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学位論文の内容の要旨

専　攻	医学専攻	部　門 (平成27年度以前入学者のみ記入)	
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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		

(論文要旨)

Background

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) and hypertension. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are antihyperglycemic drugs used for the treatment of diabetes, and have been shown to improve diabetic complications in patients with type 2 diabetes, including cardiovascular (CV) death. Furthermore, several clinical studies have shown that the administration of an SGLT2 inhibitor remarkably decreases blood pressure (BP). Interestingly, several clinical studies have shown that the SGLT2 inhibitor-induced reduction in BP is not concomitant with a notable change or compensatory increase in heart rate (HR). These papers suggested that SGLT2 inhibitors can attenuate sympathetic nerve activity (SNA). Our previous animal studies using a telemetry system showed that treatment with an SGLT2 inhibitor significantly decreased BP and SNA in high salt-treated obese rats, and metabolic syndrome rats. SGLT2 inhibitors have also been shown to significantly decrease norepinephrine production and turnover in brown adipose tissue in mice, and high fat-induced elevation of norepinephrine levels in the kidney and heart in rats in a published paper. Although the precise mechanism responsible for SNA reduction is unclear. Clinical studies have indicated that the blood glucose-lowering effect induced by SGLT2 inhibitors was significantly attenuated in patients with diabetes and CKD with a reduced glomerular filtration rate. However, the effects of an SGLT2 inhibitor on BP and SNA in non-diabetic patients with CKD have not previously been investigated. Therefore, the present study aimed to examine the effects of an SGLT2 inhibitor on BP and SNA in non-diabetic adenine-induced CKD rats. To determine the salt-sensitivity of BP, we administered a high salt diet (HSD) to non-diabetic adenine-induced CKD rats.

Methods and data

Five-week old male Wistar rats were subjected to right nephrectomy. After 1 week of acclimatization, rats were treated with vehicle (0.5% carboxymethylcellulose, p.o., n=6) or adenine (200 mg/kg per day, p.o., n=14) for 2 weeks. Next, a radio-telemetry device was implanted in all animals. Thereafter, rats received a normal salt diet (NSD, 0.3% NaCl) for 9 days. Subsequently, the chow was switched to a HSD (8% NaCl), and adenine-treated rats were treated with vehicle (n=7) or luseogliflozin (10 mg/kg per day, p.o., n=7). After 5 days, the chow was again switched to NSD in all animals. The radio-telemetry system was used for the measurement of BP in conscious animals. A telemetry catheter was inserted into the femoral artery and animals were maintained under stress-free conditions for 7 days for recovery. All animals underwent a 24-hour acclimatization period on a telemetry receiver panel. Twenty four-hour BP measurement was undertaken during the experimental period. Moreover, we calculated the 12-hour dark-period (18: 00- 06: 00) and 12-hour light-period (06: 00- 18: 00) mean

arterial pressure (MAP) to evaluate the BP circadian rhythm. We also investigated SNA with low frequency (LF) of systolic BP (SBP), locomotor activity (LA), and their circadian rhythm using the telemetry system as previously described.
The data of present study showed that 1. Luseogliflozin, significantly attenuated the HSD-induced elevation of BP in adenine-induced CKD rats. 2. Luseogliflozin suppressed SNA in HSD-treated CKD rats. 3. In adenine-induced CKD rats, luseogliflozin did not significantly affect LA.
Findings and Discussion
Our data indicate that treatment with an SGLT2 inhibitor decreases the salt-sensitivity of BP, which is associated with the attenuation of SNA in non-diabetic CKD rats, independent of blood glucose changes. BP control is the one of the most important aspects of cardiovascular disease management in patients with CKD. In this regard, Wanner et al. showed that although treatment with an SGLT2 inhibitor elicits less glucose-lowering effect in patients with type 2 diabetes and CKD compared with the type 2 diabetic patients without CKD, its cardioprotective effect is not influenced by reduced renal function. The effect of an SGLT2 inhibitor in non-diabetic CKD patients is currently being investigated in a large clinical study. Although the primary endpoint of this study is the renal outcome, the effects of the SGLT inhibitor on BP are expected to be clarified in this patient population.

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