Activation of the Sympathetic Nervous System via Reactive Oxygen Species in the Brain Induced by Salt Loading: Role of NAD(P)H Oxidase and Effects of Angiotensin Receptor Blockers.

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Summary

A high salt diet (HS) causes sympathetic hyperactivity and increases resting blood pressure (BP) in spontaneously hypertensive rats (SHR). Reactive oxygen species (ROS) in the rostral ventrolateral medulla (RVLM) are increased in hypertensive rats and AT1 receptor stimulation activates ROS generation. We examined whether HS increases ROS in the RVLM of SHR and, if so, whether this increase in ROS generation is caused by central angiotensin II activation via NAD(P)H oxidase. Male 6-week-old SHR and Wistar-Kyoto rats (WKY) were fed an HS (8% NaCl) or regular salt diet (0.5% NaCl: RS) for 6 weeks. BP was measured by the tail-cuff method. At 12 weeks of age, systolic BP was significantly higher in HS-SHR than in RS-SHR from 8 weeks of age on (214 ± 4 mmHg vs 172 ± 4 mmHg, n = 8, P < 0.05). Urinary norepinephrine excretion was significantly higher in HS-SHR than in RS-SHR at 12 weeks of age (2.09 ± 0.10 μg/day vs 1.47 ± 0.05 μg/day, n = 5, P < 0.05).

ROS levels in the RVLM were evaluated by measuring the levels of thiobarbituric acid-reactive substances (TBARs). TBARs levels were significantly higher in the RVLM of HS-SHR than RS-SHR (9.9 ± 0.5 μmol/g wet wt vs 8.1 ± 0.6 μmol/g wet wt, n = 5, P < 0.05). To confirm the role of ROS in the RVLM in BP regulation, tempol was microinjected bilaterally into the RVLM of 12-week-old SHR. Microinjection of tempol into the RVLM induced a significantly greater BP depression in HS-SHR than in RS-SHR. Intravenous hexamethonium induced a significantly greater decrease in BP in HS-SHR than in RS-SHR, indicating enhanced sympathetic outflow in HS-SHR. Angiotensin II type1 receptor (AT1R) expression in the RVLM was measured by Western blotting and NAD(P)H-dependent superoxide production in the RVLM was measured by lucigenin luminescence. AT1R expression in the RVLM was significantly higher in HS-SHR than in RS-SHR (5.1 ± 0.5 vs 3.4 ± 0.3, n = 6, P < 0.05). NAD(P)H-dependent superoxide production was higher in the RVLM from HS-SHR than in that from RS-SHR. These results suggest that SHR on an HS diet have significantly increased ROS generation in the RVLM resulting in further BP elevation by activation of the sympathetic nervous system. Increased ROS generation is probably due to NAD(P)H oxidase activation via central angiotensin system.