博士論文　（要約）

Low dose N-nitro-L-arginine Methyl Ester (L-NAME) causes salt sensitive hypertension via increases in activation of Na^+-Cl^- cotransporter (NCC).

(一酸化窒素の低下はナトリウムークロール共輸送体を活性化し、食塩感受性高血圧を発症させる)

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Abstract

Salt-sensitive hypertension has a high prevalence with increasing age or diabetes. It is well known that endothelial function is also impaired with aging and diabetes, as well as with nitric oxide (NO) synthesis decline. NO is not only a potent vasodilator but also possibly regulates sodium homeostasis at kidney tubules; however, the precise mechanism is still unclear. We hypothesized that blockade of nitric oxide synthesis by N-nitro-L-arginine Methyl Ester (L-NAME) has a direct effect on sodium channels in the kidney. In this study, low dose L-NAME or high salt loading alone did not change blood pressure in C57BL/6J mice, but L-NAME shifted the pressure natriuresis curve toward the right and induced salt-sensitive hypertension. No significant morphological changes were observed in the kidney. However, significant changes in sodium and chloride excretion were observed after hydrochlorothiazide treatment, but not by amiloride treatment, which was consistent with increases in p-NCC in the kidney. This highly suggested that NCC, not epithelial sodium

channel (ENaC), was activated by L-NAME to cause salt-sensitivity. In NCC-deficient mice, L-NAME failed to induce salt-sensitivity. Moreover, the p-NCC expression was increased by L-NAME in mDCT cells. L-NAME increased oxidative stress and pSPAK signaling, which was normalized by 4-hydroxy-2,2,6,6–tetramethylpiperidin-1-oxyl (TEMPO), a superoxide dismutase (SOD) mimetics. Consistently, TEMPO attenuated the L-NAME-induced increases in superoxide, mean blood pressure and p-NCC expression in the C57BL/6J mice with salt loading. To conclude, low-dose L-NAME inappropriately and directly activates NCC in both vivo and vitro and finally induces salt-sensitive hypertension. NO deficiency may be one cause of age- or diabetes-related salt-sensitive hypertension.

Key words:

Salt-sensitive hypertension; natriuresis; nitric oxide; L-NAME; oxidative stress; renal sodium channels; NCC; ENaC; aging; SPAK