# Brain-tissue nNOS activity and Effects of Intracerebroventricular Infusion of nNOS Inhibitor on Sympathetic Outflow in Dahl Salt Hypertensive Rats.

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## Summary

We have demonstrated that intraperitoneal administration of 7-nitroindazole (7-NI), an inhibitor of neuronal nitric oxide synthase (nNOS), markedly increases tonic sympathetic outflow in Dahl salt-sensitive (DS) hypertensive rats. This result suggests that a neuronal NO-mediated suppressive mechanism to the sympathetic system might be developed and enhanced in the brain of DS hypertensive rats. However, there are three major limitations. First, 7-NI may lack selectivity to nNOS. Second, because 7-NI was administered systemically to the brain and not locally, the exact target organ of the inhibitor could not be determined. Third, the tissue concentration or activity of NOS in the vessels of DS hypertensive rats has been reported to be less than normal. To overcome these limitations, we measured brain-tissue nNOS activity and concentration, and examined the effects of intracerebroventricular (icv) administration of a specific nNOS inhibitor, S-methyl-thiocitrulline (SMTC), on renal sympathetic nerve activity (RSNA) in Dahl rats.

**Methods and Results:** DS and Dahl salt-resistant (DR) rats were fed a regular salt (0.4% NaCl) or a high salt (8% NaCl) diet for 4 weeks. After the sodium load, the brain stem nNOS activity was determined by the citrulline method. The concentration of nNOS was analyzed by Western Blot with anti-nNOS antibody and by the enhanced chemiluminesence method. The DS hypertensive rats showed significant increases in nNOS activity and protein abundance of the brain stem.. Using conscious rats instrumented chronically, RSNA was measured in both baroreceptor (BR)-loaded and -unloaded states, before and after icv administrations of artificial cerebrospinal fluid (aCSF, 100 μl), SMTC (50 nmole) and L-Arginine (1000 nmole). The BR unload was performed by decreasing arterial pressure with occlusion of the inferior vena cava. The icv administration of SMTC increased both resting and BR-unloaded RSNA concomitant with an increase in MAP in the DS hypertensive rats. The increases were suppressed by the sequential icv administration of L-Arginine.

**Conclusion:** Neuronal NO may suppress tonic sympathetic discharge, generated before baroreflex-mediated inhibition in DS rats. The neuronal NO-mediated suppression mechanism may be markedly enhanced in salt-induced hypertension.