報告番号	香大医博甲　第　716号

様式１０７

学位論文審査の結果の要旨

平成 31 年 1 月 15 日

審査委員	主　査	村尾 孝児	印	
	副主査	中村 隆範	印	
	副主査	白神 豪太郎	印	
願出者	専攻	分子情報制御医学専攻	部門	生体情報学
	学籍番号	15D741	氏名	Tuba Musarrat Ansary
論文題目	Responses of renal hemodynamics and tubular functions to acute sodium–glucose cotransporter 2 inhibitor administration in nondiabetic anesthetized rats			
学位論文の審査結果	(合格) ・ 不合格　（該当するものを○で囲むこと。）			

〔 要 旨 〕

The aim of this study was to examine the effects of acute administration of luseogliflozin, the sodium–glucose cotransporter 2 (SGLT2) inhibitor, on renal hemodynamics and tubular functions in anesthetized non-diabetic Sprague Dawley (SD) rats and 5/6 nephrectomized (Nx) SD rats. Renal blood flow (RBF), mean arterial pressure (MAP), and heart rate (HR) were continuously measured and urine was collected directly from the left ureter. Intraperitoneal injection of luseogliflozin (0.9 mg kg^{-1}) did not change MAP, HR, RBF, or creatinine clearance (CrCl) in SD rats (n = 7). Luseogliflozin significantly increased urine volume, which was associated with significantly increased urinary glucose excretion rates ($P < 0.001$). Similarly, luseogliflozin significantly increased urinary sodium excretion from 0.07 ± 0.01 at baseline to 0.76 ± 0.08 μmol min^{-1} at 120 min ($P < 0.001$). Furthermore, luseogliflozin resulted in significantly increased urinary pH ($P < 0.001$), and decreased urinary osmolality and urea concentration in SD rats ($P < 0.001$, respectively). Similarly, in Nx SD rats (n = 5–6), luseogliflozin significantly increased urine volume and urinary glucose excretion ($P < 0.001$) without altering MAP, HR, RBF, or CrCl. Luseogliflozin did not elicit any significant effects on the other urinary parameters in Nx SD rats. These data indicate that SGLT2 inhibitor elicits direct tubular effects in non-diabetic rats with normal renal functions.

There were several concerns raised by the reviewers. First point was the specific reason why 5/6 nephrectomy (Nx) rat model was used. Previous studies have shown that 5/6 Nx rats are characterized by single nephron hyperfiltartion and intraglomerular hypertension. It has also been reported that SGLT2 inhibitors decrease the incidence of event by reduction in intra-glomeruar pressure characterized by glomerular filtration rate in patients with diabetes. Although it is suggested that SGLT2 inhibitors cause afferent arteriole vasoconstriction and reduce hyperfiltration, it is difficult to exclude its blood sugar-lowering effect in diabetic condition. Therefore, we aimed to examine the acute effects of SGLT2 inhibitor in non-diabetic hyperfiltration condition. Our results showed that luseogliflozin did not alter blood sugar level and renal hemodynamics in non-diabetic Nx rats. The stronger hemodynamic response observed in diabetes is may be due to the greater tubular glucose and sodium delivery and which is absent in non-diabetic condition.

Another concern was regarding the dose of luseogliflozin for intraperitoneal injection. There were no previous reports that show acute administration of luseogliflozin. In the preliminary experiments, luseogloflozin was solubilized in as much as less vehicle (2-hydroxylpropyl-β-cyclodextrin: HP-β-CD). To check its effectiveness, we measured urinary glucose levels. We found that 0.9 mg kg^{-1} is the highest dose to increase most urinary glucose excretion with least amount of vehicle. In our protocol with intravenous administration, we found that vehicle had significant effects on urinary parameters. Previously, it has been demonstrated that intravenous administration of HP-β-CD in anesthetized rats slightly increased sodium and potassium excretion. We tried to reduce the unspecific effect of vehicle and our results showed that intraperitoneal administration of vehicle had minimal effects on renal parameters.

In clinical setting, chronic SGLT2 inhibitor treatment can decrease systolic blood pressure by 3-4 mmHg in patients with diabetes. The reviewer raised the issue why blood pressure was not changed in our experiments. The answer is that this may be because our studies examined the effect of acute treatment with SGLT2 inhibitor in both non-diabetic animals. Indeed, we previously reported that chronic treatment with SGLT2 inhibitors significantly decreased blood pressure in hypertensive rats. On the other hand, our studies showed that luseogliflozin caused natriuresis in non-diabetic subjects. These data suggest that, that administration of SGLT2 inhibitor might also be beneficial in treating diuretic resistant patients without hyperglycemia.

掲 載 誌 名	Scientific Reports 第 7 巻, 第 1 号		
(公表予定) 掲 載 年 月	2017年8月	出版社 (等) 名	Nature

(備考) 要旨は, １, ５００字以内にまとめてください。