Enhancement of Endothelium-Dependent Relaxation (EDR) in the Aorta from SHRSP at Developmental Ages of Hypertension, and Effects of Hypotensive Treatment on EDR in SHRSP. Takeshi Onda, Megumi Hamano, Satoshi Mashiko, Isao Tomita, *Masahiko Ikeda, and *Takako Tomita. University of Shizuoka School of Pharmaceutical Sciences, *Graduate School of Health Sciences, 52-1 Yada, Shizuoka, 422.

Introduction

It has been demonstrated that an increase in shear stress and flow induces a release of nitric oxide from the endothelium and relaxation of vascular smooth muscle. On the other hand, there are several studies showing an attenuation in EDR in SHR. In this study, we examined EDR in aortas from SHRSP at developmental (8 weeks) and established (20 weeks) stages of hypertension in comparison with that of age-matched WKY, and further the change in EDR by hypotensive treatment on SHRSP.

Materials and Methods

SHRSP and WKY were maintained under a specific pathogen free (SPF) condition by brother-sister breeding in our laboratory. Male SHRSP and WKY at 8-weeks of age (an early hypertensive age) and 20-weeks of age (a late hypertensive age) were used. Systolic blood pressure was measured by a tail pulse pick-up method. Ring segments (3mm) of thoracic aortas were mounted in organ baths which contained Tyrode's solution (pH 7.3, 37°C) aerated with O_2/CO_2 gas (95:5). Acetylcholine (ACh: 3×10^{-9} ~ 10^{-5} M) and ionomycin (4×10^{-8} ~ 10^{-6} M) were applied cumulatively on aortic rings precontracted with phenylephrine (Phe: 10^{-6} M) to measure EDR. For the experiment of hypotensive treatment, 4-week old male SHRSP and WKY were divided into two groups. One group (8 rats, treated group) had free access to a regular diet (Clea CE-2) containing hypotensive drugs (reserpine 2.8mg, methyclothiazide 100mg and hydralazine 200mg/kg diet) and 1% KCl in place of water for 5 weeks. Another group (8 rats, non-treated group) was given water and the same diet without drug-supplement.

Results

Systolic blood pressure (mmHg) at 8-weeks of age was 138 (WKY), 200 (SHRSP). Phe-induced contraction was not significantly different between both strains. At 8-weeks of age, ACh and ionomycin-induced EDR in SHRSP aortas was significantly enhanced compared with that in WKY aorta. N^G -monomethyl L-arginine (1mM), a nitric oxide precursor inhibitor, and mechanical denudation of the endothelium abolished the relaxation in both strains. Pretreatment of aortas with indomethacin (10^{-5} M), an cyclooxygenase inhibitor, did not significantly alter the relaxation by acetylcholine. There was no difference in endothelium-independent relaxation by sodium nitroprusside (10^{-9} ~ 10^{-6} M) and 8-Br cGMP (10^{-6} ~ 10^{-3} M). At 20-weeks of age, however, ACh-induced relaxation in SHRSP markedly diminished compared with that of 8-week old SHRSP and WKY rats at 8 and 20-weeks of age. Indomethacin-pretreatment of aortas from 20-week old SHRSP prevented the attenuation of the relaxation and masked the difference between SHRSP and WKY. A five week-hypotensive treatment lowered blood pressure of SHRSP from 207 to 151mmHg on average. The hypotensive treatment in SHRSP significantly reduced ACh-induced EDR compared with that in non-treated SHRSP.

Discussion and Conclusion

These results suggest that the aorta from SHRSP at 8-weeks of age releases more endothelium-derived relaxing factor (EDRF) to oppose development of hypertension whereas in SHRSP at 20-weeks of age, EDR is counteracted by increased release of endothelium-derived contracting factor (EDCF) resulting from functional changes in the endothelium due to a long duration of hypertension. Thus, the endothelium regulates vascular smooth muscle tone by a release of EDRF in response to changes in blood pressure at an early hypertensive age.