Effects of Antihypertensive Drugs on Decreased Neuroactivity of Calcitonin Gene-Related Peptide (CGRP)-Containing Vasodilator Nerves in Spontaneously Hypertensive Rats (SHR). Hiromu Kawasaki and Koichiro Takasaki. Department of Pharmacology, Miyazaki Medical College, 5200 Kiyotake, Miyazaki 889-16.

We have demonstrated that the rat mesenteric resistance vessels are innervated by calcitonin gene-related peptide (CGRP)-containing vasodilator nerves (Kawasaki et al., Nature 335: 164-167, 1988). Furthermore, we have shown that CGRP-containing vasodilator nerves control the vascular tone and suppress the adrenergic nerve-mediated vasoconstriction (Kawasaki et al., J Pharmacol Exp Ther 252: 403-409, 1990). A recent study has demonstrated that neuroactivity of CGRP-containing vasodilator nerves in SHR decreases with age and suggested possible contribution of decreased neurogenic vasodilation to the development and maintenance of hypertension in SHR (Kawasaki et al., Circ Res 67: 733-743, 1990). The present study examined the effect of chronic treatment with antihypertensive drugs on the decreased neuroactivity of CGRP-containing vasodilator nerves in SHR.

Male SHR (8-week-old) received 0.1% captopril, 0.1% propranolol, 0.05% pindolol or 0.005% hydralazine in drinking water and 0.01% nicardipine in food for 7 weeks. At 15 weeks of age, mean carotid blood pressure was measured under pentobarbital anesthesia, and then the mesenteric vascular bed was isolated and prepared for perfusion. The preparation was perfused with Krebs solution at a constant flow rate of 5 ml/min, and changes in perfusion pressure were measured by a pressure transducer. An active tone of the preparation was produced by perfusing Krebs solution containing 7 µM methoxamine and 5 µM guanethidine (adrenergic neuron blocker). Perivascular nerve stimulation (PNS) was applied at 1-8 Hz for 30 sec via platinum ring electrodes placed around the superior mesenteric artery.

Chronic treatment with captopril, pindolol, propranolol, hydralazine and nicardipine significantly decreased mean blood pressure of SHR. In the perfused mesenteric vascular bed with active tone, PNS produced a frequency-dependent decrease in perfusion pressure or vasodilation. The PNS-induced vasodilation was abolished by 500 nM tetrodotoxin (neurotoxin), cold storage denervation (4°C for 72 hr), 500 nM capsacin (peptidergic toxin), and 1 µM human CGRP(8-36) (CGRP receptor antagonist), indicating that the response is neurogenic and mediated by CGRP-containing nerves. In control SHR, the neurogenic vasodilation was significantly smaller in aged SHR (15 week-old) than in young SHR (8 week-old) and age-matched WKY. The vasodilation was significantly greater in captopril-treated SHR than in control SHR. However, chronic treatment with pindolol, propranolol, hydralazine, or nicardipine has no such effect. There was no significant difference in vasodilator response to exogenous CGRP (10 and 100 pmol) between captopril-treated and control SHR.

These results suggest that chronic treatment with captopril reverses the decreased neuroactivity of CGRP-containing vasodilator nerves in SHR.