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Short communication

Effect of a SGLT2 inhibitor on the systemic and intrarenal renin–angiotensin system in subtotally nephrectomized rats

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ABSTRACT

We aimed to examine the effects of a sodium glucose co-transporter 2 (SGLT2) inhibitor on systemic and intrarenal renin–angiotensin system (RAS) in subtotally nephrectomized non-diabetic rats, a model of chronic kidney disease (CKD). Oral administration of the selective SGLT2 inhibitor, TA-1887 (10 mg/kg/day), for 10 weeks induced glycosuria. However, plasma renin activity, plasma angiotensinogen levels, kidney angiotensin II contents and renal injury were not significantly affected by TA-1887. These data indicate that chronic treatment with an SGLT2 inhibitor does not activate the systemic and intrarenal RAS in subjects with non-diabetic CKD.

Sodium glucose co-transporter 2 (SGLT2) in the proximal tubular S1 segment reabsorbs approximately 90% of the filtered glucose in urine,[1] and SGLT2 inhibitors have been used as novel hypoglycemic agents for patients with type 2 diabetes.[1] More recently, the EMPA-REG OUTCOME trial has shown that treatment with the SGLT2 inhibitor, empagliflozin, improves cardiovascular event and all-cause mortality in patients with type 2 diabetes and established cardiovascular disease.[2] Additionally, sub-analyses of the EMPA-REG OUTCOME study have identified a potential reduction of rates of hospitalization for heart failure in patients treated with empagliflozin.[3] Interestingly, these beneficial effects of the SGLT2 inhibitor were independent of changes in glycemic control, plasma lipid levels and blood pressure.[2, 3]

However, side effects of SGLT2 inhibitors, particularly polyuria and polydipsia, have been reported during the early stages of treatment.[4] These clinical symptoms indicate that SGLT2 inhibitors promote diuresis and negative water balance. We recently demonstrated that treatment with SGLT2 inhibitors caused temporary natriuresis and body fluid loss in obese rats.[5, 6] Similarly, in patients with type 2 diabetes, urinary excretion of sodium significantly increased for only a few days and then returned to pre-treatment levels during chronic treatment with an SGLT2 inhibitor.[7] These data indicate that the diuretic effect of a SGLT2 inhibitor is soon compensated for, possibly by an adaptive physiological mechanism. In this regard, Cherny et al[8] reported that urinary angiotensinogen (AGT) excretion, which reflects intrarenal renin–angiotensin system (RAS) activity,[9, 10] was significantly increased by treatment with a SGLT2 inhibitor in patients with type 1 diabetes mellitus. These data suggest that intrarenal RAS is activated to compensate for acute loss of sodium and body fluid. In contrast, a recent study by Shin et al[11] showed that during treatment with a SGLT2 inhibitor, type 2 diabetic rats exhibited a significant decrease in urinary AGT excretion and an associated reduction in blood glucose levels. Thus, the effects of SGLT2 inhibitors on intrarenal RAS activity are still controversial because of a lack of data from direct measurements of intrarenal angiotensin II levels.

In the present study, we directly measured the angiotensin II content of renal tissues to determine whether a SGLT2 inhibitor

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Table 1
Systemic and renal parameters in non-diabetic 5/6 nephrectomized rats.

	Vehicle (n = 7)	TA-1887 (n = 8)
Urine volume (ml/24 h)	52 ± 1	89 ± 4*
Urinary glucose excretion (mg/day)	3 ± 1	1933 ± 339*
Blood pressure (mmHg)	150 ± 3	147 ± 2
Body weight (g)	483 ± 7	456 ± 13
Kidney weight (g)	2.2 ± 0.2	3.0 ± 0.2*
plasma BUN (mg/dl)	45 ± 3	55 ± 6
Plasma creatinine (mg/dl)	0.9 ± 0.1	0.8 ± 0.1
Creatinine clearance (ml/min)	3.0 ± 0.5	2.1 ± 0.2
Urinary albumin excretion (mg/day)	151 ± 4	159 ± 5

All data are mean ± SEM. *P < 0.05 vs. vehicle.

alters intrarenal RAS activity. Blood glucose level is a critical factor determining intrarenal AGT expression and associated RAS activity.[10] Furthermore, side effects of SGLT2 inhibitors, particularly polyuria and polydipsia, have been clinically reported during the early stages of treatment,[4] leading to restricted use of SGLT2 inhibitors, particularly concerning in patients with chronic kidney disease (CKD). Therefore, we examined the effect of an SGLT2 inhibitor in non-diabetic rats subjected to subtotal nephrectomy, to avoid possible effects of blood glucose changes on intrarenal RAS activity.

Thirty male 4-week-old Sprague Dawley (SD) rats were purchased from Japan SLC Inc. (Shizuoka, Japan). The rats were

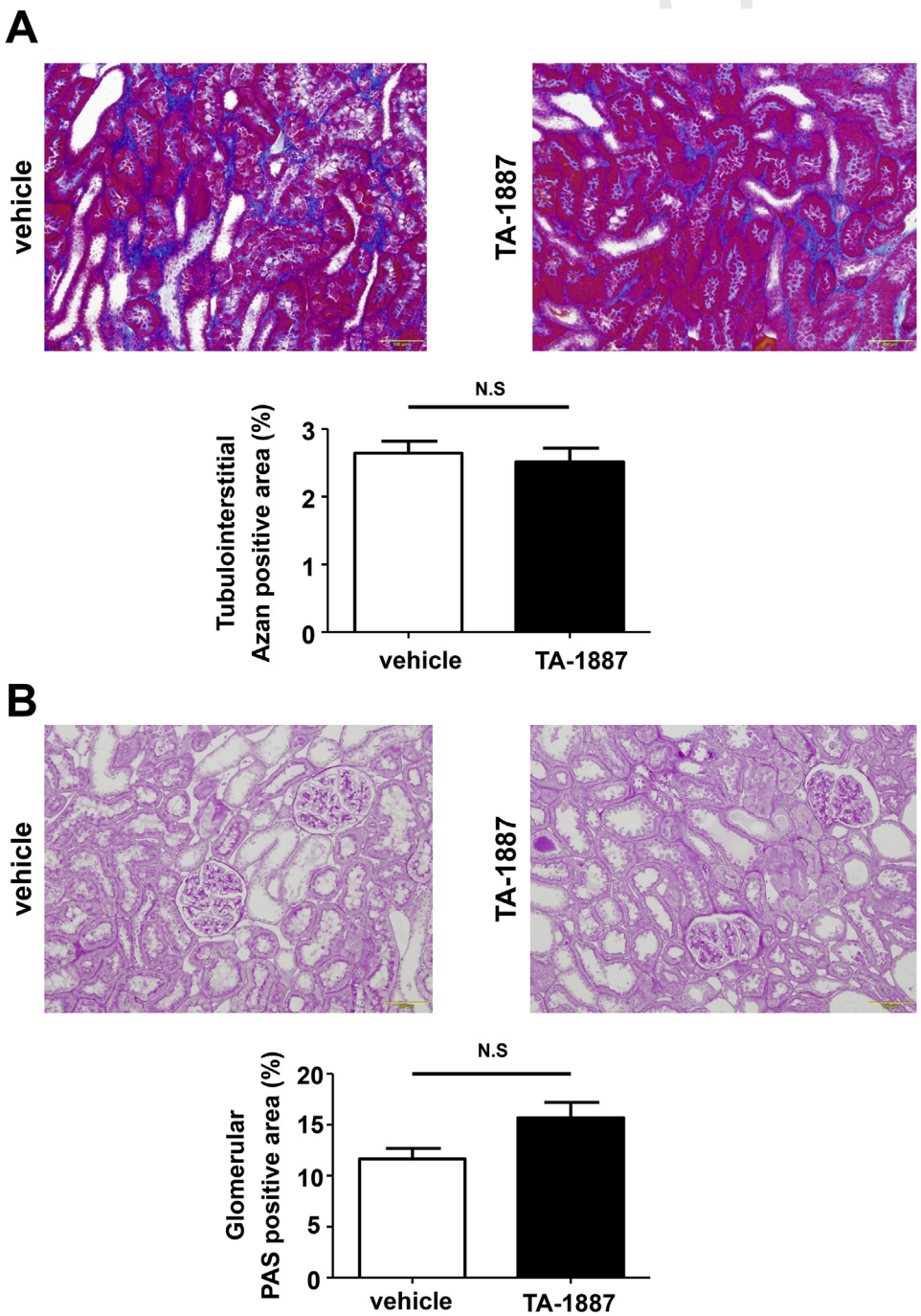

Fig. 1. Effects of the sodium glucose co-transporter 2 (SGLT2), TA-1887, on glomerular and tubulointerstitial injuries in non-diabetic 5/6 nephrectomized rats. A, Tubulointerstitium stained with Azan reagents (200× magnification). B, Glomeruli stained with periodic acid-Schiff (PAS) reagents (200× magnification). Neither tubulointerstitial Azan-positive area nor glomerular PAS-positive area differs between vehicle- and TA-1887-treated non-diabetic 5/6 nephrectomized rats.

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