Blood pressure-related attenuation of Angiotensin II-induced contraction in the thoracic aorta from SHRSP at developmental ages of hypertension. Hideya Mizuno, Satoshi Mashiko*, Takeshi Onda*, Issao Tomita*, Masahiko Ikeda and Takako Tomita. University of Shizuoka Graduate School of Health Sciences, *School of Pharmaceutical Sciences, 52-1 Yada, Shizuoka, 422

We have reported that acetylcholine-induced endothelium-dependent relaxation in the thoracic aorta from SHRSP at developmental ages of hypertension was significantly enhanced in comparison with that of age-matched WKY. In adult SHRSP at established ages of hypertension, however, the relaxation markedly diminished compared with those observed in age-matched WKY and young SHRSP (CEPP, Onda et al. 21, 857-863, 1994). These results suggested that endothelial functions are subject to changes not only in response to shear-stress but also to hypertension. Angiotensin II (AngII) is a potent vasoconstrictor peptide. Although there is heterogeneity in vascular responses to AngII, the presence of the endothelium reduces the contraction by AngII in rat and rabbit aortae, and several arteries from other species. In rat carotid artery both endothelium-dependent relaxation and smooth muscle contraction seem to be mediated through AT1 receptor. It was examined in this study whether AngII-induced contraction is modified in thoracic aorta with the endothelium when blood pressure was maneuvered genetically and by hypotensive treatment.

Animals: Male SHRSP at 8-12-week old (developmental ages of hypertension) and age-matched WKY, five week-hypotensively treated SHRSP from 4 week of age by giving diet containing reserpine 2.8 mg, hydralazine hydrochloride 200 mg, methyclothiazide 100 mg/kg and 0.1% KCl, and 9-week old male SHRSP, WKY and their F1. Measurement of contraction to AngII: Thoracic aortae from rats were cut into rings (3mm long), and they were mounted in organ baths filled with Tyrode's solution (pH 7.3, 37°C) aerated with O2/CO2 gas (95:5) and tension was measured isometrically at 2 g of resting tone. AngII (10^{-9} - 10^{-6} M) -induced contraction in intact aortic rings from 12-week old SHRSP significantly diminished compared with that of age-matched WKY. Their responses, however, were comparable to each other either in endothelium-denuded rings or in intact rings treated for 30 min with 1mM NG-monomethyl-L-arginine (a nitric oxide synthase inhibitor). Contraction responses to phenylephrine (10^{-8} -10^{-6} M) were also to the same degree in both strains. Systolic blood pressure in 9-week old WKY, F1 and SHRSP was 134±0.6 (n=4), 167±2.7 (n=9) and 190±3.2 (n=4) mmHg, respectively. AngII-induced contraction in intact rings from these 3 groups was greatest in the order of WKY > F1 > SHRSP (p < 0.01 vs each other group). There was a negative correlation between blood pressure and the contraction (r=-0.759, n=17). Five week-hypotensive treatment reduced systolic blood pressure of SHRSP from 196±10.0 (n=8) to 153±7.1 (n=8). The hypotensive treatment significantly augmented AngII-induced contraction to the level comparable to that of non-treated WKY accompanying with a decrease in blood pressure. But phenylephrine (10^{-6} M)-induced contraction was unaltered. There was also a significant negative correlation (r=-0.659, n=32) between their blood pressure and AngII-induced contraction.

These results, together with the results of acetylcholine-induced endothelium-dependent relaxation, strongly suggest that the release of nitric oxide from the endothelium is hemodynamically stimulated in SHRSP aorta at early hypertensive ages to counteract high blood pressure.