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Inhibition of NHE3 in the proximal tubule of the kidney by an orally absorbable NHE3 inhibitor attenuates angiotensin II-induced hypertension in mice

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We have recently shown that angiotensin (ANG II)-induced hypertension was attenuated in mice with global (*Nhe3*$^{-/-}$) and *Nhe3*$^{-/-}$ mice with transgenic rescue of the NHE3 gene selectively in small intestines (tg*Nhe3*$^{-/-}$), suggesting a significant role of NHE3 in the development of ANG II-dependent hypertension. The present study tested whether the pharmacological inhibition of NHE3 mainly in the proximal tubule of the kidney attenuates ANG II-dependent hypertension induced by a slow pressor dose of ANG II supplemented with 2% high salt diet. 9 groups (n=6-12) of adult male C57BL/6J mice were infused with or without ANG II (500 μg/kg/day, i.p. via mini pump) and supplemented with or without a 2% NaCl diet to slowly and moderately increase blood pressure (SBP) in 2 weeks. ANG II alone increased SBP from 116±2 mmHg to 140±2 mmHg ($p<0.01$), and supplement of ANG II with a 2% NaCl diet further increased SBP to 147±4 mmHg ($p<0.05$). Concurrent treatment with an orally active, absorbable NHE3 inhibitor AVE0657 (Sanofi-Aventis; 20 mg/kg/day, p.o.) significantly decreased SBP to 125±4 mmHg in ANG II-infused mice ($p<0.01$), and to 134±6 mmHg in ANG II-infused mice supplemented with 2% NaCl ($p<0.01$), respectively. Further treatment with AVE0657 and losartan, an AT1 receptor blocker (20 mg/kg/day, p.o.), completely normalize SBP in mice treated with ANG II and 2% NaCl to control (115±5 mmHg, $p<0.01$). AVE0657 significantly increased 24 h urinary Na^+ excretion ($p<0.01$) but had no effect on 24 h fecal Na^+ excretion in control or ANG II-infused mice. These results provide preclinical evidence that orally absorbable NHE3 inhibitors may be pharmacologically beneficial to treat ANG II-dependent hypertension by inhibiting NHE3 and Na^+ reabsorption in the proximal tubule of the kidney.

Biography

Xiao C Li is a Senior Research Scientist in the Receptor and Signal Transduction Laboratory in the Department of Pharmacology and Toxicology at University of Mississippi Medical Center, Jackson, Mississippi, USA. She has received Postdoctoral research training in Cardiovascular Pharmacology at Monash University, Melbourne, Australia, and in Molecular Pharmacology at University of Michigan, USA respectively. She has more than 20 years of research experience in G Protein-Coupled Receptor Pharmacology and angiotensin II-dependent hypertension, and authored more than 40 peer-reviewed articles in high impact journals such as *Hypertension, Kidney International, Clinical Science, Biochemical Pharmacology, American Journal of Physiology, and Pharmacological Research* etc., and a book in the renin-angiotensin system research field, and many were recognized by editorial commentaries, color cover highlights, and the faculty of 1000. Currently, she is working as a Co-Investigator in several research grants from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of General Medical Sciences (NIGMS), and National Heart, Lung, and Blood Institute (NHLBI).

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