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Salt-sensitive Hypertension in MnSOD Deficient Mice is Associated with Activation of NFkB and Upregulation of NAD(P)H Oxidase in the kidney

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Background : Oxidative stress plays a major role in the pathogenesis of hypertension and its renal and cardiovascular complications. Oxidative stress occurs when production of reactive oxygen species (ROS) exceeds the capacity of the antioxidant defense system. Mitochondria are a major source of intracellular production of ROS which are normally contained by mitochondrial antioxidant system including MnSOD. Consequently, MnSOD deficiency increases susceptibility to oxidative stress and its adverse consequences. Earlier studies in our laboratories have shown that consumption of high salt diet results in hypertension, renal senescence, and interstitial inflammation in MnSOD deficient (MnSOD+/-) mice.

Methods : Present study was undertaken to determine the effects of high salt diet on key mediators of inflammation in the MnSOD+/- mouse kidney. To this end wild type (MnSOD+/+) and MnSOD deficient mice were randomized to receive regular (0.4% NaCl) or high salt (4% NaCl) diet for 4 months. Tail arterial pressure and urine albumin excretion were measured, kidney was then harvested and processed for determination of mediators of oxidative stress and inflammation.

Result : Consumption of high salt diet resulted in a significant rises in arterial pressure and urinary albumin excretion in the MnSOD deficient mice. Hypertension and albuminuria were accompanied by activation of NFkB, upregulation of NAD(P)H oxidase subunits ($gp91^{phox}$, $p47^{phox}$, $p67^{phox}$, and rac1), PAI-1, iNOS, oxidized LDL receptor (LOX-1), and CD36 in the kidneys of SOD deficient mice. In contrast, high-salt diet did not significantly alter either blood pressure, urine protein excretion, or the measured inflammatory mediators in the wild type mice.

Conclusion : Thus salt-induced hypertension in MnSOD deficient mice is associated with activation of intrarenal inflammatory and oxidative pathways.

Key Words : Salt-sensitive hypertension, MnSOD, Oxidative stress