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Role of Oxidative Stress in Central Pressor Mechanism in Salt-Sensitive Hypertension

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Summary

We have been proposed that the central sympathetic nervous system plays an important role of salt-sensitive hypertension. For example, the sympathetic nerve activity was enhanced in salt-sensitive hypertensive patients and rats, leading the suppressed renal sodium (Na) excretion, and resultant Na retention and hypertension. And then, we suggested that central sympathetic activation caused these abnormalities. Recently, several groups including us indicated that oxygen reactive species (ROS) generation was up-regulated in salt-sensitive hypertension, suggesting that ROS overproduction may contribute to its pathogenesis. Moreover, it has been reported that ROS may be related to blood pressure (BP) regulation through the sympathetic nervous system. We demonstrated that Intracerebroventricular hyperosmotic saline-induced increase in BP and sympathetic nerve activity were enhanced in salt-loaded adrenomedullin (AM) knockout mice, and these responses were inhibited with pretreatment of tempol, a membrane-permeable superoxide dismutase mimetic. In addition, hypertonic saline increased ROS production, measured by the lucigenin chemiluminescence method, in the isolated hypothalamus and this response was greater in salt-loaded AM knockout mice than in salt-loaded wild-type ones. Because AM is considered to be an intrinsic antioxidant, endogenous AM in the brain may inhibit sympathetic activation through its antioxidant action. Thus, we examined the role of ROS in central sympathetic activation of salt-sensitive hypertensive animal models, Dahl salt-sensitive (S) rats. Intracelebroventricular injection of tempol decreased BP and renal sympathetic nerve activity in salt-loaded and non-salt-loaded Dahl S rats but this extent was greater in salt-loaded Dahl S rats. Intracelebroventricular injection of an NADPH oxidase inhibitor diphenyleneiodonium decreased BP and renal sympathetic nerve activity in salt-loaded Dahl S rats but did not in non-salt-loaded rats. Moreover, NADPH-induced ROS production from the isolated hypothalamus was increased in salt-loaded Dahl S rats. Moreover, the hypothalamic expression of NADPH oxidase subunits ($p22^{phox}$, $p47^{phox}$ and $gp91^{phox}$) mRNA expression was enhanced in salt-loaded Dahl S rats. Therefore, central ROS overproduction may enhance sympathetic drive of BP regulation of salt-sensitive hypertension.