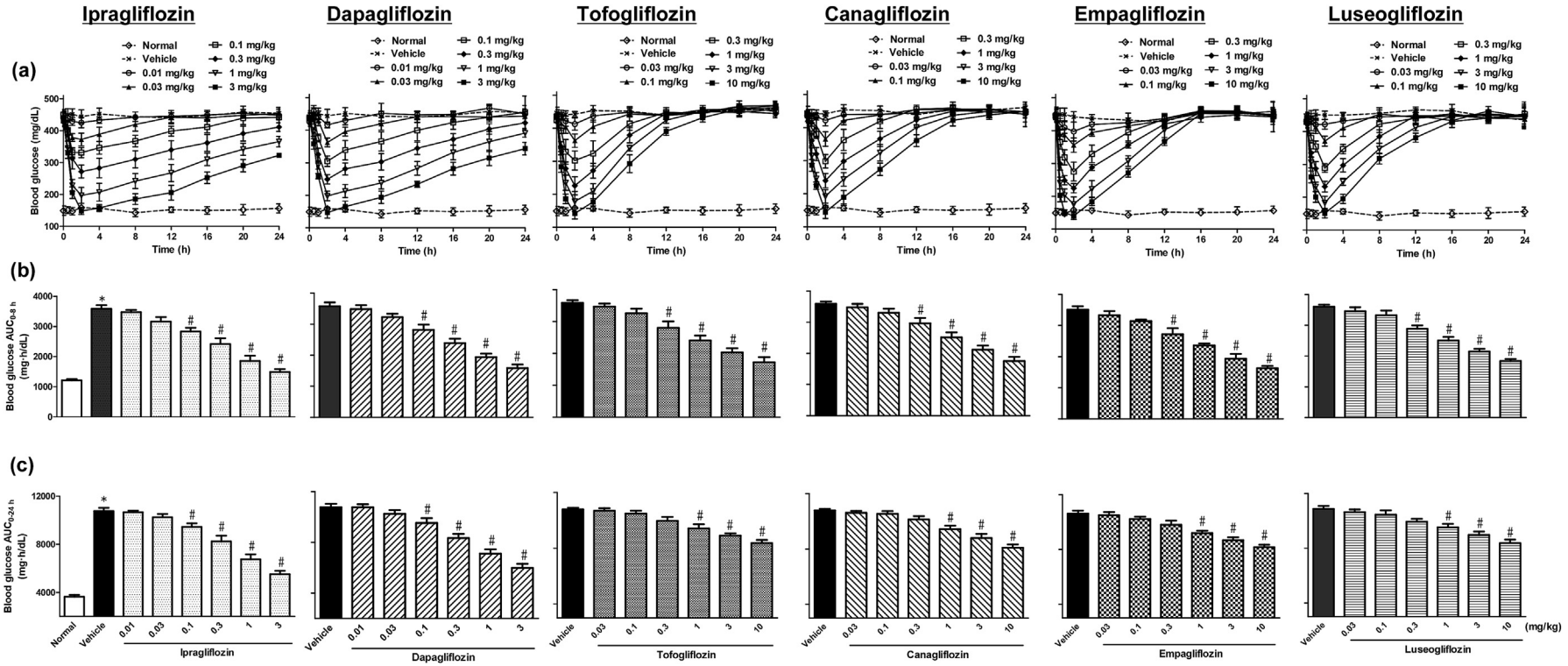

Fig. 3. Effects of SGLT2 inhibitors on blood glucose levels under nonfasting conditions in diabetic mice. (a) Time course of changes in blood glucose levels and the area under the blood glucose concentration–time curve (AUC) for (b) 8 h and (c) 24 h. The values are the mean ± SEM for five animals in each group. $^{*}P < 0.05$ vs. normal group, $^{\#}P < 0.05$ vs. vehicle group.

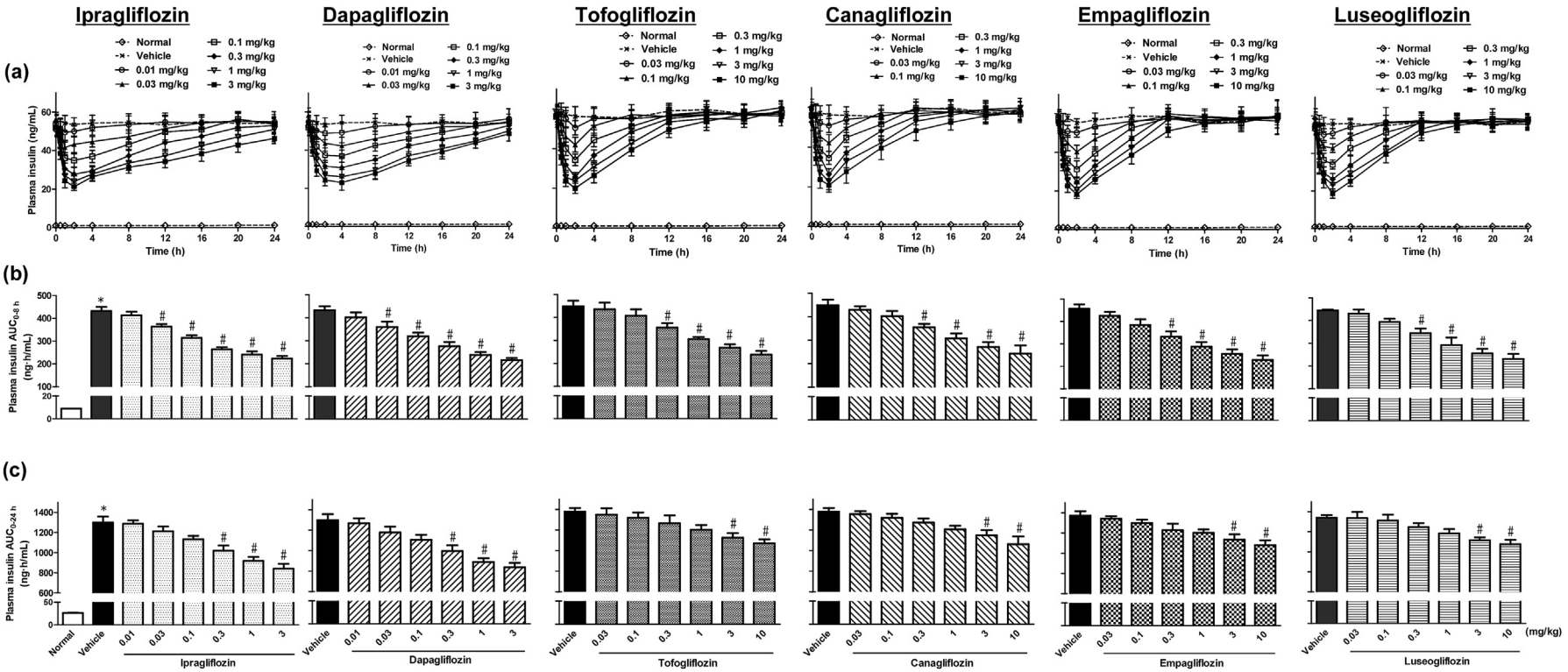

Fig. 4. Effects of SGLT2 inhibitors on plasma insulin levels under nonfasting conditions in diabetic mice. (a) Time course of changes in plasma insulin levels and the area under the plasma insulin concentration–time curve (AUC) for (b) 8 h and (c) 24 h. The values are the mean ± SEM for five animals in each group. $^{*}P < 0.05$ vs. normal group, $^{\#}P < 0.05$ vs. vehicle group.

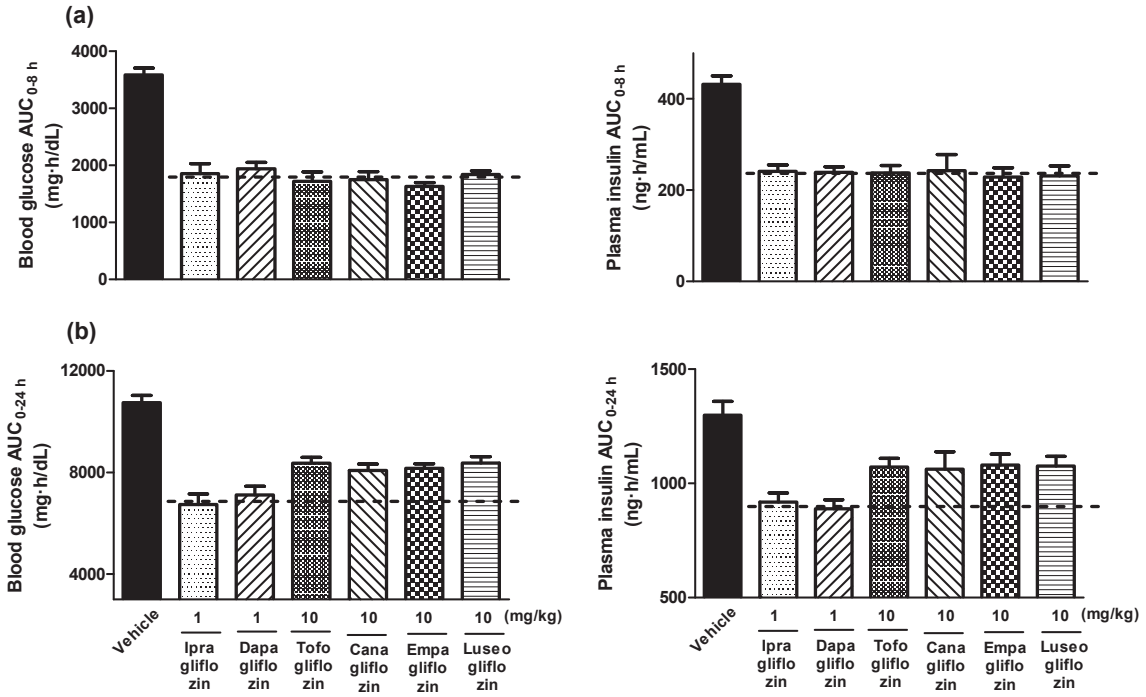

Fig. 5. Effects of SGLT2 inhibitors on blood glucose and plasma insulin levels under nonfasting conditions in diabetic mice. The area under the blood glucose (left) and plasma insulin (right) concentration–time curve (AUC) for 8 h (a) and 24 h (b). The values are the mean ± SEM for five animals in each group.

ipragliflozin and dapagliflozin in duration of action, supporting the correlation of long action with high distribution and long retention in the kidney, as shown in the pharmacokinetic experiment, and with a persistent increase in urinary glucose excretion, as shown in the pharmacodynamics experiment. Based on these pharmacokinetic, pharmacodynamic, and pharmacologic results, these six SGLT2 inhibitors were classified with respect to duration of action into two categories: long-acting, comprising ipragliflozin and dapagliflozin; and intermediate-acting, comprising tofogliflozin, canagliflozin, empagliflozin, and luseogliflozin. Further, the

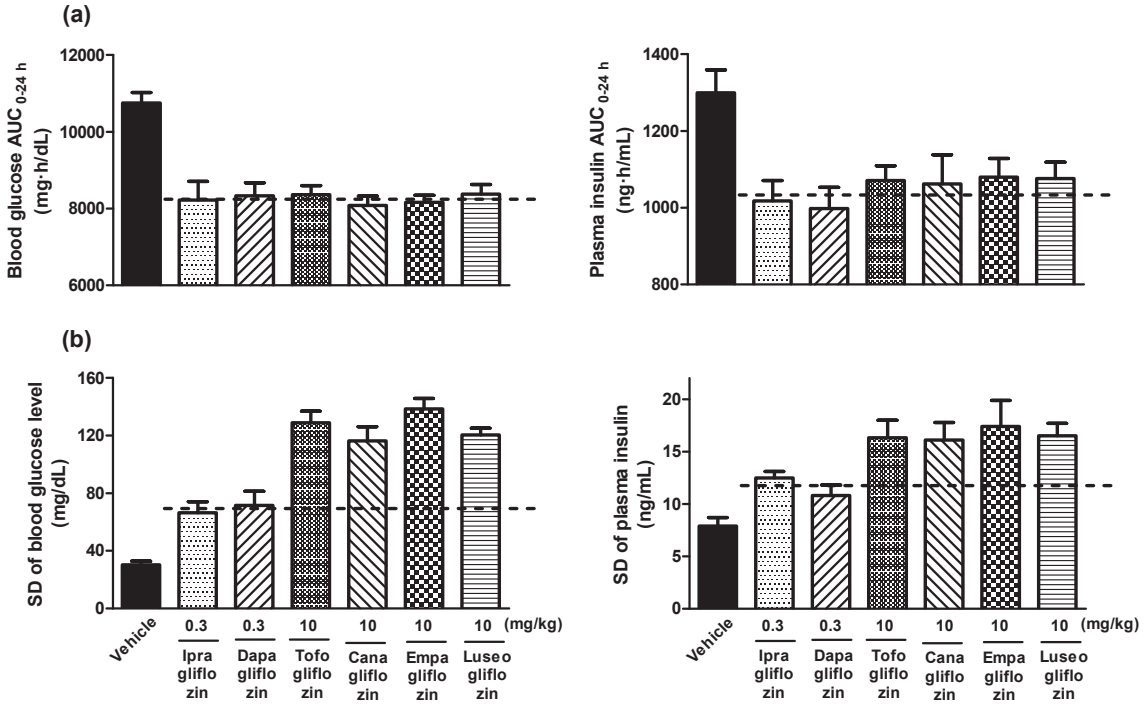

Fig. 6. Effects of SGLT2 inhibitors on variability of blood glucose and plasma insulin levels in diabetic mice. (a) The area under the blood glucose (left) and plasma insulin (right) concentration–time curve (AUC) and (b) standard deviation (SD) of blood glucose and plasma insulin levels for 24 h. The values are the mean ± SEM for five animals in each group.

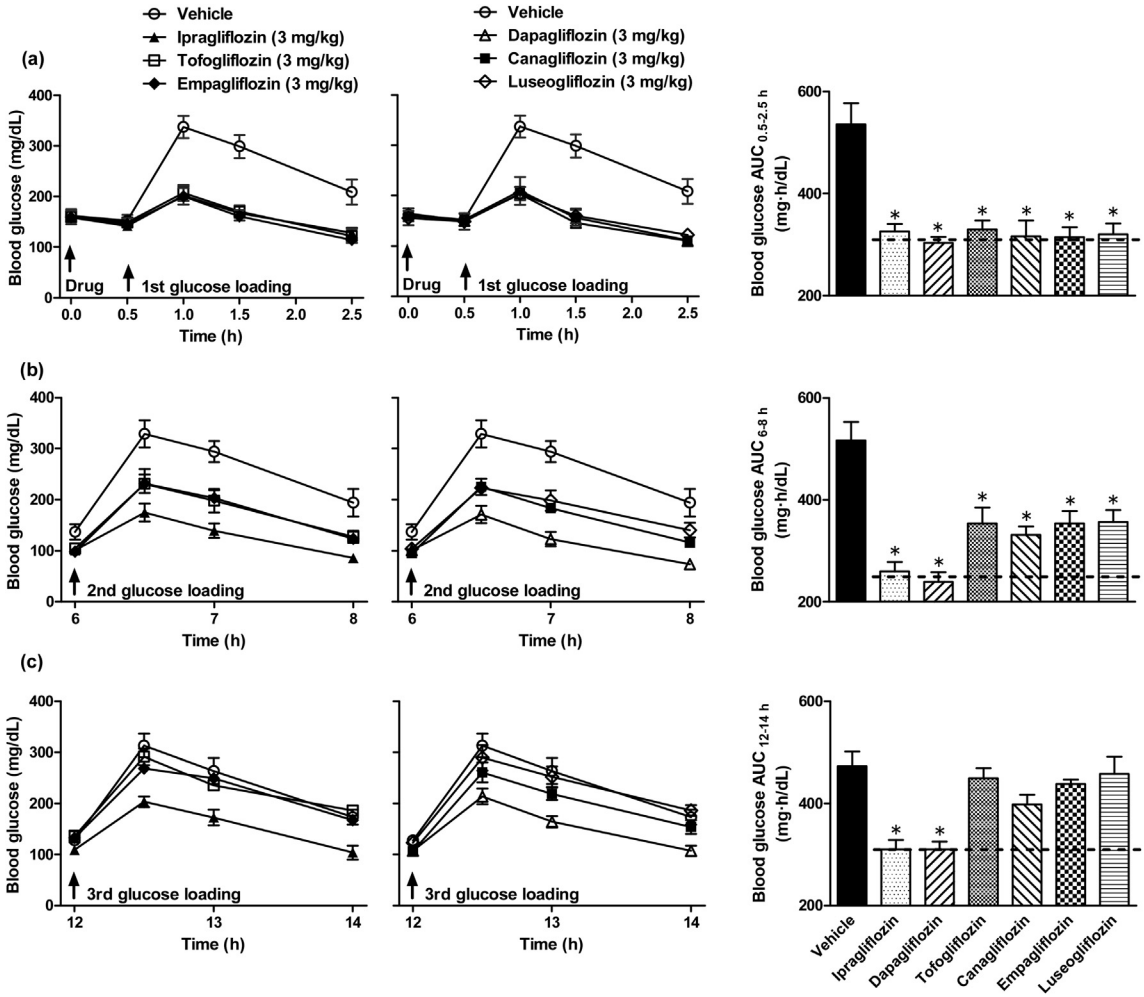

Fig. 7. Durability of SGLT2 inhibitors on glucose tolerance during repetitive oral glucose tolerance tests in diabetic mice. Each SGLT2 inhibitor (3 mg/kg) was administered orally to diabetic mice fasted for half a day, and glucose solution was orally loaded (a) 0.5, (b) 6, and (c) 12 h after dosing. The values are the mean ± SEM for five animals in each group. $^{*}P < 0.05$ vs. vehicle group.

pharmacologic experiments confirmed that the daily variability (standard deviation) of blood glucose and plasma insulin levels was small with the long-acting SGLT2 inhibitors. A recent study has suggested that, to improve diabetic conditions—particularly complications—blood glucose control should be performed with focus not only on long-term average blood glucose levels using decrease in HbA_{1c} as a measure, but also on minimizing daily variations in blood glucose level (22). In addition, the usefulness of new measures of blood glucose control, including the standard deviation of blood glucose (SDBG) and mean amplitude of glucose excursion (MAGE), has been extensively reported (23). Long-acting SGLT2 inhibitors may therefore serve as excellent treatments for diabetes in terms of not only potency but also quality, by exerting antihyperglycemic effects and improving glucose tolerance through persistent increases in urinary glucose excretion. In contrast, intermediate-acting SGLT2 inhibitors may provide better glycemic control when given twice daily rather than once daily. Clinically, all SGLT2 inhibitors are prescribed on a once daily basis, likely due in part to differences in pharmacokinetics between mice and humans, but the efficacy may be enhanced by increasing the duration of action through modifications to the formulation.

The OGTT performed to investigate the time to onset of action of each drug revealed significant improvement in glucose tolerance with ipragliflozin and luseogliflozin, regardless of time of administration with respect to glucose loading, providing evidence for their superiority of fast onset. These results are consistent with findings regarding the shortest T_{max} in the pharmacokinetic experiments. Since all SGLT2 inhibitors are at least 100 times more selective for SGLT2 than for SGLT1, inhibition of SGLT1-mediated intestinal glucose absorption is likely not involved in the onset or duration of action. In clinical practice, SGLT2 inhibitors are all administered once daily, generally before or after breakfast. The results of this study suggest that fast-acting SGLT2 inhibitors can exert maximum efficacy regardless of dosing timing, thereby potentially reducing the aforementioned daily variation in blood glucose level.

No substantial species-specific differences in *in vitro* inhibitory activity for SGLT2 have been reported among the six SGLT2 inhibitors evaluated in the present study (8–13). However, a number of species-specific differences in pharmacokinetic properties have been observed, particularly with respect to elimination half-life of drug in plasma between humans and rodents including mice. Therefore, the duration of action in humans may differ from that noted in mice in our study. The results of the study suggest close correlation of duration of action with not only plasma drug concentration but also drug distribution and retention in the kidney, warranting further clinical studies on the duration of action of SGLT2 inhibitors and drug distribution in the kidney.

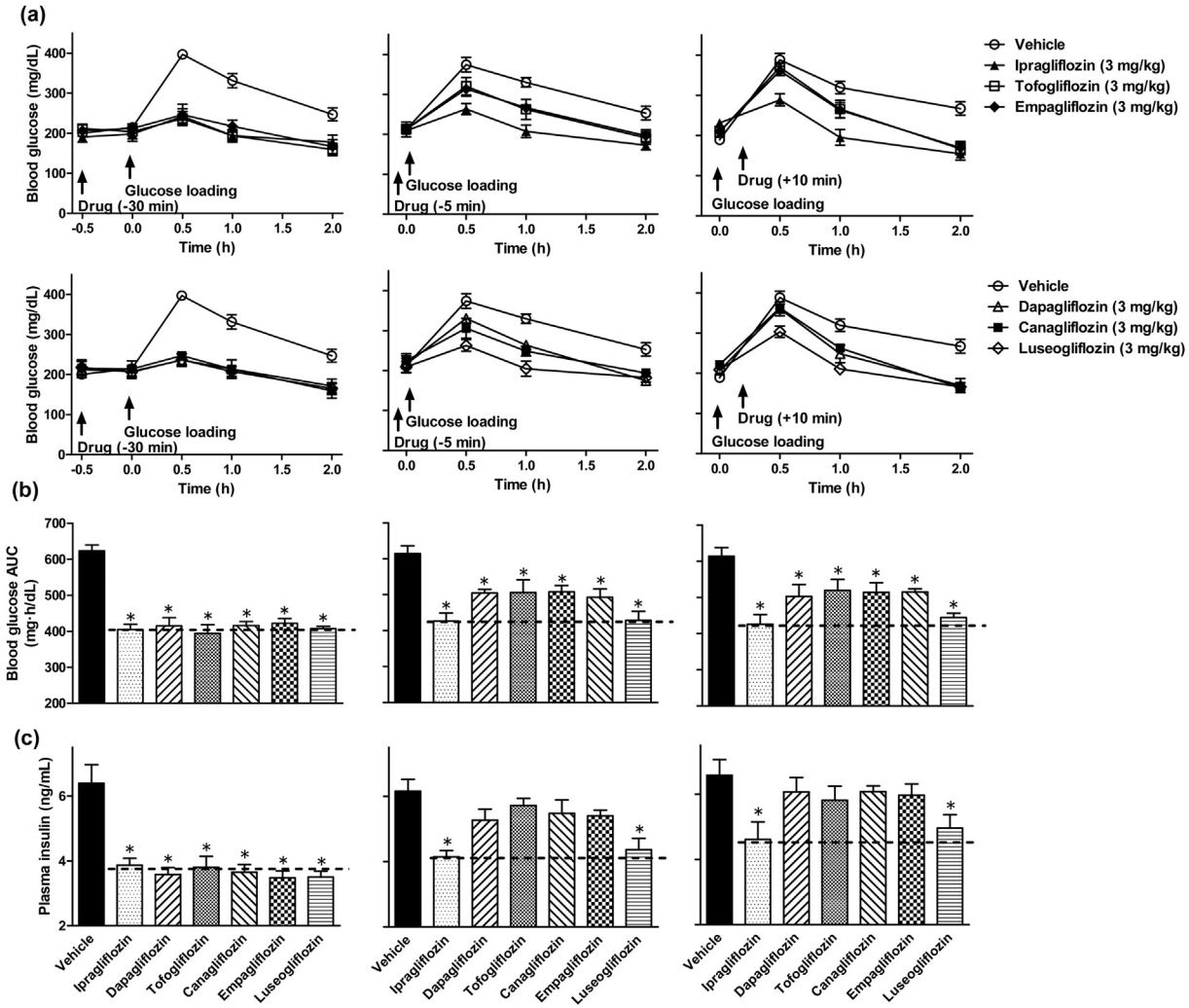

Fig. 8. Rapid-onset of SGLT2 inhibitors on glucose tolerance during the oral glucose tolerance test in diabetic mice. Each SGLT2 inhibitor (3 mg/kg) was administered orally to diabetic mice fasted for half a day at 30 min before (left), 5 min before (center), or 10 min after (right) oral glucose loading. (a) Time course of changes in the blood glucose level and (b) the area under the blood glucose concentration–time curve (AUC) during the oral glucose tolerance test (OGTT). (c) Plasma insulin level at 30 min during the OGTT. The values are the mean ± SEM for five animals in each group. $^*P < 0.05$ vs. vehicle group.

In summary, based on the pharmacokinetic, pharmacodynamic, and pharmacologic results obtained in this study, the six SGLT2 inhibitors were classified with respect to duration of action as either long-acting or intermediate-acting, and fast-acting drugs were also identified. The present study is the first to examine and compare properties of several SGLT2 inhibitors, and we expect our findings to be useful for both clinical and nonclinical investigation of SGLT2 inhibitors for diabetes. Our study involved single administration, and parameters were limited to blood glucose and plasma insulin levels and glucose tolerance; therefore, we were unable to sufficiently differentiate SGLT2 inhibitors with respect to pharmacologic effects. Future studies should conduct detailed comparison of effects on improvement in type 2 diabetes by repeated administration based on diversified pharmacologic parameters. However, despite these shortcomings, the present results suggest that while all SGLT2 inhibitors significantly increase urinary glucose excretion and attenuate hyperglycemia, the difference in the quality of daily blood glucose control associated with duration and onset of pharmacologic effects of each drug might result in slightly different degrees of improvement of type 2 diabetes.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgments

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