1) Sex Difference in Cerebrovascular Atherogenesis in Rats - A Preliminary Report. Ryoichi Horie*, Yukio Yamori^o, Michiya Ohtaka^o, Yasuo Nara^o, Akira Ooshima^o and Hajime Handa*. Japan Stroke Prevention Center, Department of Pathology, Shimane Medical University^o, Izumo 693 and Department of Neurosurgery, Faculty of Medicine, Kyoto University*, Kyoto 606.

INTRODUCTION The first detection of ring-like fat deposition in the mesenteric arteries of substrains of SHR (YAMORI, Y.: Tr. Soc. Pathol. Jap. 63:226, 1974) and the device of a new method for the "macroscopical" detection of "cerebrovascular" ring-like fat deposition, i.e., Barium Contrasted Sudan Staining Method called BCSS method (YAMORI, Y., HORIE, R.: Jap. Heart J., 16:332, 1975) has made a rapid progress in the studies on cerebrovascular atherogenesis in rats.

Using the BCSS method, 5 important factors for the development of cerebrovascular atherogenesis were qualitatively and quantitatively clarified. These are hypertension, hemodynamic derangement, hypercholesterolemia, the nervous system and genetic factors. Based on our experimental results, relationship among hypertension, hemodynamic derangement, hypercholesterolemia, the nervous system and genetic factors in the development of cerebrovascular atherogenesis was summarized as the initiation mechanism of stroke in relation to cerebrovascular atherogenesis (HORIE, R.: Jap. Circ. J., 41:915, 1977). Especially, concerning the important role of hypercholesterolemia and genetic factors, since the establishment of suitable animal models for cerebrovascular atherogenesis, i.e., hypertensive arteriolipidosis-prone rats (ALR)(YAMORI, Y.: Jap. Heart J., 18: 602, 1977) which develop ring-like fat deposition even in the cerebrovascular system within a few weeks, and the development of normotensive atherogenic rats (NAR)(HORIE, R., YAMORI, Y.: Jap. Heart J., 19:627, 1978) which develop a similar cerebrovascular atherogenesis without hypertension, emphasis has been placed on genetic factors for arterio- or athero-sclerosis. The establishment of ALR and further studies using them verified genetical difference in the lipid metabolism of them compared with rats which show low or no susceptibility to vascular atherogenesis. On the other hand, development of NAR clearly substantiated the existence of genetical susceptibility to cerebrovascular atherogenesis indifferent to hypertensive genetic factors.

However, in our experiments up to the present, mainly male animal models were used for the convenience of standardization. In the present study, sex difference in cerebrovascular atherogenesis was investigated, especially about above-mentioned important factors in the development of cerebrovascular atherogenesis, the mesenteric arteries were also investigated as compared with the cerebrovascular system.

MATERIALS AND METHODS Used stroke-prone and resistant-SHR (SHRSP and SHRSR) were F₄₅₋₄₇ generation of SHR maintained at Japan Stroke Prevention Center (Izumo, Japan). (1)52 rats of SHRSP (A₁-sb strain, male: 24 rats, female: 28) were fed on a high fat-cholesterol (HFC) diet (including fat 20%, 5% cholesterol, 2% cholic acid) from the age of 60 days for 3 weeks. After blood pressure (tail pickup method), gain in body weight and serum cholesterol level (the enzymatic method) were checked, cerebrovascular fat deposition was investigated by the BCSS method. (2)Using F₁ generation (male: 17 rats, female: 13) and F₂ generation (male: 16 rats, female: 10) of NAR above-mentioned procedures were applied to the analysis of sex differences. In these rats, fat deposition in the mesenteric arteries was also investigated. (3)More than 100 rats including male and female stroke-prone SHR (A₁-sb, A₃ and A₄ strains) and experimental hypertensive rats (DOCA hypertensive rats and renal infarction hypertensive rats) were used for the analysis of relationship between blood pressure and serum cholesterol level in relation to sex difference. (4)The experimental system of YAMORI'S PREPARATION-II (YAMORI, Y., HORIE, R., SATO, M. and FUKASE, M.: Stroke, 7:385, 1976) was applied to 32 rats (male: 14 rats, female: 18) of Wistar-Kyoto rats (WK). (5)Difference in the degree of cerebrovascular fat deposition between 14 castrated male SHRSP (A₁-sb strain) and 12 untreated male SHRSP (A₁-sb strain) was examined by the BCSS method.

RESULTS WITH DISCUSSION Generally, males showed higher susceptibility to vascular fat deposition than females. However, serum cholesterol level in females was higher than that in males in spite of higher level of blood pressure in males although strain differences in both serum cholesterol level and blood pressure were suggested. In NAR without hypertension, males also showed high susceptibility to vascular fat deposition. Further, castrated male showed susceptibility. In YAMORI'S PREPARATION-II, males revealed higher susceptibility in cerebrovascular atherogenesis than females (Table).

Sex (No. of Rats)	Fat Deposition (%)	No.of Sudanophilic Rings	Blood Pressure (mmHg)	Serum Cholesterol (mg/dl)	Gain in Body Weight (g)
Male (15)	85.7**	12.3±0.7*	138 ± 4	310.0±30.6	47 ± 8
Female (17)	29.5	5.8±0.6	135 ± 7	349.5±28.2	42 ± 5

- 1) Data are M±SE. *,**: Significant difference from female group(p<0.05, 0.01)
2) All rats were fed on a HFC diet from the age of 45 days for 7 weeks

In addition, cerebral arteries and mesenteric arteries showed different susceptibility to fat deposition in males and females. From these results, it was suggested that high susceptibility to cerebrovascular fat deposition in male rats might be partly due to high blood pressure and the difference in sex hormone. Estrogen might protect the development of vascular fat deposition in relation to the development of hypertension (YAMORI, Y., SATO, M., HORIE, R. and OHTA, K.: Jap. Heart J., 17:404, 1976).

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