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New insights into the roles of the Na^+/H^+ exchanger 3 in pressure natriuresis and angiotensin II-induced hypertension

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It is well established that a physiological pressure natriuretic response plays a key role in maintaining normal blood pressure and body salt and fluid balance, but the mechanisms underlying the pressure natriuresis response and its resetting to higher pressures in hypertension remain incompletely understood. Here we used wild-type (WT), global (*Nhe3*$^{-/-}$), kidney- (tg*Nhe3*$^{-/-}$) or proximal tubule-specific knockout (PT-*Nhe3*$^{-/-}$) of the Na^+/H^+ exchanger 3 (NHE3) to test the hypothesis that NHE3 in the proximal tubule of the kidney plays a critical role in the pressure natriuretic response and the development of angiotensin II (ANG II)-induced hypertension. 3 groups (n=8-12 per group) of adult male WT, *Nhe3*$^{-/-}$, tg*Nhe3*$^{-/-}$, and PT-*Nhe3*$^{-/-}$ mice (n=8-12 per group) were prepared for the standard pressure natriuretic experiment and ANG II-induced hypertension, respectively. The pressure natriuresis response was studied using the mesenteric and celiac occlusion technique to elevate renal perfusion pressure equally by 25 mmHg in all strains of mice. Under basal conditions, *Nhe3*$^{-/-}$, tg*Nhe3*$^{-/-}$, and PT-*Nhe3*$^{-/-}$ mice had significantly lower systolic blood pressure ($p<0.01$) and mean intra-arterial blood pressure than WT mice ($p<0.01$). 24 h fecal Na^+ excretion was significantly increased ($p<0.01$), whereas 24 h urinary Na^+ excretion was significantly reduced in both *Nhe3*$^{-/-}$ and tg*Nhe3*$^{-/-}$ mice ($p<0.01$). However, no difference was found in fecal Na^+ excretion between WT and PT-*Nhe3*$^{-/-}$ mice, whereas 24 h urinary Na^+ excretion was significantly increased in PT-*Nhe3*$^{-/-}$ mice ($p<0.01$). In response to increased renal perfusion pressure, the pressure natriuresis response increased 4-folds in WT mice ($p<0.01$), and only 2-fold in *Nhe3*$^{-/-}$ and tg*Nhe3*$^{-/-}$ mice ($p<0.01$). By comparison, the pressure natriuresis response increased 7-folds in PT-*Nhe3*$^{-/-}$ mice ($p<0.01$). To determine the role of NHE3 in ANG II-induced hypertension, ANG II was infused in WT, *Nhe3*$^{-/-}$, tg*Nhe3*$^{-/-}$, and PT-*Nhe3*$^{-/-}$ mice for 2 weeks (1.5 mg/kg/day, i.p.). ANG II induced robust hypertension in WT mice ($p<0.01$), as expected, but the hypertensive response to ANG II was significantly attenuated in global *Nhe3*$^{-/-}$, kidney-selective tg*Nhe3*$^{-/-}$, and PT-*Nhe3*$^{-/-}$ mice. Our results support the hypothesis that NHE3 in the proximal tubule of the kidney plays a key role in the regulation of physiological pressure natriuretic responses and the development of ANG II-induced hypertension.

Biography

Jia L Zhuo is a Full Professor and the Director of Receptor and Signal Transduction Laboratory in the Department of Pharmacology and Toxicology at the University of Mississippi Medical Center, Jackson, USA. He has over 30 years of sponsored research experience on the roles of Endocrine, Paracrine, and Intracrine Angiotensin II in the kidney and hypertension, supported by National Health and Medical Research Council of Australia (NHMRC) and National Institute of Health (NIH). He has authored >110 peer-reviewed articles and book chapters with many recognized by editorials, cover highlights, and the Faculty of 1000. He is a Fellow of The American Association for The Advancement of Science (AAAS), American Heart Association (AHA), and American Society of Nephrology (ASN), a permanent member for NIH/Center for Scientific Review Hypertension and Microcirculation Study Section. His research is currently supported by 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) respectively.

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