Endothelium-Dependent Relaxation and Effects of Chronic Treatment with Carvedilol in Mesenteric Artery of Stroke-Prone Spontaneously Hypertensive Rats. Fumiko Sasaki, Shoko Tanaka, Kazuo Yamamoto*, Keiichi Shimamura*, Tomoko Shibutani[†], Hiroo Hashimoto[†], Makoto Tanaka[†] and Satoru Sunano. Faculty of Pharmaceutical Sciences, Kinki University, Higashi-Osaka 577, *Research Institute of Hypertension, Kinki University, Osaka-sayama 589 and [†]Tokyo R & D Center, Daiichi Pharmaceutical Co., Ltd. 1-16-13, Kitakasai, Edogawa-ku, Tokyo 134.

It has been shown that endothelium-dependent relaxation in artery of spontaneously hypertensive rats (SHR) is impaired. This functional change has been reported to be prevented by chronic antihypertensive treatment. In the present experiments, effects of N^G-nitro L-arginine (L-NNA) and indomethacin (INDO) on the endothelium-dependent relaxation to acetylcholine (ACh) in mesenteric artery from Wistar Kyoto rats (WKY) and stroke-prone SHR (SHRSP) was studied. Effects of chronic treatment with carvedilol, an α , β -adrenoceptor antagonist, on endothelium-dependent relaxation were also studied. [Methods] SHRSP and control normotensive WKY were used in the present experiments. These rats were sacrificed at 16 weeks of age. Ring preparations of 1.5 mm width were made from the second order branch of the superior mesenteric artery. These preparations were mounted in organ baths filled with a modified Tyrode's solution. The tension changes of the preparations were measured isometrically by a force-displacement transducer. Endothelium-dependent relaxation was observed by cumulative application of ACh to the preparations precontracted by noradrenaline. Structure of endothelium was observed by scanning electron microscope. Antihypertensive treatment of SHRSP with carvedilol was begun at the age of the weaning (5 weeks) and continued until 16 weeks of age. Carvedilol was administrated by mixing the drug with chow. The dose of the drug was increased with age to maintain desired blood pressure (200 mmHg).

[Results and Discussion] Systolic blood pressure of the rats at age of 16 weeks were 130.9 ± 1.1 mmHg, 234.9 ± 3.3 mmHg and 198.7 ± 3.1 mmHg in WKY, SHRSP and SHRSP treated with carvedilol, respectively.

In the preparations from SHRSP, endothelium-dependent relaxation induced by ACh was impaired significantly. Furthermore, preparations from SHRSP showed contraction in response to high concentrations of ACh. The relaxation was attenuated by L-NNA, but not abolished completely in the preparations both from WKY and SHRSP. It was also demonstrated in the present experiment that the preparations from WKY also indicated contraction in high concentration of ACh in the presence of L-NNA. The relaxation to ACh was not affected by INDO in the preparations from WKY. On the other hand, in the preparations from SHRSP, contraction to high concentration of ACh disappeared in the presence of INDO. Treatment with carvedilol improved the impairment of endothelium-dependent relaxation of preparation from SHRSP.

Endothelial surface was rough and protrusion toward the lumen and crater-like invagination were often seen in the preparation from SHRSP, while that from WKY was well arranged. Treatment of SHRSP with carvedilol prevented these abnormalities.

In conclusion, the impairment of endothelium-dependent relaxation in the preparation from SHRSP is attributable to the decrease of endothelium-derived nitric oxide (NO) production and/or the increase of endothelium-derived contracting factor (EDCF) production. Although EDCF is released in the both preparations from SHRSP and WKY, the contraction by EDCF was diminished by sufficient amount of NO in the preparation from WKY. Carvedilol treatment prevented the impairment of the endothelium-dependent relaxation in the preparation from SHRSP, probably by preventing the structural alteration of endothelium.