2) Structural and Functional Changes of Mesenteric Vascular Beds in Spontaneously Hypertensive Rats. Koichiro Kishi and Tsutomu Inoue. Department of Pharmacology, Jichi Medical School, Tochigi-ken 329-04.

It has been shown that the elevated blood pressure of spontaneously hypertensive rats (SHR) is associated with an increased peripheral resistance, which can be induced by morphological and/or functional changes of resistance vessels. In this study, to elucidate possible mechanisms of the development of hypertension, we investigated morphology and reactivity of mesenteric resistance vessels from SHR and age-matched Wistar Kyoto rats (WKY).

Isolated perfused mesenteric vascular beds were prepared from male 6-, 11- and 18-week-old SHR and WKY. In the morphometric study, thin cross-sections of the large mesenteric arteries were stained with modified Azan stain and were studied morphometrically at the light microscope level. In the perfusion study, isolated mesenteric vascular bed preparations were perfused with modified Krebs-Henseleit solution. The perfusion fluid was bubbled with 95% O₂, 5% CO₂ mixture, kept at 37 °C, and maintained at the flow rate of 1.0 ml/min by a peristaltic pump. The perfusion pressure was recorded via a side arm with a pressure transducer. KCl and norepinephrine (NE) were injected intraluminally into the perfusion fluid in a volume of 0.1 ml. H-7, a potent inhibitor of protein kinase C, and 12-O-tetradecanoylphorbol-13-acetate (TPA), a protein kinase C activator, were mixed into the perfusion fluid.

The wall and media of the large mesenteric arteries were significantly thicker in SHR than in WKY at all ages investigated. The difference was apparent even in 6-week-old rats. Flow rate - perfusion pressure curves indicated that the vascular mechanical resistance became higher in SHR preparations than in WKY preparations as rats grew older. This may be caused by the wall thickening in resistance vessels of SHR. The pressor response to KCl became higher in SHR preparations than in WKY preparations as rats grew older. This may be caused by the media thickening in resistance vessels of SHR. The pressor response to NE was significantly higher in SHR preparations than in WKY preparations at all ages investigated. In marked contrast to the vascular mechanical resistance and the pressor response to KCl, the pressor response to NE was extremely higher in SHR than in WKY at the age of 6 weeks. Therefore, the extremely high NE response in younger SHR may not be caused by the structural alteration in resistance vessels. It may be caused by a functional change which is regulated by the signal transduction process in smooth muscle cells of resistance vessels. In the preparations from 6-week-old SHR, the pressor response to NE was inhibited less potently by H-7 than in those from WKY. Although, by the double-reciprocal plot, the maximum percent of inhibition by H-7 of NE-induced pressor response was estimated not to be significantly different between SHR and WKY preparations, the H-7 dose value for the half maximum inhibition of NE response was estimated to be significantly larger in SHR than in WKY. The maximum pressor response to TPA was approximately 50% higher in 6-week-old SHR preparations than in WKY preparations.

These results suggest that the development of hypertension in SHR may be caused by genetic structural and functional abnormalities of resistance vessels. Both abnormalities may be caused by the hyperreactivity to NE, the primary transmitter, through an altered signal transduction process, including the regulation of protein kinase C, in smooth muscle cells of resistance vessels. Furthermore, we found an enhanced activity of cytosolic Ca²⁺-dependent neutral proteinase (calpain) in the cytosol fraction from mesenteric vascular beds of SHR. The enhanced calpain activity may cause the structural and functional changes in resistance vessels and the development of hypertension in SHR, because calpain has been shown to modulate protein kinase C, phospholipase C, membrane-lining proteins, cytoskeletal proteins and several receptors. Further research is needed to determine the cause of the altered regulation of calpain activity in resistance vessels and to determine whether it is important in the development of hypertension in SHR.