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様式１０７

学位論文審査の結果の要旨

令和
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論文題目	Effects of an SGLT2 inhibitor on salt sensitivity of blood pressure and sympathetic nerve activity in a non-diabetic rat model of chronic kidney disease			
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 luseogliflozin, the selective sodium-glucose cotransporter 2 (SGLT2) inhibitor, on blood pressure (BP) and sympathetic nerve activity (SNA) in non-diabetic rat with chronic kidney disease (CKD). Uninephrectomized Wistar rats were treated with adenine (200 mg/kg/day) for 14 days to induce renal injury. After stabilization with a normal salt diet (NSD, 0.3% NaCl), high salt diet (HSD, 8% NaCl) was administered for 5 days. Mean arterial pressure (MAP) was continuously monitored using a telemetry system. We also analyzed the low frequency (LF) of systolic BP (SBP), which reflects SNA and the locomotor activity (LA). In adenine-induced CKD rats, HSD for 5 days significantly increased the mean MAP from 106 ± 2 to 148 ± 3 mmHg. However, MAP was decreased to 96 ± 3 mmHg within 24 hours after switching back to NSD (n=7). Treatment with the SGLT2 inhibitor, luseogliflozin (10 mg/kg/day, p.o., n=7), significantly attenuated the HSD-induced elevation of MAP, which was associated with a reduction in LF of SBP. On the other hand, luseogliflozin did not show any effects on LA in adenine-induced CKD rats. These data indicated that treatment with an SGLT2 inhibitor attenuates the salt-sensitivity of BP, which is associated with SNA inhibition in non-diabetic CKD rats.

There were concerns raised by the reviewers. First, they asked the reason why adenine-induced CKD rat model was used. I have explained that adenine-treated rats develop severe renal tissue injury that closely resembles those in CKD patients with uremia. Previous studies showed longer-term treatment with adenine in rats develops tubulointerstitial injury and decreases GFR. Indeed, our data showed that adenine (200 mg/kg/day) treatment for 2 weeks resulted in massive interstitial cellularity, widespread tubular dilations and significant increases in plasma BUN levels. Five-days treatment of luseogliflozin did not show any changes in renal function and tubulointerstitial fibrosis. I understand that the 5-days treatment would be too short to reveal the clinical situation. However, I was not able to administer HSD in adenine-treated rats, because of very bad general condition with high risk of death. Future studies should be performed in adenine-treated CKD rats with mild HSD to examine the effects of luseogliflozin with longer period. I also agree with the reviews concern that it would be better to analyze others urinary parameters (e.g. urine volume, albumin/ creatinine ratio) and direct SNA markers (e.g. arterial norepinephrine). Another reviewers' question was regarding the reasons why luseogliflozin was chosen in the present study, because several SGLT2 inhibitors are now commercially available (luseogliflozin, empaliflozin, canagliflozin, dapagliflozin, ipragliflozin, ertugliflozin, remogliflozin etabonate, sergliflozin etabonate, sotagliflozin, tofogliflozin). I explained that it is because our previous studies showed remarkable reductions in BP and SNA with luseogliflozin in different hypertensive models. Two reviewers asked the expression of SGLT2 and distribution of luseogliflozin in adenine-induced CKD rats. I explained that SGLT2 expressed mostly in S1 segment of proximal tubular cells. Furthermore, previous studies have shown that the expression of SGLT2 is increased in patients with diabetes. Although we previously showed that SGLT2 expression is increased metabolic syndrome rats, it is still not clear whether SGLT2 expression is actually increased in CKD subjects. Additional experiments are also necessary to determine the distribution of luseogliflozin. Another question was the mechanism as to why HSD increased the LA during inactive period in all groups. I explained my speculation that HSD change the behaviors of sleeping, food/water intake and urine excretion, all of which may influence the LA changes. Luseogliflozin may not affect these HSD-induced changes in behavior. By these presentation and discussion, all reviewers agree to confer a degree on one.

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