VASCULAR LESIONS IN THE VARIOUS SUBSTRAINS OF SPONTANEOUSLY HYPERTENSIVE RATS AND THE EFFECTS OF CHRONIC SALT INGESTION

FUMITADA HAZAMA, AKIRA OOSHIMA, TOSHINARI TANAKA,
KAZUHIKO TOMIMOTO, AND KOZO OKAMOTO

Among different races, countries and districts there are definite differences in incidence of hypertensive vascular diseases, for example cerebral bleeding^{5,23,24}. Hereditary and dietary factors presumably play significant roles. Experimental studies under controlled conditions and utilizing suitable animals are indispensable for analysis of the related factors. For confirmation, hypertensive vascular changes in the spontaneously hypertensive rats were histopathologically studied and related to the difference of substrains. Dietary effects of sodium chloride on these vascular changes were investigated by providing the animals with 1% saline for drinking.

OKAMOTO and Aoki¹⁵ succeeded in separating a colony of spontaneously hypertensive rats (SHR) by selective inbreeding of Wistar rats from the Animals Center Laboratory, Kyoto University School of Medicine. The brother-sister inbreeding was continued up to the thirty-third generation, and this inbred strain is now regarded as 'pure' from the biological view point. SHR always have hypertensive vascular changes including varying degrees of malignant findings in many organs, therefore are regarded as the most suitable experimental materials for the study of essential hypertension in humans. In maintaining the strain, crossbreedings were repeatedly carried out and 8 substrains are now available. The primary purpose of the present study is to determine the role of the hereditary factor in development of

hypertensive vascular diseases by studying pathologically the vascular changes in these various substrains of SHR.

In the preliminary experiments, it was found that SHR given 1% saline instead of tap water for drinking developed a high incidence of cerebrovascular diseases as well as findings of malignant hypertension in the kidneys, heart *etc.*. There were differences among the substrains in the incidence of these pathological changes^{6,7,17}. The second purpose of the present study is to determine in detail the dietary effect of sodium chloride on hypertensive vascular changes and to elucidate the different pathological changes of various substrains.

MATERIALS AND METHODS

The spontaneously hypertensive rats of F₂₁-F₂₇ (F₂₈ in C), which belong to the substrains A₁, A₁-sb, A₂, A₃, B₁, B₂, B₂-ob and C, were allotted into two groups. The genealogical outline of these substrains is shown in Figure 1. One group of animals, of both sexes,

Key Words:

Spontaneously hypertensive rat
Vascular lesion
Substrain
Hereditary factor
Chronic salt ingestion

(Received on October 18, 1973; Accepted for publication: September 26, 1974)

Department of Pathology, Kyoto University School of Medicine, Kyoto

This research is supported in part by a Grant-in-aid for Scientific Research from the Ministry of Education, and the Science and Technology Agency, Japan

Fig.1. The genealogical outline of the substrains of SHR.

was fed on normal stock chow diet CA-1 (Nihon Clea Co., Tokyo, Japan) and ordinary tap water for drinking *ad libitum* (Control group). To the second group of animals, males only, 1% saline was provided for drinking *ad libitum* after 2 months of age (NaCl group). Behavior of these animals was carefully observed, and soon after natural death autopsies were done. Tissues for microscopical examination were taken from various organs such as the brain, kidneys, heart, testes, ovaries, pancreas, adrenals, mesenteric arteries *etc.*. The brain was sliced into 4 or 5 frontal sections and the heart into 3 horizontal sections. All were fixed in 10% formalin and embedded in paraffin. Histological sections were cut 5 μ in thickness and stained with hematoxylin-eosin staining. Statistically the substrains A₁ and A₁-sb, as well as B₁ and B₂ were treated as one substrain.

RESULTS

Neurological Symptoms

Some animals in the control group began to show neurological symptoms after 200 days. Five weeks after the initiation of salt loading, that is when the rats were over 90 days of age, neurological symptoms such as involuntary movements, disturbance in gait, paresis or paralysis of the extremities, urinary incontinence, piloerection, irritability or hypokinesia *etc.* were observed.

Macroscopic findings

In brain sections from both groups macroscopic findings such as massive intracerebral hemorrhage (Fig. 4 a,b), subarachnoid hemorrhage and infarct with or without cyst formation (Fig. 5 a,b) were observed. The brain was sometimes markedly swollen and anemic. Some animals revealed a nephrosclerosis and the surface of the kidneys had a fine granular appearance. The heart from both groups was usually hypertrophic. Old animals in the control group often had a periarteritis nodosa in the mesenteric arteries. This finding, however, was rarely observed in the NaCl group.

Microscopic findings

Brain: In some animals massive intracerebral hemorrhages were observed, and were localized in most cases in the cerebral cortex and subcortical white matter (Fig. 6). Rarely were they observed in the basal ganglia. In the hemorrhagic foci dilated thin-walled arteries (microaneurysms) were often observed (Fig. 7). A combined form of hemorrhage and infarct was also present. In those cases hemorrhagic focus and infarct were sharply separated and the surrounding parenchyma of the hemorrhagic focus was irregularly destroyed by hemorrhage yet without necrotic tendency. These findings differed from those seen with hemorrhagic

TABLE I INCIDENCES OF CEREBROVASCULAR DISEASES

	$A_1 \& A_1-sb$				A_2				A_3				$B_1 \& B_2$				B_2-ob				C			
	M		F		M		F		M		F		M		F		M		F		M		F	
Control	Total Cases	62	38	43	39	63	39	58	65	12	12	15	17											
	Intracerebral hemorrhage and/or Infarct	Cases (%)	19 (30.6)	1 (2.6)	12 (27.9)	5 (12.8)	30 (47.6)	11 (28.2)	2 (3.1)	4 (33.3)	4 (33.3)	2 (13.3)	1 (5.9)											
	Intracerebral hemorrhage	Cases (%)	1 (1.6)	0 (0.0)	0 (0.0)	1 (2.6)	2 (3.2)	3 (7.7)	0 (0.0)	1 (8.3)	1 (8.3)	0 (0.0)	0 (0.0)											
	Infarct	Cases (%)	19 (30.6)	1 (2.6)	12 (27.9)	4 (10.3)	30 (47.6)	10 (25.6)	2 (3.1)	3 (25.0)	3 (25.0)	2 (13.3)	1 (5.9)											
	Fibrinoid necrosis	Cases (%)	3 (4.8)	0 (0.0)	3 (7.0)	0 (0.0)	7 (11.1)	4 (10.3)	1 (1.5)	1 (8.3)	2 (16.7)	0 (0.0)	1 (0.0)											
NaCl	Total Cases	35	19	31	33	14	21	10																
	Intracerebral hemorrhage and/or Infarct	Cases (%)	25 (71.4)	10 (52.6)	26 (83.9)	20 (60.6)	9 (47.6)	0 (0.0)																
	Intracerebral hemorrhage	Cases (%)	7 (20.0)	2 (10.5)	12 (38.7)	4 (12.1)	2 (14.3)	0 (0.0)																
	Infarct	Cases (%)	25 (71.4)	10 (52.6)	22 (71.0)	19 (57.6)	9 (64.3)	0 (0.0)																
	Fibrinoid necrosis	Cases (%)	12 (34.3)	6 (31.6)	11 (35.5)	7 (21.2)	3 (21.4)	0 (0.0)

Fig. 2. Time reference of intracerebral vascular diseases. Solid circles indicate the intracerebral hemorrhage and/or infarct.

infarct.

New and old infarcts were also found in most cases in the cortex and subcortical white matter (Fig. 8,9), but rarely in the basal ganglia. The localization corresponded to the border between the two main cerebral arteries. Old infarcts showed a cyst formation in case of the larger one and glial scar in a smaller one. Around the infarcts small fresh hemorrhages or deposits of hemosiderin were often observed.

Pial arteries were in general thickened due to cellular hyperplasia of the arterial wall as well as hyaline degeneration. Some arteries showed marked proliferation of adventitial cells, and sometimes fibrinoid necrosis (Fig. 10). Arterial lumina were narrowed or completely occluded in severe cases. The wall of intracerebral arterioles and small arteries showed also hyaline degeneration and in some cases fibrinoid necrosis with a slight increase in the number of cells (Fig. 11,12,13). Arterial lumina were also narrowed. In or near the foci of infarcts some were completely occluded by thrombi. A deeply stained eosinophilic substance, resembling fibrinoid, was often observed around affected arteries.

The incidences of cerebrovascular diseases are

summarized in Table I. In the control group, the male rats showed a higher incidence of intracerebral hemorrhage and/or infarct than did the female. There were differences in incidence among the substrains of control SHR. Male rats in the substrain A₃ of the control group showed the highest incidence; 47.6% revealed intracerebral hemorrhage and/or infarct. The differences in incidence between A₃ and A₂ ($p < 0.05$), A₃ and B₁ & B₂ ($p < 0.01$), A₃ and C ($p < 0.05$) were statistically significant. As shown in the table, the incidences of cerebrovascular diseases in the NaCl group were significantly higher than those in the control group. In the NaCl group, substrain A₃ also showed the highest incidence, 83.9%.

Fig. 2 shows the time references of intracerebral vascular diseases, intracerebral hemorrhage and/or infarct. In the control group, intracerebral vascular diseases occurred mostly in rats over 200 days of age. A₁ and A₁-sb, and A₃ showed a tendency to develop vascular lesions somewhat earlier than the other substrains. On the other hand, many animals in the NaCl group developed cerebrovascular diseases much earlier, between 35 and 140 days after the initiation of NaCl loading, at which time the animals

TABLE II INCIDENCES OF PATHOLOGICAL CHANGES IN THE KIDNEY

	<i>A₁ & A₁-sb</i>		<i>A₂</i>		<i>A₃</i>		<i>B₁ & B₂</i>		<i>B₂-ob</i>		<i>C</i>	
	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>	<i>M</i>	<i>F</i>
<i>Control</i>												
Total Cases	63	36	46	43	63	40	62	65	12	12	17	19
Cellular hyperplasia of arterioles and small arteries	40 (63.5)	13 (36.1)	31 (67.4)	15 (34.9)	52 (82.5)	27 (67.5)	38 (61.3)	30 (46.2)	9 (75.0)	6 (75.0)	6 (35.3)	5 (26.3)
Fibrinoid necrosis	14 (22.2)	2 (5.6)	6 (13.0)	1 (2.3)	10 (15.9)	4 (10.0)	1 (1.6)	0 (0.0)	2 (16.7)	1 (8.3)	2 (11.8)	1 (5.3)
Glomerular change	22 (34.9)	3 (8.3)	21 (45.7)	4 (9.3)	37 (58.7)	13 (32.5)	16 (25.8)	8 (12.3)	4 (33.3)	1 (8.3)	4 (23.5)	1 (5.3)
Thyroid-like change	17 (27.0)	2 (5.6)	15 (32.6)	1 (2.3)	31 (49.2)	2 (5.0)	18 (29.0)	4 (61.5)	4 (33.3)	1 (8.3)	3 (17.6)	1 (5.3)
<i>NaCl</i>												
Total Cases	34	19	22	22	33	22	33	14	14	21	21	9
Cellular hyperplasia of arterioles and small arteries	32 (94.1)	18 (94.7)	22 (100.0)	22 (100.0)	26 (78.8)	26 (100.0)	26 (78.8)	12 (85.7)	12 (85.7)	17 (81.0)	17 (81.0)	4 (44.4)
Fibrinoid necrosis	25 (73.5)	9 (47.4)	19 (86.4)	19 (86.4)	14 (42.4)	14 (63.6)	14 (42.4)	7 (50.0)	7 (50.0)	9 (42.9)	9 (42.9)	1 (11.1)
Glomerular change	24 (70.6)	11 (57.9)	17 (77.3)	17 (77.3)	16 (48.5)	16 (72.7)	16 (48.5)	10 (71.4)	10 (71.4)	6 (28.6)	6 (28.6)	1 (11.1)
Thyroid-like change	10 (29.4)	10 (52.6)	15 (68.2)	15 (68.2)	12 (36.4)	12 (54.5)	12 (36.4)	5 (35.7)	5 (35.7)	7 (33.3)	7 (33.3)	1 (11.1)

TABLE III INCIDENCES OF PATHOLOGICAL CHANGES IN THE HEART

	A ₁ & A ₁ -sb			A ₂			A ₃			B ₁ & B ₂			B ₂ -ob			C		
	M	F		M	F		M	F		M	F		M	F		M	F	
Control	Total Cases			64	37		45	41		64	40		62	61		12	12	19
	Cellular hyperplasia of arterioles and small arteries			25 (39.1)	11 (29.7)		24 (53.3)	24 (58.5)		46 (71.9)	27 (67.5)		29 (46.8)	26 (42.6)		6 (50.0)	5 (41.7)	4 (21.1)
	Fibrinoid necrosis			1 (1.6)	0 (0.0)		1 (2.2)	1 (2.4)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)
	Infarct (Scar)			14 (21.9)	7 (18.9)		10 (22.2)	3 (7.3)		15 (23.4)	12 (30.0)		10 (16.1)	13 (21.3)		2 (16.7)	1 (8.3)	3 (15.8)
	Fibrosis			29 (45.3)	9 (24.3)		24 (53.3)	10 (24.4)		46 (71.9)	20 (50.0)		30 (48.4)	12 (19.7)		8 (66.7)	2 (16.7)	4 (21.1)
	Hyaline degeneration of arteries			33 (51.6)	16 (43.2)		27 (60.0)	20 (48.8)		45 (70.3)	30 (75.0)		33 (53.2)	34 (41.7)		5 (41.7)	4 (33.3)	8 (42.1)
NaCl	Total Cases			23	16		16	21		21	31		31	14		14	21	10
	Cellular hyperplasia of arterioles and small arteries			20 (87.0)	14 (87.5)		14 (87.5)	21 (100.0)		21 (100.0)	28 (90.3)		28 (90.3)	12 (85.7)		12 (85.7)	8 (38.1)	3 (30.0)
	Fibrinoid necrosis			3 (13.0)	4 (25.0)		4 (25.0)	5 (23.8)		5 (23.8)	5 (16.1)		5 (16.1)	1 (7.1)		1 (7.1)	0 (0.0)	0 (0.0)
	Infarct (Scar)			5 (21.7)	4 (25.0)		4 (25.0)	5 (23.8)		5 (23.8)	6 (19.4)		6 (19.4)	1 (7.1)		1 (7.1)	3 (14.3)	0 (0.0)
	Fibrosis			8 (34.8)	7 (43.8)		7 (43.8)	9 (42.9)		9 (42.9)	12 (38.7)		12 (38.7)	7 (50.0)		7 (50.0)	3 (14.3)	2 (20.0)
	Hyaline degeneration of arteries			7 (30.4)	7 (43.8)		7 (43.8)	8 (38.1)		8 (38.1)	5 (16.1)		5 (16.1)	4 (28.6)		4 (28.6)	5 (23.8)	3 (30.0)

Fig.3. Time reference of the fibrinoid necrosis of small arteries and arterioles in certain organs. Solid circles indicate fibrinoid necrosis.

were between 90 and 200 days of age.

Kidneys: Small arteries and arterioles, including afferent arteries, revealed a general cellular hyperplasia. Arterial walls were thickened due to hyperplasia of medial smooth muscle cells and adventitial cells. A few of the small arteries showed a partial hyperplasia of medial cells which protruded into the arterial lumen. Arterial lumina were, consequently, narrowed or occluded (Fig. 14,15). Hyaline degeneration was observed in the arterial walls. Some small arteries and arterioles revealed fibrinoid necrosis (Fig. 16). The central portion of severely affected arteries which formed small nodules showed fibrinoid necrosis and hemorrhage often accompanied by periarterial lymphoid infiltration (Fig. 17). These findings were more often observed in the NaCl group. In the medium sized arteries, the intima was thickened as a result of what appeared to be vacuolated cells in the subendothelial layer. These vacuolated cells were confirmed electron microscopically to be of smooth muscle cell origin. The medial cells also showed vacuolar degeneration. Thrombi and fibrinoid necrosis were often observed in the glomeruli together with a proliferation of degenerated epithelial cells (Fig. 18). The tubuli in the

animals which survived longer were dilated and filled with colloid-like casts (Fig. 19).

Main pathological changes in the kidneys are shown in Table II. The incidence was higher in males than females. When determining changes in the male animals only, A₃ showed the highest incidence of cellular hyperplasia of small arteries and arterioles, while substrain C had the lowest incidence. On the other hand the incidence of fibrinoid necrosis was the highest in A₁ & A₁-sb, B₂-ob and A₃ showed also high incidences, while B₁ & B₂ the lowest incidence. The differences between B₁ & B₂ and the other substrains with an exception of C were statistically significant. By salt loading, pathological changes were markedly increased in incidence in each substrain. The differences in incidence of fibrinoid necrosis among the NaCl and control groups in each substrain except B₂-ob were statistically significant. A₃ and A₁ & A₁-sb in the NaCl group showed very high incidences of fibrinoid necrosis. A₃ developed the change in more than 85% of animals. The differences between A₃ and A₂ ($p < 0.01$), A₃ and B₂-ob ($p < 0.05$), A₃ and C ($p < 0.01$), and A₁ & A₁-sb and C ($p < 0.05$) were statistically significant.

The development of pathological changes in

Fig. 4a.
Fig. 4b.

Fig. 5a.
Fig. 5b.

the kidneys was much accelerated by NaCl treatment as was observed in the case of cerebrovascular diseases.

Heart: Arterial walls showed thickening due to cellular hyperplasia and hyaline degeneration. Protrusion of proliferated vascular smooth muscle cells in the lumen were often observed in the

small arteries (Fig. 20). Perivascular fibrosis accompanying adventitial cell proliferation as well as diffuse fibrosis were common findings (Fig. 21). Some animals showed scar formation especially in the apex which appeared to be an old infarct. In the medium sized arteries, vacuolar degeneration and hyaline degeneration

Fig.6.
Fig.7.

Fig.8.
Fig.9.

were also present. Some vascular smooth muscle cells contained very large nuclei, which suggest proliferation of these cells (Fig. 22).

Incidences of pathological changes in the heart are shown in Table III and here again there

were differences in the incidences among substrains. A₃ in the control group showed the highest incidence of pathological changes such as fibrosis, while C had the lowest incidence. By NaCl treatment the incidences of cellular hyper-

Fig.10.
Fig.12.

Fig.11.
Fig.13.

Fig.14.
Fig.16.
Fig.18.

Fig.15.
Fig.17.
Fig.19.

Fig.20.
Fig.22.
Fig.24.

Fig.21.
Fig.23.
Fig.25.

plasia and fibrinoid necrosis of small arteries and arterioles were augmented. On the other hand the incidences of old infarct, fibrosis, hyaline degeneration remained unchanged or were somewhat reduced.

Other organs: Small arteries and arterioles in the other organs such as testes (Fig. 23), pancreas, thyroid, adrenal and the wall of intestinal tract frequently showed cellular hyperplasia and fibrinoid necrosis. Such vascular changes were encountered in the testes at a high rate even when there were no severe vascular changes in other organs. In the adrenal cortex, hemorrhage and thrombus were often observed (Fig. 24). In hemorrhagic foci dilated arteries (microaneurysms) were often found.

Mesenteric arteries often showed the findings of periarteritis nodosa: that is cellular hyperplasia of medial and adventitial cells with lymphoid cell infiltration (Fig. 25). These were often accompanied by subendothelial deposition of a fibrinoid material. Periarteritis nodosa did not occur before 200 days of age.

The time references of the development of fibrinoid necrosis of small arteries and arterioles in some organs is indicated in Fig. 3. In the control group fibrinoid necrosis was rare before 200 days of age. The substrains A_1 & A_1 -sb, and A_3 showed a tendency to develop fibrinoid necrosis earlier than did the other substrains. The development of this changes was much accelerated by NaCl loading. Here also the differences in incidence of fibrinoid necrosis were observed among the substrains of SHR, as regards those treated with NaCl as well as the controls.

DISCUSSION

Pathological findings of vascular lesions in various organs in SHR have been reported by *Okamoto et al.*^{1,5} *Okamoto*,¹³ and *Ooshima et al.*¹⁸ In nontreated SHR, hypertensive vascular changes are always observed to a varying degree. That is: small arteries and arterioles always show cellular hyperplasia and hyaline degeneration and sometimes fibrinoid necrosis. Cerebral bleeding, softening, nephrosclerosis, myocardial infarction, myocardial fibrosis and periarteritis nodosa of the mesenteric arteries are prominent features of the sequelae of hypertensive vascular changes. While investigating these pathological changes we had the impression that some litter-mates and their cognates showed a tendency to develop cerebrovascular diseases with a high incidence. The present study was undertaken to relate the

vascular lesions to the different SHR substrains.

There were definite differences in the incidence of intracerebral vascular diseases, cerebral bleeding and infarct. It was found that the male A_3 animals showed a very high incidence of 48% in the cerebrovascular diseases and that the occurrence of the cerebral lesions in this substrain was much earlier than the other substrains except for A_1 & A_1 -sb which also showed a high incidence and early onset of cerebrovascular lesions. These facts suggest that a hereditary factor plays an important role in development of intracerebral vascular diseases, and that it is possible to produce a good experimental model for studies on cerebrovascular diseases by the selective breeding from this substrain A_3 .

Although the incidences of infarct were much higher than those of intracerebral bleeding, it appears reasonable to consider both conditions together as similar hypertensive vascular changes were encountered in both. As outlined in a previous report,¹⁷ microaneurysms, which are regarded as the causative change in cerebral bleeding, were found not only in the case of cerebral hemorrhage but also in the case of infarct. Vascular changes caused by hypertension are presumably the basic condition required to develop both microaneurysm and arterial occlusion.

The findings of malignant hypertension, cellular hyperplasia and fibrinoid necrosis of small arteries and arterioles, were often observed in the various organs. There were also differences among the substrains in the incidence and the time of occurrence of fibrinoid necrosis. The incidences and the onsets of malignant findings of the arteries coincided with those of the cerebrovascular lesions. The male A_3 animals showed the highest incidence of fibrinoid necrosis and these animals plus A_1 & A_1 -sb rats showed a tendency to develop the change earlier than the other substrains.

*Aoki et al.*¹ reported previously that there were no definite differences in blood pressure among the various substrains at the age of 6 months. However, it was found that the substrains A developed hypertension earlier than the substrains B and C.⁶ Therefore the differences of hypertensive vascular changes in incidence among the substrains of SHR may be explained in some extent by the developmental course of hypertension.

The differences in the incidence of vascular lesions among substrains may be explained also

by the differences of susceptibility of the vascular system to certain pressor agents or excessive stress. Differences of various properties among these substrains have been reported, although they have yet to be correlated to the differences of vascular lesions.^{1,2,18} It was shown in the present study, that those substrains which had higher incidences of vascular lesions in the nontreated group, showed also a tendency to have higher incidences of vascular lesions and severer changes in the NaCl group. *Aoki et al.*¹ reported utilizing blood pressure as an index to support the fact that certain SHR substrains were more sensitive to same salt regimen than were others. Endogenous factors in the vascular system have yet to be elucidated.

It was found in the previous studies^{6,7,17} confirmed by the present experiments with controls that NaCl loading in drinking water accelerates and increases the development of hypertensive vascular changes and sequential pathological lesions in the brain, kidneys *etc.* of SHR. The incidence of cerebrovascular lesions was particularly enhanced by salt loading.

The augmentation of vascular changes in SHR by NaCl loading may be explained by the pressor effect of sodium chloride on the one hand and toxicity of NaCl on the other hand. It is already established that chronic ingestion of sodium chloride develops hypertension in rats^{3,10,11,13,22} *Barsanti et al.*² showed that chronic ingestion of 1% salt solution causes accelerated hypertension leading to death in the SHR at a more rapid rate than in the normal rat given 1% salt or in the SHR given tap water. *Aoki et al.*¹ also found that the development of hypertension was accelerated and hypertension was enhanced by chronic excess sodium intake, and that various substrains of SHR showed some difference in sensitivity to salt ingestion, although there was some discrepancy between salt sensitivity and toxicity in certain substrains. In light of the present data, it appears that the hypertensive effect of sodium chloride indeed plays a role in development of vascular changes, but that the explanation does not end there.

Severe vascular changes and early occurrence of lesions in SHR given 1% NaCl cannot be explained only by pressor effect of sodium chloride, therefore toxicity of salt itself must be considered. *Koletsky*^{10,11} regards the glomerular and the vascular lesions in rat with salt hypertension as the result from the injurious effect of the salt itself. The fact that the toxicity

of sodium chloride is especially strongly observed in SHR compared with normotensive rats, shows that the condition of hypertension itself seems to be a modifying factor of the toxicity of NaCl. Electron microscopically as well as radioautographically it was shown that the smooth muscle cells of the arterioles and small arteries have a tendency to proliferate under hypertensive condition in SHR⁸ and the proliferating immature smooth muscle cells are susceptible to the toxicity of sodium chloride. It has been reported by *Wessels and Losse*²⁵ that Na⁺ content in the aorta in their hereditary spontaneously hypertensive rats was higher than that in the normotensive rats. *Inatome et al.*⁹ obtained a similar result in SHR.

In case of salt loading, there were differences of cerebrovascular lesions, nephrosclerosis as well as generalized vascular changes in the incidences among various substrains. Although the incidences were indeed increased, the order of incidences in the NaCl group was almost parallel that in the nontreated control group. Here also some genetic predisposition must be assumed. *Dahl et al.*^{4,20,21} separated salt-susceptible rats from salt-resistant ones, and related the difference with that of mineral corticoids. Though this approach indeed holds much interest, further studies must be done to determine how the differences among the substrains take place.

SUMMARY

Hypertensive vascular lesions in the spontaneously hypertensive rats (SHR) were histopathologically studied and related to the difference of substrains. The effects of chronic salt ingestion on these vascular changes were investigated by providing the animals with 1% saline for drinking instead of tap water. SHR developed benign or malignant hypertension in the generalized small arteries and arterioles and sequelae in the various organs such as cerebrovascular diseases, arteriolar nephrosclerosis *etc.* There were definite differences in incidence of the hypertensive vascular changes in the brain, kidneys and other organs among the various substrains of SHR. By salt loading, the hypertensive vascular changes, in particular cerebrovascular diseases, were much accelerated and accentuated with different incident rates according to the substrains. The male animals showed higher incidences of the vascular lesions than did the female both in the control and salt-treated groups. Substrain A₃ proved to have a peculiar nature with regard to the cerebro-

vascular diseases and malignant hypertension. Cerebrovascular diseases and fibrinoid necrosis of the generalized small arteries and arterioles with the highest incidences both in the nontreated and salt-treated cases were seen among the males of A₃ group. These facts suggest that the hereditary factor as well as chronic salt ingestion play important roles in development of hypertensive vascular diseases. However, further investigation is required to elucidate the mechanisms responsible for the differences among the substrains.

Acknowledgement

Thanks are due to M. Ohara, Kyoto University for assistance with the manuscript.

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LEGENDS FOR FIGURES

- Fig.4a, b. Intracerebral hemorrhage accompanying subarachnoidal hematoma in a control SHR.
- Fig.5a, b. Cortical infarct in a control SHR.
- Fig.6. Massive cortical hemorrhage in a SHR treated with NaCl. $\times 58$.
- Fig.7. Dilated artery (microaneurysm) in the focus of intracerebral hemorrhage in a NaCl-treated SHR. $\times 290$.
- Fig.8. Cortical and subcortical infarct with cyst formation in a control SHR. $\times 58$.
- Fig.9. Small focus of cortical infarct with necrotized arteries in a control SHR. $\times 145$.
- Fig.10. Pial arteries with marked cellular hyperplasia and fibrinoid necrosis in a control SHR. $\times 145$.
- Fig.11, 12. Intracerebral arterioles in and near the infarcts in SHR treated with NaCl. The arteriolar walls show fibrinoid necrosis and a slight cellular hyperplasia. The arteriolar lumina are narrowed and in part occluded by thrombus (Fig.12). $\times 290$.
- Fig.13. As in Figs.11, 12. $\times 580$.
- Fig.14. Proliferated smooth muscle cells of a renal small artery protrud into the arterial lumen (nontreated SHR). $\times 580$.
- Fig.15. Cellular hyperplasia, consisted of smooth muscle cells as well as adventitial cells, of a small renal artery in a control SHR. $\times 290$.
- Fig.16. As in Fig.15, but with accompanying angioneclerosis. $\times 290$.
- Fig.17. Fibrinoid necrosis and hemorrhage in a nodular hyperplasia of renal small artery in a control SHR perplasia of renal small artery in a control. $\times 290$.
- Fig.18. Glomerular change in a control SHR. Fibrinoid necrosis of the afferent artery and glomerular capillary and proliferation and degeneration of glomerular epithelial cells are noted. $\times 290$.
- Fig.19. Dilatated renal tubuli filled with colloid-like casts in a control SHR. $\times 145$.
- Fig.20. Cellular hyperplasia and hyaline degeneration of the cardiac small arteries and scar formation in a NaCl-treated SHR. $\times 290$.
- Fig.21. Diffuse fibrosis of the myocardium in a control SHR. $\times 145$.
- Fig.22. Medium sized cardiac artery in a control SHR. Note hyaline degeneration and large nuclei. $\times 145$.
- Fig.23. Cellular hyperplasia with fibrinoid necrosis of the testicular small arteries in a control SHR. $\times 145$.
- Fig.24. Dilated artery (microaneurysm) with thrombus formation in the adrenal cortex in a control SHR. $\times 29$.
- Fig.25. Periarteritis nodosa of the mesenteric arteries in a control SHR. $\times 29$.