

学位論文審査結果の要旨

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(学位論文審査結果の要旨)

Cardiorenal protective effects of sodium-glucose cotransporter 2 inhibition in combination with angiotensin II type 1 receptor blockade in salt-sensitive Dahl rats

【主論文審査結果の要旨】

著者らは論文において下記の内容を述べている。

Objective: The kidney plays a central role in regulating the salt sensitivity of blood pressure (BP) by governing sodium excretion and reabsorption via renal sodium transporters. We hypothesized that sodium-glucose cotransporter 2 (SGLT2) inhibition and angiotensin II type 1 receptor (AT1R) blockade can synergistically reduce renal sodium reabsorption by beneficially effects on these transporters, leading to lower BP and ameliorating renal and cardiac damage.

Methods and Results: Dahl salt-sensitive rats were treated orally for 8 weeks with a normal salt diet (0.3% NaCl), a high-salt diet (8% NaCl), high-salt diet with ipragliflozin (0.04%), high-salt diet with losartan (0.05%), or high-salt diet with a combination of ipragliflozin and losartan. The combination treatment significantly reduced BP and increased daily urine sodium excretion compared with losartan or ipragliflozin monotherapy, leading to greater improvement in BP salt sensitivity than ipragliflozin monotherapy. The combination treatment significantly ameliorated glomerulosclerosis and reduced cardiomyocyte hypertrophy compared with losartan or ipragliflozin monotherapy. The protein

expression levels of Na⁺/H⁺ exchanger isoform 3 (NHE3) and Na⁺-K⁺-Cl⁻ cotransporter 2 (NKCC2) in the kidney were significantly decreased with losartan monotherapy and combination treatment, but not with ipragliflozin monotherapy.

Conclusions: Inhibition of SGLT2 in combination with an ARB effectively improved BP salt sensitivity by reducing renal expression levels of sodium transporters including NHE3 and NKCC2, which eventually led to improvement of BP salt sensitivity and cardiorenal protection.

本論文は、ダール食塩感受性ラットにおいて、SGLT2 阻害薬（イブラグリフロジン）と ARB（ロサルタン）を使用した SGLT2 と AT1R を介したシグナル阻害が、食塩感受性、心肥大、および腎糸球体硬化を改善することを明らかにした。また、その機序として、併用療法における腎 NHE3 および NKCC2 蛋白質レベルの高食塩による活性化の抑制であることを示唆した論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

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