6) N^{G} -monomethyl-L-arginine (L-NMMA)-induced pressor response in SHR in comparison with WKY. Jun Yamazaki, Naoya Fujita and Taku Nagao. Department of Toxicology and Pharmacology, Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113

Nitric oxide (NO) accounts for most of the biological actions of endothelium-derived relaxing factor (EDRF) and is synthesized in vascular endothelium from L-arginine. Several vasodilators including acetylcholine have been shown to interact with endothelial cells and induce the release of NO that relaxes the smooth muscle. Such vasodilators have been shown to cause weaker endothelium-dependent relaxation of isolated conduit arteries in hypertensive animals. This implies that an impairment of the relaxation mechanisms has occurred in these arteries in the hypertensive animals. Besides, a systemic administration of N^{G} -monomethyl-L-arginine (L-NMMA), the NO pathway inhibitor, has been shown to increase arterial pressure in rabbits, guinea pigs and rats. These observations indicate that the basally synthesized NO causes a hypotensive effect and contributes to the level of arterial pressure. In order to investigate whether or not hypotensive effect of basal NO *in vivo* is preserved during the development of hypertension, the effect of L-NMMA on arterial blood pressure was examined in age-matched spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto rats (WKY).

Thirty-nine male SHR (CRJ; 5-6, 12-14, 40 and 50-51 weeks old) and 21 normotensive WKY (CRJ; 5-6 and 12-14 weeks old) were used in the present study. Part of them were anesthetized with urethane (1g/kg, i.p.) and α -chloralose (25mg/kg, i.p.). In the experiment with conscious rats, they were restrained in a cage. A catheter was inserted into a tail artery for measurement of the arterial pressure. Drugs were administered into tail vein. Increasing doses of L-NMMA (3, 10, 30 and 100mg/kg) were applied in the experiment to investigate dose-response relationship to L-NMMA.

Intravenous administration of L-NMMA (3-100mg/kg) produced dose-dependent sustained hypertensive actions and bradycardia in conscious and anesthetized SHR and WKY.

L-arginine HCl (300mg/kg, i.v.) caused a slight hypotensive effect. Preadministration of L-arginine strongly diminished the pressor response to L-NMMA in anesthetized SHR (51w). The increase in arterial pressure by L-NMMA was also inhibited by the postadministration of L-arginine.

L-NMMA (30mg/kg, i.v.) shortened the duration of the depressor response to acetylcholine Cl (10 μ g/kg, i.v.). The shortening of the duration was overcome by L-arginine HCl (100mg/kg, i.v.). However, L-NMMA had no effect on the peak of the depressor response to acetylcholine.

L-NMMA (3-30mg/kg, i.v.) produced hypertensive actions to the same degree in the established stage of conscious and anesthetized SHR (40-50w). L-NMMA (3-100mg/kg, i.v.)-induced increase in arterial pressure in SHR (12-13w) was similar to that in age-matched WKY, as in the case with age-matched SHR and WKY (5-6w). The bradycardia was in almost the same degree in age-matched SHR and WKY (5-6w and 12-13w). No decrease was observed in L-NMMA response during the development and establishment of hypertension in SHR (5-6, 12-13 and 50w).

These results indicate that 1) the basal synthesis of NO from L-arginine contributes to the level of arterial pressure in SHR, 2) the hypotensive effect of basal NO is not apparently impaired by the developed hypertension in SHR and 3) L-arginine-derived NO plays some role in the duration of acetylcholine-induced depressor response *in vivo*.