Cholesterol Synthesis Inhibitor increases blood pressure in SHR and WKY/Izm. Nanfang.Li, Kenji Kizawa#, Makoto Sawamura, Yasuo Nara#, and Yukio Yamori. Graduate school of Human and Environmental Studies, Kyoto University, Kyoto-fu 606. #Biochemical Research Institute, Kanebo Co. Lim. Kanagawa-ken. Simane Medical University, Izumo-si 693.

<Object> In experimental hypertensive animal models including SHR, high cholesterol diet inhibits the increase in blood pressure. Serum cholesterol is thought to affect vascular reactivity through the alteration in lipid composition of plasma membrane. Recently it has been revealed that mevalonate metabolites play unique and important roles in various cellular functions in addition to that in cholesterol synthesis. Inhibition of the mevalonate (MVA) synthesis by cholesterol lowering drugs was reported to perturb intracellular signal transduction pathways. This led us to examine the effect of HMG CoA reductase inhibitor on blood pressure as well as vascular reactivity in SHR and WKY/Izm.

<Methods> In vivo experiments: Male 8-13 week-old WKY/Izm and SHR rats were fed with normal or high fat cholesterol (HFC, 20% suet, 5% cholesterol, 2% sodium cholate) diet. Pravastatin and/or squalene were administered orally, and blood pressure was measured with tail cuff method every week.

In vitro experiments: The thoracic aorta were removed from male 10-12 week-old WKY/Izm and cut into helical strips. They were pre incubated with various amounts of simvastatin for 10 minutes followed by stimulation with norepinephrine (NE) to record isometric contraction. In other experiments the strips were pre incubated with simvastatin and contracted with NE, and then the relaxation reaction was examined with acetylcholine (ACh) or nitroprusside. In some experiments MVA or squalene was added in the pre incubation solution.

<Results> Blood pressure in SHR increased significantly with administering 1mg pravastatin/kg/day for a week (pravastatin: 209.0 ± 17.6 mmHg, control: 188.0 ± 9.2 mmHg $p < 0.05$, $n=10$), while in WKY/Izm the increase in blood pressure was observed at 3 weeks later (pravastatin: 139.4 ± 11.1 mmHg, control: 128.2 ± 5.2 mmHg, $p < 0.05$, $n=10$). Larger effects were observed with 10 mg pravastatin/kg/day in SHR (pravastatin: 216.9 ± 12.2 mmHg, control: 198.0 ± 12.8 mmHg, $p < 0.05$, $n=10$) as well as in WKY (pravastatin: 150 ± 5.7 , control 132.4 ± 5.7 mmHg $p < 0.05$, $n=10$). This effect of pravastatin was inhibited by 1% squalene. The increase in blood pressure by 10mg pravastatin /kg/day was also observed when HFC diet was fed.

The vasocontraction induced by NE was inhibited by simvastatin in a dose dependent manner (10^{-7} - 10^{-4} M). However, this effect was not reversed by adding MVA or squalene at a concentration of up to 1mM. On the other way, endothelium-dependent relaxation induced by ACh was also diminished by the treatment with simvastatin. MVA had no effect again. Further examination showed that simvastatin did not decrease the relaxation induced by nitroprusside, suggesting NO synthesis in endothelial cells was the target of the drug.

<Conclusion> cholesterol synthesis inhibitor increased blood pressure which was probably due to blocking NO synthesis in endothelial cells.