Arch. Jap. Chir., 46 (3), 191~213, Mai, 1977

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Studies on Stroke in Relation to Cerebrovascular Atherogenesis in Stroke-prone Spontaneously Hypertensive Rats (SHRSP)

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Received for Publication March, 10, 1977

Introduction

During this past quarter of a century, highest values have been reported for Japanese death rate from vascular disease in the central nervous system[1]. Further, among all the countries of the world stroke has most frequently occurred in Japanese[2]. Now, such a tendency seems to be continuing, as population indexes for aged people have been showing acceleratingly increased values[3]. Of course it has been continually emphasized that it is absolutely necessary to find drastic countermeasures for stroke. However, such studies on the pathogenesis of cerebrovascular lesions have been limited by the lack of an appropriate animal model.

Recently, Okamoto, Yamori and Nagaoka[4] reported the establishment of the stroke-prone spontaneously hypertensive rat (SHRSP) in which stroke (cerebral hemorrhage and/or softening) developed spontaneously, and with a high incidence (more than 80% in males)

The establishment of SHRSP proved to be very beneficial. First, it experimentally showed the surpassing importance of hypertension[4~5], as has been guessed epidemiologically by many clinicians[6~11]. Second, based on the evidence obtained by successive selective breeding of stroke-prone and -resistant SHR, it suggested the important role of genetic factor[12]. Finally, it threw light on studies for clarifying the pathogenetic mechanisms of stroke, as pathological findings of cerebrovascular lesions in SHRSP were verified to correspond well to those in humans[13~15]. Especially, as Yamori reported[13], SHRSP develop stroke just like that in Japanese people, i. e., "arterionecro-thrombogenic stroke", in contrast to "athero-thrombogenic stroke" in the people of USA and European countries.

This study was supported by grants from NIH (HL 17754), the Science and Technology of the Government of Japan, the Japanese Ministry of Education and the Japanese Society for the Promotion of Science.

Key Words Stroke-prone SHR (SHRSP), Cerebrovascular atherogenesis, Cervical sympathectomy Cerebral circulation, Cerebrovascular reactivity, Prophylaxis of stroke

This should be noted as compared with Ooneda's "plasmatic arterionecrosis" in humans[15]. Such facts promise a further prophylactic approach to stroke in "Japanese" people using this newly-found suitable model.

However, when SHRSP were established in 1974, two important problems about the suitability as a model for stroke in humans remained unsolved.

The first problem was the difference in predilection sites of stroke between SHRSP and humans. In SHRSP, the most predominant site for stroke was the cortical region, in contrast to the relatively low incidence of stroke in the human cortex. On the other hand, the common site for stroke in SHRSP and humans was the basal ganglia, where the incidence was the highest in man, and next to the highest in SHRSP.

The other problem was cerebrovascular atherogenesis considering the possibility of SHRSP as a suitable model for "athero-thrombogenic stroke" For the etiology and pathogenesis of stroke[16~17], emphasis has been placed on atherosclerosis in the cerebrovascular system, but a suitable experimental model for the study of cerebral atherosclerosis related to stroke has not yet been obtained[18~20].

The first problem was previously reported in relation to cerebral circulation and the initiation mechanism of stroke[22].

In the present studies, considering the possibility of SHRSP as a suitable model for "athero-thrombogenic stroke", the problem of cerebrovascular atherogenesis was persued for clarifying the initiation mechanism and for prophylaxis of stroke.

Materials and Methods

SHRSP[1] used or examined in this study were the F_{23}-F_{36} generation of SHR maintained at the Department of Pathology, Faculty of Medicine, Kyoto University (Kyoto, Japan). Stroke (cerebral hemorrhage and/or infarction) developed in these rats spontaneously. The incidence of stroke in these SHRSP, which died a natural death, was 84% in males and 80% in females. Controls were stroke-resistant SHR (SHRSR)[4] (the incidence of stroke about 7%), and normotensive control rats of Wistar-Kyoto (WK), from which the SHR had been derived.

Apoplectic gene-free renal infarction hypertensive rats (RHR) were experimentally produced[21] from WK.

All numerical data were statistically analyzed by the Student t-test.

Chapter 1. Atherogenesis in the Cerebrovascular System of SHRSP.

Part 1. Detection of cerebrovascular fat deposition in SHRSP.

(1) 60 rats of SHR, RHR, and WK at the age of 60 days were fed on high fat cholesterol diet (HFC diet[26~27,29~32] ; 20% suet, 5% cholesterol and 2% cholic acid) with or without 1% salt in drinking water for 1 to 30 weeks. Some groups of SHR and RHR were treated with hydralazine hydrochloride (80 mg/L) in drinking water during hypercholesterolemic diet feeding. In order to observe fat deposition in the cerebrobasal arteries

"as a whole", the following 3 methods were utilized : (I) microsurgical extirpation of the circle of Willis and basilar arteries, followed by Sudan III staining, (II) Sudan III staining of cerebral vessels from inside by perfusion with Sudan III solution following the preperfusion of 200 ml of heparinized physiological saline (at 38°C) with final systolic pressure of rats through an aortic cannula, and (III) 75% barium sulfate with 10% gelatin was perfused through an aortic cannula after preperfusion of 200 ml of heparinized physiological saline (at 38°C), with the pressure equal to the systolic pressure of individual rats (checked before perfusion). The brain was removed after being kept at −20°C in a freezer for one hour, fixed 10% cold formalin and stained by Sudan III (Barium Contrasted Sudan Staining method : BCSS method)[24].

(2) Above-mentioned BCSS method was applied to 5 SHRSP and 5 RHR fed on an HFC diet and lateral lenticulostriate arteries were gradually microsurgically extirpated by repeating Sudan III staining of the brain for the identification of arterial fat deposits.

(3) Five male SHRSP and RHR at the age of 60 days, with blood pressure over 200 mmHg, were fed on an HFC diet for 2 weeks. Five min., 2 hours, and 20 hours after the injection of 250 mg/Kg horseradish peroxidase (type 2-Sigma), the rats under Nembutal anesthesia (30 mg/Kg, i. p.) were fixed by perfusion through an aortic cannula with an aldehyde fixative, a mixture of paraformaldehyde and glutalaldehyde in cacodylate buffer (pH 7. 2). The basilar arteries removed from the brain were incubated at room temperature for 20 min. in diaminobenzidine solution in Tris-Buffer (pH 7. 4). Small parts of arteries which appeared to be brown macroscopically were refixed in osmium-tetroxide, dehydrated in graded alcohol, and embedded in EPON, and prepared as ultrathin sections for light and electron microscopical observations.

Part 2. Studies on initiation mechanisms of cerebrovascular atherogenesis in rats.

(1) More than 200 rats including SHRSP, RHR and WK (30 or 60 days old) were fed on an FHC diet with 1% salt in the drinking water for one week, respectively. Control rats were fed on an ordinary laboratory stock chow diet containing 6% fat (F_{11} diet, FUNAHASHI Farm). The rats were killed, mesenteric arteries were extirpated free from the surrounding fat tissue (as described in our previous reports[26~28]), and then examined for sudanophilic rings. Fat deposits in the cerebrobasal arteries were macroscopically observed using the BCSS method. The amount of fat deposition in the mesenteric arteries was classified into five grades: 0, 1, 2, 3, and 4. "Grade" in the results indicated mean values of the grades of fat deposits. The number of sudanophilic rings in the circle of Willis was counted to show its mean values as "SR". Blood pressure in the rats of the experimental group were checked repeatedly without anesthesia by a "tail-pulse-pickup" method[5] Serum cholesterol level was measured by the ZURKOWSKI method[28]. Gain in body weight after the HFC diet was checked for an index of food intake.

(2) In YAMORI's preparation-I[24] using 142 SHRSP (A_{1-sb}) and 98 RHR, topographical study on cerebrovascular fat deposition was performed. The number of sudanophilic rings

(SR) was counted at intervals of 0-3, 3-6, 6-9, 9-12 mm apart from the portion of carotid fork, basilar head, and vertebrobasilar junction.

(3) Twenty-four normotensive WK, 60 days old, and five WK, 46 days old, were operated on as follows, under Nembural anesthesia (40 mg/Kg, i. p.), to induce artificial hemodynamic derangements in the cerebrobasal arteries. Carotid aretries were bilaterally or unilaterally ligated with great care in order to prevent vagal irritation or injury which might cause cerebral hypoxia due to respiratory disturbances. (All 40-day-old WK were used for bilateral carotid artery ligation). Basilar arteries were ligated after being exposed with a cervical transclival approach by a microsurgical technique. Sham operations were performed as follows: pontine arteries were exposed through the cervical transclival approach and two pontine arteries were bilaterally electrocoagulated at their origin from the basilar artery. These operated rats were fed on an HFC diet with 1% salt in the drinking water for ten weeks. Serum cholesterol level, tail blood pressure, an body weight were measured while these rats were on the HFC diet. In order to observe deposition in the cerebrobasal arteries, the BCSS method was utilized. Fat deposits were observed not only macroscopically but also by light or electron microscopic techniques after the preparation of ultrathin sections from the specimens refixed in osmium tetroxide and embedded in EPON. Diameters of the carotid and basilar portions in the posterior communicating arteries were measured with a micrometer by use of a microscope.

(4) 40 male SHRSP (A_3 strain), at the age of 60 days, were applied to YAMORI's Preparation I. On half of them, bilateral cervical sympathectomy was performed by microsurgical technique using a microscope for microneurosurgery to avoid irritation or injury to surrounding vessels or attached nerves and tissues. Rats were especially carefully operated on in the area of bifurcation of the carotid artery. All rats were fed on an HFC diet for 3 weeks. Blood pressure, body weight and serum cholesterol level were repeatedly checked during the experimental period. The BCSS method was used to detect cerebrovascular fat deposition.

In order to confirm the reliability of surgical sympathectomy and to observe the appearance of innervation in the basilar artery, fluorescene microscopic study was also performed, i. e., after decapitation, basilar arteries were dissected out by microneurosurgical technique using a microscope, carefully avoiding damage to the adventitia of arteries, especially when stripping the arachnoid membranes surrounding the vessels. Then these arteries were immersed into icecold Krebs-Ringer bicarbonate buffer containing 14% glyoxylic acid for 10 minutes. Finally, the vessels were stretched flat on slide glass, quickly dried, and mounted in liquid paraffin for fluorescence microscopy.

Chapter 2. Prophylactic Trials for Stroke in SHRSP, in Relation to the Effect of High Fat Cholesterol Diet

Part 1. Incidence of stroke and hypertension levels in SHRSP and RHR fed on an HFC diet.

(1) Seventy SHRSP, 30 RHR, and 10 WK, from the age of 60 days, were fed on an HFC diet. Control groups for these groups were fed on normal laboratory stock diet. These rats were examined for blood pressure, body weight, and serum cholesterol level every 2 weeks until they died naturally. All rats were examined at autopsy and after fixation in 10% formalin, brains, hearts, and kidneys were embedded in paraffin and made into histological sections stained with hematoxylin eosin for microscopical observation.

(2) About 60 RHR were fed on the HFC diet or on the normal laboratory stock diet at the age of 60 days. Blood pressure and body weight were repeatedly measured.

Part 2. Mechanism of lowering effect of HFC diet on hypertension from the view point of vascular reactivity.

(1) To examine vascular reactivity, 7 SHRSP fed on an HFC diet for 2 months and 7 SHRSP fed on a normal diet were cannulated through the femoral artery under chloralose (40 mg/Kg, i.v.) anesthesia and injected intravenously with 1, 3, 10, 30, μg/Kg of norepinephrine, and changes in direct blood pressure were recorded by a pressure transducer connected to a polygraph (Nihon-Koden, RM-45).

(2) Forty SHRSP and 20 WK from the age of 40 days were fed on HFC diet. Control group for these were fed on normal laboratory stock diet. These rats were repeatedly checked for blood pressure, body weight. Regional cerebral blood flow (rCBF) was repeatedly measured by FUJITANI, et al's modification of the hydrogen clearance method[23] in the frontal and tempotal regions of the cerebral cortex.

Under Nembutal anesthesia (40 mg/Kg, i. p.), rats were placed in a stereotaxic apparatus, and enamel-insulated platinum electrodes (0.3 mm in diameter and 25 mm in length) were bilaterally implanted into frontal and temporal regions of the cortex, 2mm and 2.5mm apart from the midsagittal line, 2 mm anterior and posterior ot the bregma, and 2.5 mm in depth from the cortical surface. These electrodes and a reference electrode on the sagittal line, 4 mm anterior to the bregma, were connected to a miniature receptacle and the whole assembly was fixed with dental cement on the skull.

In conscious rats put in a small gas chamber, rCBF was measured 2 weeks after the operation and periodically thereafter.

In addition, chemical cerebrovascular reactivity was determined by detecting an increase in rCBF responsed to 10% CO_2 inhalation.

Results

Chapter 1. Atherogenesis in the Cerebrovascular System of SHRSP

Part 1. Detection of cerebrovascular fat deposition in SHRSP

(1) By the 3 afore-mentioned methods, such ring-like fat deposits (as previously reported to be in the mesenteric arteries)[25~27] were clearly noted in the circle of Willis and basilar arteries "as a whole" in SHRSP and RHR on an HFC diet (Fig. 1). These findings

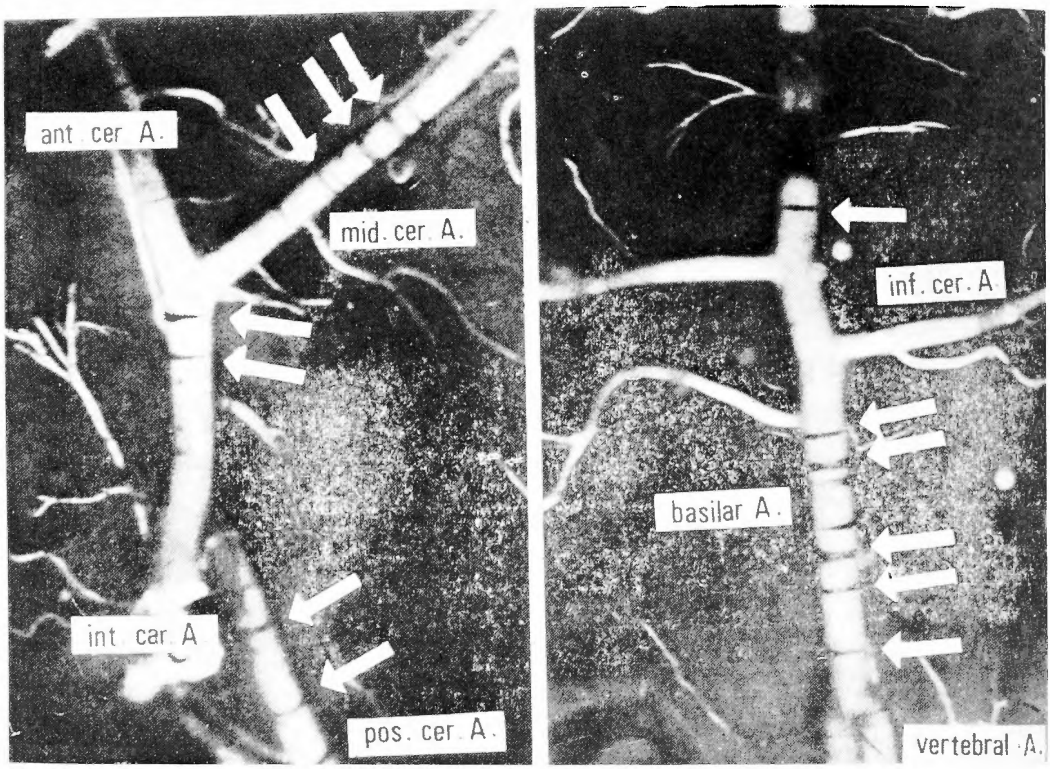

Fig. 1. Ring-like fat deposition in the cerebrobasal arteries detected by BCSS method.

appeared to be similar to a "ring-like" form of atherosclerosis in the circle of Willis and basilar arteries in human brains, as noted at autopsy.

All SHRSP which survived over 80 days on an HFC diet developed aortic fatty streaks; in all cases with over 1 year survival, atheromatous lesions were clearly recongnized, while such was observed in 75% of cases with over 250 day survival. In some cases with 1 year survival, calcifications were detected.

(2) Three of 5 SHRSP and all of 5 renal infarction hypertensive rats showed ring-like fat deposition, even in the lateral lenticulostriate arteries.

(3) Vital microscopic observation : Ring-like depositions of peroxidase reaction products were observed to correspond to the localization of fat deposition, especially to the vasodilated segments of extirpated cerebrobasal arteries.

Light microscopic finding : Two hours after injection : Many brown pigments of peroxidase reaction products were noted mainly in the intercelluar space of medial smooth muscle cells. Twenty hours after injection : Reaction products were noted diffusely in adventitia.

Electron microscopic findings : Endothelial changes : The most striking changes was the appearance of foam cells. Sometimes vacuoles in these cells contained homogeneous

material or myelin-like structure, and sometimes they seemed to be empty. Pinocytotic vesicles were increased in number, and often electron dense materials appeared in them 5 min. after injection. Changes in the media : Smooth muscle cells frequently containing various type of fat deposites were observed. Foam cells which contained numerous large and small vacuoles in the cytoplasm also appeared in the media. Electron dense particles were often seen near the vacuoles 2 hours after injection. In addition to atrophy of smooth muscle cells, extracellular space of the media was widened because of an increase in elastin and swollen collagen. Twenty hours after the injection, electron dense bodies were observed in the cytoplasm of fibrocyte which appeared outside the outer elastic lamella.

Part 2. Studies on the initiation mechanism of cerebrovascular atherogenesis in rats.

(1) For male hypertensive rats fed on an HFC diet from the age of 30 days, arterial fat deposition in the brain and mesenteric arteries is summarized in Fig. 2.

No SHRSP on an HFC diet for one week had fat deposition in the circle of Willis, while 50% of them had ring-like fat deposits in the mesenteric arteries, even in the prehypertensive stage from 30 to 37 days after birth. After two weeks of the HFC diet, in all SHRSP, no fat deposits were noted in the circle of Willis, but such were clearly observed in the mesenteric arteries.

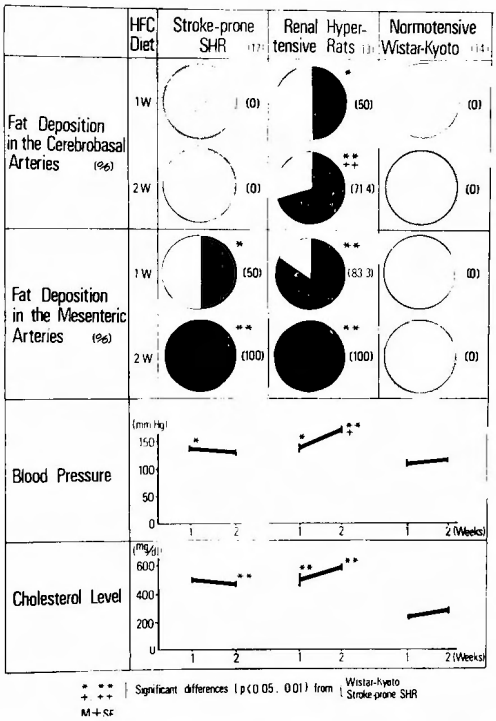

Fig. 2. Arterial fat deposition in the cerebral and mesenteric arteries of male hypertensive rats fed on an HFC diet from the age of 30 days.

For RHR on an HFC diet for one week, 50% had sudanophilic rings in the circle of Willis, and 100% showed such in the mesenteric arteries. After two weeks on an HFC diet, fat deposits in the circle of Willis were noted in 83.3% of RHR, while the sudanophilic rings in the mesenteric arteries were observed in all rats.

Normotensive WK did not show such fat deposition in either the circle of Willis or the mesenteric arteries after 1 or 2-week-feeding of the HFC diet.

Statistically significant differences in the incidence of fat deposition are shown in Fig. 2. RHR, and SHRSP in prehypertensive stage showed a clear susceptibility to fat deposition in mesenteric arteries compared to normotensive WK. Especially RHR showed such susceptibility also in the circle of Willis, as compared to prehypertensive SHRSP and WK. There was no significant difference in serum cholesterol levels and gain in body weight between SHRSP and RHR. Therefore, the difference in fat deposition seemed to be caused by the difference in blood pressure.

These comparative results indicated that fat depositions in the circle of Willis had a greater tendency to depend on high blood pressure than those in the mesenteric arteries.

The effect of blood pressure control on arterial fat deposition in cerebral arteries of male SHRSP fed on an HFC diet for ten weeks from the age of 30 and 60 days is shown in Fig. 3.

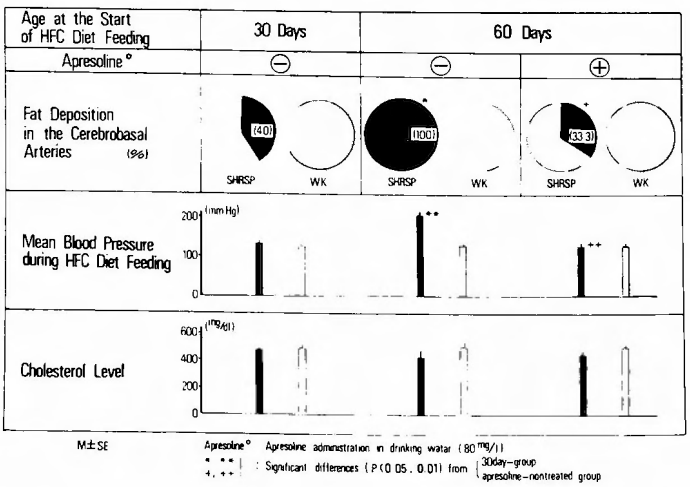

Fig. 3. Arterial fat deposition in the cerebral arteries of Apresoline -treated and- untreated male SHRSP fed on an HFC diet for 10 weeks from the age of 30 or 60 days.

Around the age of 40 days, SHRSP showed an initial blood pressure increase over that of WK and at the age of 70 to 90 days, then had stable hypertension. However, SHRSP treated with Apresoline maintained a normotensive range of blood pressure not significantly different from that in WK.

Fat deposits in the cerebral arteries were noted in 100% and in 40% SHRSP fed on an HFC diet from the age of 60 days and 30 days, respectively. In contrast to these

hypertensive group, only 30% of antihypertensive agent-treated SHRSP fed one an HFC diet from the age of 60 days had fat deposition.

Normotensive WK never showed fat deposition.

Serum cholesterol level showed no significant differences.

These facts again obviously indicated the importance of hypertension as a factor for arterial fat deposition.

Thus, from these facts, it was possible to obtain the relationship between blood pressure and arterial fat deposition in the cerebral arteries of SHRSP, RHR and WK fed on an HFC diet for ten weeks.

The number of sudanophilic rings in the cerebrobasal arteries was counted and plotted against the blood pressure of SHRSP, RHR and WK fed on an HFC diet for ten weeks. Some of these rats had been treated with an antihypertensive agent, (Apresoline, 80 mg in the drinking water.) A significant linear correlation ($Y=0.084x-8.65$, $r=0.645$, p 0.001) was noted between the number of rings (Y) and blood pressure (X).

(2) Sudanophilic rings were mainly located in the arterial wall near branchings such as the carotid fork, basilar head and vertebrobasilar junction (Fig. 4).

(3) Acute fat deposition were noted in the circle of Willis of WK on an HFC diet for ten weeks from the age of 60 days after operation. All six bilateral ligations, four of six unilateral carotid ligations, and three of six basilar ligation resulted in development of fat

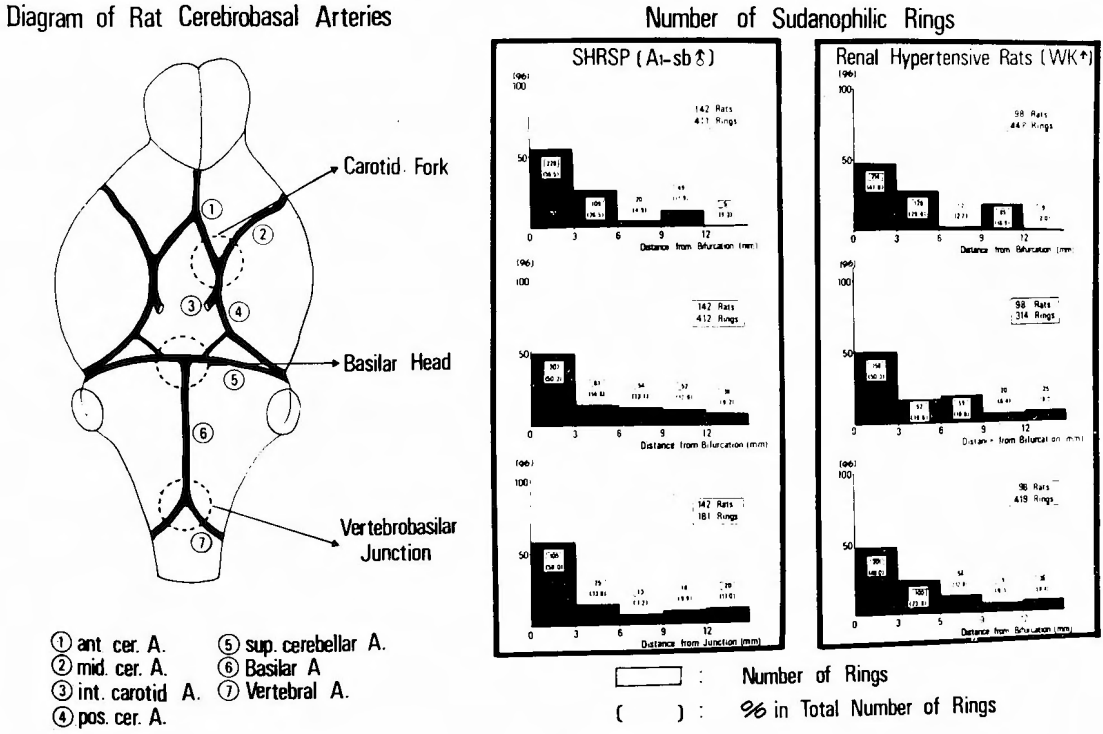

Fig. 4. Localization of fat deposition in rat cerebrobasal arteries.

deposition in the posterior communicating artery.

These deposits were noted bilaterally (in four cases) or unilaterally (in two cases) after unilateral carotid ligation, and unilaterally on either side after basilar artery ligation. However, electrocoagulation of pontine arteries as a sham operation never resulted in fat deposition.

The group of five young WK, in which carotid arteries were bilaterally ligated at the age of 40 days, showed more widespread distribution of fat deposition ; three of them had ring-like fat deposits in the posterior cerebral and posterior communicating arteries bilaterally, one of them in the basilar cerebral artery bilaterally.

These fat depositions were rings-like and identical to those observed in hypertensive rats on an HFC diet[31~36]. Histological study also confirmed that these arterial lesions were similar to those in hypertensive rats[26~28] The intima of these regions were thickened with foam cell formation and smooth muscle cells in the media showed severe fatty degeneration

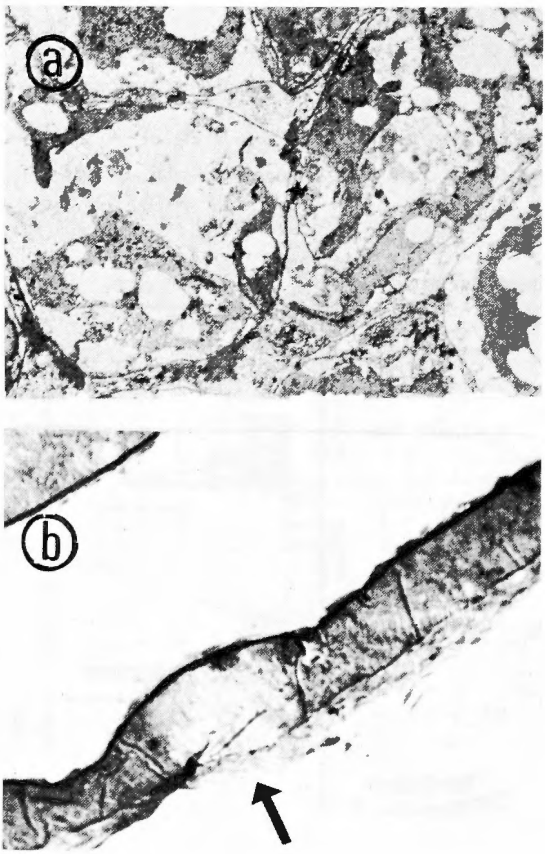

Fig. 5. Fatty degeneration of media in the cerebrovascular system (a) Electron microscopically noted foam cells in the media of a basilar artery (b) Thichening of media with fat-laden foam cells (indicated with an arrow)

with vacuolation, partial necrosis, and destruction. In the intercellular spaces of the media, collagen fiber formation was noted. The internal elastic lamellae were degenerated and sometimes fragmented, or their fenestrae were widened in the damaged wall, where a few medial cells protruded into the intima.

It was clearly noted that the regions with ring-like fat deposition were dilated and frequently elongated into an S-shape. In the group of bilateral and unilateral carotid and basilar artery ligations, diameters at the carotid and basilar portions of the posterior communicating artery were significantly larger than diameters at the non-dilated communicating artery in the sham-operated group. Such marked dilatations were far beyond normal variations, although diameters of basilar portions in the posterior communicating arteries were variable. Fat deposits were located mainly at the extended walls of elongated and dilated arteries. Serum cholesterol level, blood pressure and gain in body weight showed no significant differences among four experimental groups, including the sham-operated group.

(4) After the operation, there were no respiratory disturbances recognized in any of the rats, and the fact that denervated groups showed no noradrenaline (NA) varicosities confirmed the reliability of surgical sympathectomy. Such was in contrast to the clear appearance in control group of such varicosities at the inner part of the adventitia adjacent to media in the basilar arteries.

Aa shown in Fig. 6, no fat deposit was detected in the cerebrobasal arteries of the

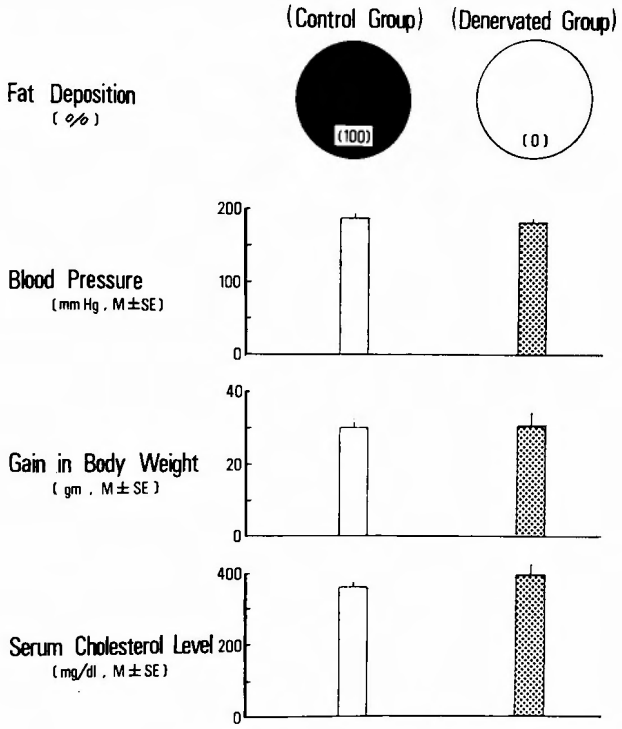

Fig. 6. Effect of innervation on atherogenesis in the cerebrovascular system of SHRSP (A_3 strain)

denervated group, as compared with the presence of clear ring-like fat deposits in all cases of the control group. Mean values of the number of sudanophilic rings in the control group were 3.2±0.7. Blood pressure (control group : 182±5mm Hg, M±SE, denervated group : 187±5), gain in body weight (31±4g, 30±2) and serum cholesterol levels (484.8±36.3mg /dl, 493.9±31.3) showed no statistically significant differences among the two group.

Fluorescence microscopic studies with highly concentrated glyoxylic acid immersion revealed that innervation in the basilar arteries appeared in ring-like or spiral form, i. e., such varicosities were detected, although meshworks of NA varicosities existed in part.

Chapter 2. Prophylactic Trials for Stroke in SHRSP, in Relation to the Effect of High Fat Cholesterol Diet.

Part 1. Incidence of stroke and hypertension levels in SHRSP and RHR fed on an HFC diet.

(1) Average life spans in rats fed on an HFC diet and in those fed on a normal diet showed no significant difference. Thus, the HFC diet had no significant influence on life span.

Serum cholesterol levels (mg/100 ml, M±SE) in male SHRSP and WK on an HFC diet were as follows : Before the loading of HFC diet -SHRSP was 100±3, WK was 156±8 ; 1 week after the loading of HFC diet - SHRSP, 411±25, WK, 239±12 ; 2 weeks after the loading of HFC diet SHRSP, 694±85, WK, 296±33 ; and over 2 months on an HFC diet SHRSP, 1,015±203, WK 367±14.

Body weight in male SHRSP fed on an HFC diet for 1 to 2 weeks after the beginning of HFC diet loading increased less than that in the normal diet group ; SHRSP on an HFC or normal diet for 2 weeks 232±6 gm, 201±4g, respectively. But 1 month after the loading the difference between SHRSP on an HFC diet and those on a normal diet became insignificant, 312 ±10 and 321±7, respectively.

Blood pressure in male SHRSP on an HFC diet was significantly lower than that in SHRSP on a normal diet : SHRSP fed on an HFC diet for 2 weeks 178±4 mmHg ; SHRSP on a normal diet, 202±3 ; SHRSP on a HFC diet for 10 weeks, 175±4 ; SHRSP on a normal diet 232±4.

Microscopical observation revealed that incidences of cerebral lesions in SHRSP on an HFC diet were only 2.4% in males (and 3.4% in females). On the other hand, the incidences in SHRSP fed on a normal diet were 83.0% in males (and 70.2% in females) (Fig. 7).

(2) As shown in table 1, for RHR fed on an HFC diet, blood pressure was significantly lower than that of RHR fed on a normal diet. However, between these 2 groups, no other significant differences were observed.

Part 2. Mechanism of the lowering effect of HFC diet on hypertension from the view point

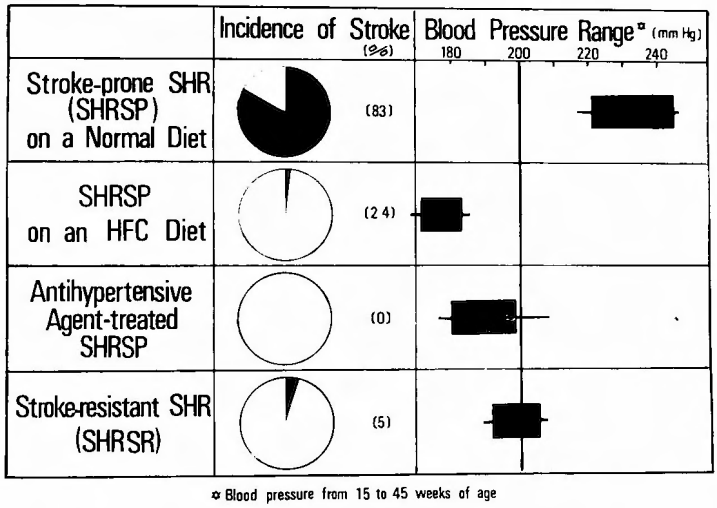

Fig. 7. Effect of HFC diet on the incidence of stroke in SHRSP.

Table 1. Effect of HFC diet on blood pressure in renal infarction hypertensive rats (RHR).

Days after operation of renal hypertension		11	24	45	77
Blood Pressure (mmHg, M±SE)	HFC diet	168±5	149±6*	172±7**	166±5**
	Control (normal diet)	170±7	185±10	200±4	195±5
Body Weight (g, M±SE)	HFC diet	130±14	119±11*	218±14	243±10
	Consrol (normal diet)	125±9	193±14	240±8	295±22

*, ** : Significant difference from control group ($p<0.1$, 0.01)

of vascular reactivity

(1) Pressor responses to norepinephrine in SHRSP fed on an HFC diet were significantly less than those in SHRSP on a normal diet : responses to 1 μg/Kg in SHRSP on an HFC diet or on a normal diet, 19 mmHg or 42 mmHg or 42 mmHg, respectively ; responses to 10μg/Kg, 52 mmHg and 86 mmHg. Duration of the response showed no significant difference between the 2 groups.

(2) As shown in Fig. 8, SHRSP fed on HFC diet showed moderate hypertension (178 ±2 mmHg : M±SE) similar to that in SHRSR, and showed no more rCBF (102.6±11.6 ml/min/100g, M±SE) decrease than SHRSR. In contrast, control SHRSP fed on a normal diet developed severe hypertension over 200 mmHg (210±9), and showed marked

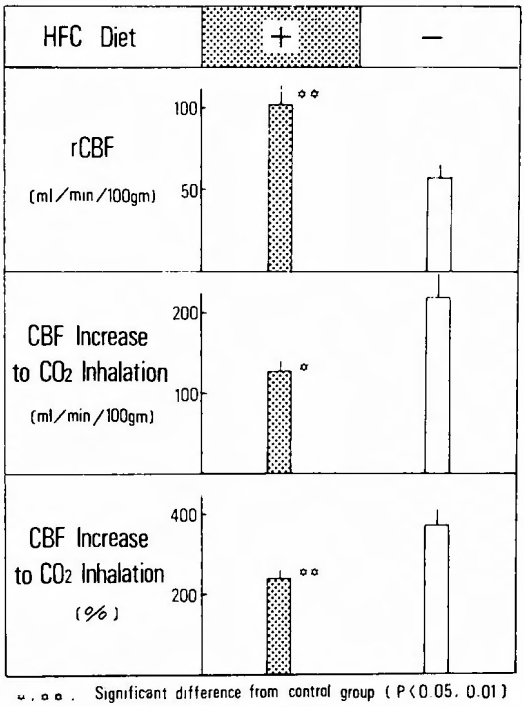

Fig. 8. Effect of HFC diet on rCBF and cerebrovascular reactivity in SHRSP.

rCBF decrease (65.6±6.8). With regard to chemical cerebrovascular reactivity, SHRSP fed on an HFC diet showed markedly reduced response to CO_2 inhalation, even in young age. That is, in SHRSP fed on an HFC diet, rCBF increase in response to CO_2 inhalation at the frontal cortex showed statistically significantly lower values (129.3±13.0 ml/min/100g, M±SE, in absolute values, 219±32.6% in percentage increase) than those in control SHRSP (24.5±2.7, 370±39.8) at the age of 60 days.

Discussion

Chapter 1. Atherogenesis in the Cerebrovascular System of SHRSP

The important role of atherosclerosis in the cerebrovascular system has been emphasized for pathogenesis of stroke in man[16,17], but as yet a suitable experimental model for such a study has not been obtained[18~21]. Above all, rats rarely have atherosclerosis or arterial fat deposition in cerebral vessels, even when on a hypercholesterolemic diet for a long period of time[20,33]. However, spontaneously hypertensive rats (SHR)[34~36], especially substrains of SHR, were noted to be exceptionally susceptible to arterial fat deposition. The successful establishment of SHRSP[4], prompted me to try experimental atherogenesis in this new strain.

An extremely rapid development of ring-like fat deposition in the mesenteric arteries

of SHRSP on a high fat cholesterol (HFC) diet was reported by YAMORI[29,30], The significance of this model for study of the pathogenetic mechanism of atherosclerosis was investigated[26~28].

When whole branches of mesenteric arteries were examined, extremely rapid development of ring-like fat deposits in the mesenteric arteries was observed macroscopically in some substrains of SHR, especially SHRSP even one week after being fed on an HFC diet with 1% salt in the drinking water, while none of the normotensive WK revealed such phenomena. The process of this ring-like fat deposition in the mesenteric arteries was already speculated from our previous experimental findings[26~28] Some authors have noted cerebral atherosclerosis is rare in rats[20~33]. However, as of yet there is no adequte reason to explain such an absence of cerebral involvement.

Barium Contrasted Sudan Staining method (BCSS method), which was devised at our laboratory, made it possible to observe ring-like fat deposition in the cerebraobasal arteries "as a whole" in hypertensive rats fed on an HFC diet.

There was ring-like fat deposition in the intracerebral arteries such as lateral lenticulostriate arteries (which are of the most importance in relation to stroke), as well as cerebrobasal arteries. Such was demonstrated by the BCSS method with microsurgical technique. Such a fact seems to be very important, because, by the light and electron microscopic studies using peroxidase, it was clarified that this ring-like fat deposition is a good indicator for increased permeability in the vascular wall.

The final morphological feature in the terminal stage of vascular fat deposition showed severe atheromatous change with calcifications.

Some analogousness to human arterial lesions was demonstrated by light and electron microscopic findings of fatty degeneration even in the cerebral arteries of hypertensive rats on an HFC diet.

Now that these experimental findings have been clarified, this experimental system (YAMORI's preparation I) can be regarded as one of the best for studies on the initiation mechanism of the arterio -or athero-sclerosis of cerebral and other peripheral arteries.

Using YAMORI's Preparation I, arterial fat deposition was examined in the circle of Willis and basilar arteries of SHRSP on an HFC diet. Here was confirmed the importance of hypertension as the most influential factor on fat deposition in the cerebrobasal artesies. This investigation partially clarifies the relationship among factors influencing fat deposition. Hypertension and increased salt intake[25~27,29~32] accelerate the development of fat deposits. The more important effect of hypertension especially on the fat deposition in the cerebrobasal arteries was noted, whether hypertension was induced spontaneously (SHRSP) or experimentally (RHR). Namely, it was noted that normotensive WK on an HFC diet never had fat deposition and that even SHRSP rarely had fat deposition in the cerebral artery under normotensive conditions (in prehypertensive stage or under treatment by antihypertensive agents). Such contrasts with the fact that some grade of fat deposition was noted in the mesenteric arteries in these SHRSP. In fact, many of our experimental cases re-

vealed that blood pressure and severity of fat deposition in the cerebral arteries had a positive corelation[32]. This is the first to prove the importance of hypertention in fat deposition of the cerebral arteries in rats. However, that hypertension is the contributing factors in atherogenesis has been supported by accumulated experimental evidence obtained mainly in dogs and rabbits[37~42]. SHRSP appear to have some genetic factor(s) for fat deposits because : (I) SHRSP on an HFC diet had sudanophilic rings in the mesenteric arteries, even in the prehypertensive (normotensive) stage, in contrast to the rare occurrence of fat deposits in normotensive WK, and (II) some SHRSP on the HFC from age 60 days and treated with antihypertensive agents still had sudanophilic rings in the circle of Willis with serum cholesterol levels the same as WK (YAMORI's Preparation III).

Hypercholesterolemia is an essential factor for arterial fat deposit. But, normotensive WK rats never showed sudanophilic rings under hypercholesterolemia equal to those of hypertensive rats. RHR had an intensified hypercholesterolemia as well as SHRSP. This finding indicates that hypertension itself augments the hypercholesteromic response[43].

Although the possible involvement of genetic factors affecting fat deposition remains to be solved, hypertension apparently is a main factor for the deposition of fat, especially in the cerebrobasal arteries of these rats.

On the other hand, we examined the distribution of cerebrovascular ring-like fat deposition for numerous hypertensive rats on an HFC diet. The predilection sites of such in the cerebral arteries were arteral bifurcations in the cerebrobasal arteries, i. e., the initial ring-like deposits were located near such branchings as the carotid fork, basilar head and vertebrobasilar junction. This finding suggested a relationship between the hemodynamics of cerebral blood flow and fat deposition in the cerebral arteries.

Moreover, ring-like fat deposits in cerebral arteries developed in relation to segmental increase in vascular permeability caused by vasoconstriction and dilatation in hypertensive rats. These findings suggested that hemodynamic alterartion indused by hypertension might be an important local factor for arterial fat deposition. Because the decisive importance of hypertension in the arterial fat deposition was observed, especially in the cerebral arteries.

Besed on these experimental findings, we speculated about the possibility of inducing fat deposition in the cerebral arteries of "normotensive" rats, and succeeded in making ring-like fat deposition, as observed in "hypertensive" rats, in the cerebral arteries of "normotensive" WK on an HFC diet after bilateral or unilateral carotid ligation or basilar ligation (YAMORI's Preparation II). The predilection sites of fat deposition in normotensive rats after these operations were the posterior communicating arteries, which frequently showed an elongation and were significantly dilated in the diameter because of the compensatory increase in blood flow. This experimental success clearly indicates the importance of hemodynamic derangement in arteral fat deposition. The hemodynamic concept of atherosclerosis was suggested from experiments by TEXON et al[44], who observed atherosclerosis of the S-shaped carotid artery autotransplanted into the femoral artery in dogs fed cholesterol plus prophylthiouracil.

The findings in the present study suggest that hemodynamic derangement induces fat deposition directly through intimal damage to increase permeability or through arterial wall extension which causes permeability increase. The present experiments generated the hypothesis that hemodynamic derangements induced by hypertension altered endotherial permeability which predisposed to lipid deposition and finally resulted in atherogenesis.

As mentioned above, in the cerebral arteries and arterioles of rats, fat deposition was producible. The most important factor for such a cerebrovascular atherogenesis in rats was hypertension. YAMORI's Preparation II proved producibility of fat deposition without hypertension and YAMORI's Preparation III and the establishment of ALR[15] (arteriolipidosis-prone rat) verified the significance of the genetic factor for atherogenesis. All of these results suggested the existence of some relationship among hypertension, hemodynamic darangement, and the genetic factor, i. e., existence of probale common mechanisms to these factors in the initiation of cerebrovascular atherogenesis in rats.

Thus, the role of innervation was analyzed as one of these common mechanisms. As compared with the control group, denervated group clearly showed low susceptibility to fat deposition in the cerebrovascular system. However, there were no significant difference noted in blood pressure, gain in body weight and serum cholesterol levels. These results suggest that innervation plays an important role in fat deposition.

On the other hand, fluorescence microscopic study with concentrated glyoxylic acid immersion revealed that appearance of innervation in the basilar artery seemed to be spiral or ring-like. This was like the fatty deposition produced by YAMORI's Preparation I, II and III, where it appeared to be clearly ring-like.

The process of ring-like fat deposition was speculated upon from these experimental findings as follows : Repetition of vasoconstriction and vasodilatation, probably due to nervous control, causes a segmental increase in vascular permeability. This is followed by ring-like fat deposition, especially in the media of vasodilated regions. The fat deposition accelerated degeneration of the media, which further dilates the arterial wall and increases the permeability, and results in the rapid development of marked ring-like lesion (Fig. 9).

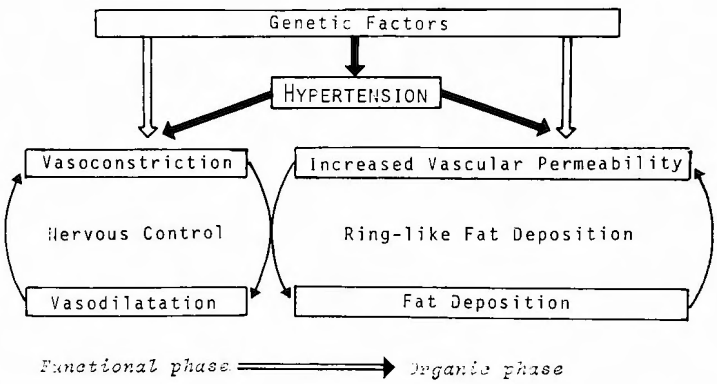

Fig. 9. Initiation mechanism of cerebrovascular atherogenesis.

Chapter 2. Prophylactic Trials for Stroke in SHRSP, in Relration to the Effect of HFC Diet

Recent statistics of WHO reported that, in Japan, the death from vascular lesions affecting the central nervous system was markedly higher (more than 60% in hypertensive complications) than that in the USA or European countries (less than 40%). However, for death from atherosclerotic and degenerative heart diseases, the rate was obviously higher in the USA or European countries (more than 60% in hypertensive complications) than in Japan (less than 30%)[46]. In Japan the dietary intake of fat is far less than in the USA of European countries. So, in order to examine whether such marked differences in death rate are related to this fat intake, we fed SHRSP and RHR on an HFC diet for a long experimental period. We then examined blood pressure and vascular reactivity, or studied vascular lesions after autopsy.

When SHRSP were fed on a hypercholesterolemic diet for a long time, they showed a marked decrease in the incidence of stroke, cerebrovascular lesions, and arterionecrosis. The incidence of histologically detected myocardial lesions in SHRSP on an HFC diet did not differ from those on a normal diet under this experimental conditions. Pressor responses to norepinephrine in SHRSP fed on an HFC diet was significantly less than those in SHRSP fed on a normal diet. The fatty degenaration in the media of the vascular wall noted in these rats was supposed to decrease the functional response of blood vessels and to limit the increase in blood pressure. As mentioned above, severe hypertension was one of the

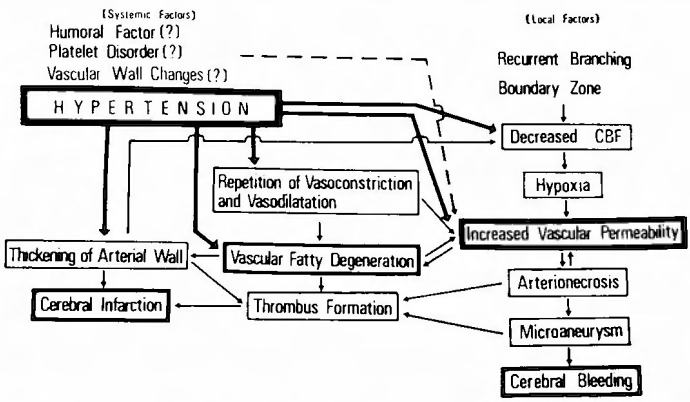

Fig. 10. Common mechanism for initiation of increased permeability among cerebrovascular atherogenesis, cerebral bleeding, and cerebral infarction.

most important systemic factors for cerebral stroke, and moderate control of blood pressure resulted in no occurrence of stroke in SHRSP. The attenuation of severe hypertension in the group on an HFC diet was supposed to decrease the incidence of the cerebral lesions.

On the other hand, the effect of HFC diet on cerebral circulation was significant. I.e., at least an early stage, this diet lowered systemic blood pressure, thus leading to a reduced incidence of "arterionecro-thrombogenic" stroke by maintaining rCBF in normal range.

Such a result occurs despite clear ring-like fat deposition in cerebrovascular system, even though chemical cerebrovascular reactivity was reduced. This reduction of chemical cerebrovascular reactivity clearly indicates that fat deposits in cerebral arteries accelerate orginic changes of cerebral arteries, i. e., cerebral arterio-or atherosclerosis.

When comparing Japan and the USA or European countries, these findings suggest that the epidemiological differences in the death rate of vascular lesions affecting the central nervous system are greatly due to such a nutritional factor.

Summary

The initiation mechanism of stroke in relation to cerebrovascular atherogenesis was clarified through the establishment of three experimental systems for studies on cerebrovascular atherogenesis in rats. Prophylactic trial for stroke was performed, by feeding a hypercholesterolemic diet and then watching the effect on systemic blood pressure and cerebral blood flow.

Chapter 1. Atherogenesis in the Cerebrovascular System of Stroke-prone Spontaneously Hypertensive Rats (SHRSP)

A new model for studies on atherogenesis in the cerebrovascular system was obtained by using SHRSP on a high fat cholesterol diet (HFC diet; 20% suit, 5% cholesterol, and 2% choicacid). Ring-like fat deposits in the cerebrobasal arteries, which were detected within a few weeks by new techniques (Barium Contrasted Sudan Staining Method : BCSS Method) for macroscopical demonstration of fat deposits "as a whole" were proved to be good quantitative indices for the initiation of atherogenesis. Analogousness to human arterial lesions was verified by light and electron microscopic findings. The final morphological feature in the terminal stage of vascular fat deposition showed severe atheromatous change with calcification.

Experimental studies using more than 200 rats including SHRSP, RHR and WK, fed on a hypercholesterolemic diet with 1% salt in the drinking water for 1 week, 2 week, 10 weeks and more than 10 weeks, revealed that the arterial fat deposition in the brain was affected by blood pressure level (BP), strain difference and age. High BP was confirmed to be more important than the other factors by the quantitative analysis of sudanophilic rings in relation to BP.

Cerebrovascular ring-like fat deposition, which was noted only in hypertensive rats but never observed in normotensive rats even after they had been fed on an FHC diet for a long time, was successfully developed in the posterior communicating or other cerebrobasal arteries in normotensive rats fed on an HFC diet for ten weeks after bilateral or unilateral carotid artery ligation or basilar artery ligation. These posterior communicating arteries with fat deposits were clearly dilated to a significant extent. Such findings supported the fact that not only high blood pressure but also hemodynamic derangement induced by hypertension or other causes were important factors for the development of fat deposition in cerebral arteries.

To clarify the existence of some relationship among hypertension, hemodynamic derangement and the genetic factor, the effect of cervical sympathectomy on cerebrovascular atherogenesis in SHRSP fed on an HFC diet was examined. As compared with the control group, denervated groups clearly showed low susceptibility to fat deposition in the cerebrovascular system. Such result suggested the important role of innervation on fat deposition. In addition, fluorescence microscopic study with concentrated glyoxylic acid immersion revealed that innervation in the basilar artery appeared to be spiral or ring-like, just as fatty deposition in SHRSP was detected to be a clear ring-like form.

Based on the above-mentioned experimental facts, the initiation mechanism of ring-like fat deposition was speculated as follows :

Repetition of vasoconstriction and vasodilatation, probably due to nervous control, causes a segmental increase in vascular permeability, then followed by ring-like fat deposition, especially in the media of vasodilatated region. This fat deposition accelerates degeneration of the media which further dilates the arterial wall and increases the permeability. The final result is rapid development of marked ring-like lesions.

Chapter 2. Prophylactic Trial for stroke in SHRSP in Relation to the Effect of HFC Diet.

SHRSP fed on an HFC diet for a long period showed marked decrease in the incidence of stroke. Blood pressure showed lower levels and rCBF was maintained in normal range despite reduction of chemical cerebrovascular reactivity, as indicated by rCBF increase in response to CO_2 inhalation. Systemic vascular reactivity, indicated by pressor response to norepinephrine, was less than that of SHRSP fed on a normal diet. The fatty degeneration of the vascular wall in SHRSP fed on an HFC diet was supposed to decrease the functional response of blood vessels and to limit the increase in blood pressure, leading to a reduced incidence of stroke. Such results suggested the importance of the nutritional factor for prophylaxis of stroke.

Aknowledgments

The author wishes to express his cordial thanks to Professor Hajime Handa (Department of Neurosurgery, Faculty of Medicine, Kyoto University) for his proper advice and hearty encouragement, and to Associate Professor Yukio Yamori (Department of Pathology, Faculty of Medicine, Kyoto University) for his excellent guidance with consistent enthusiasm, without which the present studies could not have been completed. Also invaluable were the help of Dr. Masayasu Sato, Dr. Ichiro Akiguchi, as coworkers, and Miss Yasu Okuyama who did not spare herself for the illustrations.

Further, the author should never forget the warmhearted spiritual support of his parents.

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和文抄録

Stroke-prone SHR 脳卒中易発症ラットにおける脳卒中の研究 —脳動脈硬化を中心として—

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堀　江　良　一

脳卒中モデル動物を用い，脳血管のアテローム硬化との関連性に基き，脳卒中の初期発生メカニズムを探究した．神経系の関与の下に，血管の収縮拡張の反復は分節的に脳血管の透過性亢進をもたらし，血管の壊死又は脂肪変性の出発点となる．又それに関連した脳卒中の食餌性予防法研究の第一歩として，欧米人並の高脂肪食は脳卒中発症率を減少させることを実験病理学的に最初に示し，そのメカニズムは高脂肪食負荷による血管反応性低下であることを証明した．