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Vascular Lesions Produced by Renal Cortical Extracts of Spontaneously Hypertensive Rats (SHR)

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From the renal cortical extracts of spontaneously hypertensive rats (SHR) and normal rats, the fraction without pressor effect but with vascular necrotizing effect (F_3) and the fraction with pressor effect (F_4) were isolated and compared. The pressor effect of F_4 showed no difference between SHR and normal rats. Vascular lesions of the mesentery and pancreas produced by renal extracts were examined light microscopically and electron microscopically to compare the vascular necrotizing effects of renal extracts. Both F_3 and F_4 of SHR showed more intensive vascular necrotizing effect than renal extracts of normal rats. It was speculated that F_4 of SHR contains some vascular necrotizing substance without pressor effect.

INTRODUCTION

Subsequent to GOLDBLATT's[6] experiment to cause hypertension by renal artery constriction and to produce vascular disease, various type of experimental hypertension have been conducted to study the relation between hypertension and vascular disease.

Spontaneously hypertensive rats (hereinafter reffered to as SHR) produced by OKAMOTO et al.[14] have been studied from various aspects as a hypertension model which induces hypertension similar to human essential hypertension. On the other hand, the experiment of renal extracts by WINTERNITZ et al.[20] attracted another interest from the aspect of the vascular necrotizing factor contained in the kideny, and subsequently various experiments have been conducted to see the relation between renal extracts and vascular

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diseases. In this laboratory also, the relation between renal extracts of experimentally hypertensive rats as well as normal rats and vascular diseases have been studied.[4),8),13),19)] In the present paper, the vascular necrotizing effect of renal extracts of SHR was compared with that of renal extracts of normotensive rats for the purpose of studying the vascular necrotizing factor which is contained in the kidney in hypertensive state.

MATERIAL AND METHODS

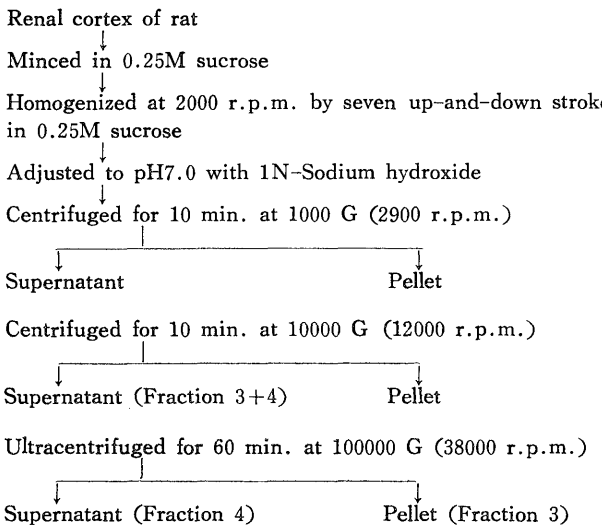
1. Preparation of renal extracts from the renal cortex

The renal cortex was obtained from SHR (24 individuals, body weight 170-390g) in which hypertension of over 160mmHg persisted for more than a month and from Wistar rats (hereinafter referred to as WR: 21 individuals, body weight 180-250g). Blood pressure was measured by tail-cuff method with Automatic Recording Apparatus USM-105T type (Ueda Electric Works, Tokyo, Japan).

2. Sampling and fractionation of renal cortex

The sampling of the renal cortex of rats was made by the method heretofore employed by this laboratory.[4),13),19)] The fractionation of the sampled renal cortex was performed by partially revising the method heretofore employed by this laboratory[4),13),19)] (Figure 1). The minced renal cortex was homogenized in 0.25M sucrose (1:9; W/V) using a teflon homogenizer. The B-60 rotor type 460 (International, Massachusetts, USA) was used for ultracentrifugation. The pellet (Fraction 3: hereinafter referred to as F_3) and the supernatant (Fraction 4: hereinafter referred to as F_4) obtained by ultracentrifugation and the mixture of F_3 and F_4 without separation by ultracentrifugation (hereinafter referred to as F_{3+4}) were dialysed over one night against 0.9% sodium chloride, and the content of

Figure 1 Fractionation of Renal Cortex of Rat



protein was measured by Biuret's method or Folin's method before the use in the experiment.

3. Measurement of pressor activity of renal extracts

The pressor activity of each fraction of renal extracts obtained from SHR and WR was measured by the method described by CONRADI et al. [2] Blood pressure was measured at the carotid artery of four bilaterally nephrectomized Wistar female rats (body weight 200-300g) with the Automatic Equilibrium Recorder AS 13 type (Shinkoh, Zushi, Japan).

4. Examination of vascular lesions produced by renal extracts

Renal extracts were injected to Wistar female rats weighting 100-140g. These rats underwent right nephrectomy and left urethral ligation under ether anesthesia so as to prevent vascular lesions produced by bilateral nephrectomy. With the lapse of 1.5-2 hours after operation, F_3, F_4 and F_{3+4} were each injected from the femoral vein at the dose of 5mg or 2mg of protein per 100g of body weight of rats. The rats were classified into seven groups as shown in Table 1. The rats injected with fraction were sacrificed 24 hours after the injection without releasing urethral ligation.

(1) Light microscopic examination: The mesentery and pancreas were examined. The mesentery was halved at the radix and the halves of the mesentery were bundled along the longitudinal direction of vessels and transversally halved again. Thus the mesentery of each rat was divided into four parts. The pancreas was also divided into four parts after being bundled. The tissue was embedded in paraffin, sliced into semi-serial sections for observation of as many vessels as possible, and stained with Hematoxylin-Eosin stain, Azan-Mallory stain, elastic fiber stain by Weigert's Resorcin-Fuchsin method, Periodic acid Schiff reaction and Phosphotungstic acid Hematoxylin stain.

(2) Ultrastructual examination: The mesentery and the pancreas of rats injected with renal extracts of SHR were examined ultrastructurally. Laparotomy was performed under anesthesia with ether and specimens were sampled while dripping 1.5% glutaraldehyde in pH 7.3 phosphate buffer to the mesentery and pancreas. The specimens were immersed in glutaraldehyde of the same concentration and fixed for four hours. They

Table 1 Experimental Groups with injection of Renal Cortical Extracts

Experimental group	Fraction	Dose of administered fraction [content of protein/100g of body weight]	Number of rats
1	SHR F_3	5 mg	10
2	SHR F_3	2 mg	6
3	SHR F_{3+4}	5 mg	8
4	SHR F_4	2 mg	8
5	WR F_3	5 mg	8
6	WR F_{3+4}	5 mg	7
7	WR F_4	2 mg	7
		Total	54 rats

were refixed with 1% osmic acid, dehydrated with alcohol, embedded in Epon 812, sliced into ultrathin sections, double stained with uranyl acetate and lead citrate, and examined with the Electron Microscope JEM-7A and JEM-100B (Japan Electron Optics Laboratory, Tokyo, Japan).

(3) Grading of severity of vascular lesions produced by renal extracts and evaluation of frequency of such vascular lesions: The arteries of the mesentery and the pancreas were classified into two groups. The arteries with three or less layers of smooth muscle cells were grouped as small arteries and arterioles (Figure 2), and those with four or more layers as medium-size arteries (Figure 3). As for the grading of severity of vascular lesions, "mild vascular lesion" was assigned when necrosis was observed on the vascular wall extending less than one quarter of the circumference (Figure 2) and "moderate vascular lesion" was assigned when necrosis of the vascular wall extended to more than one quarter of the circumference (Figure 3). The frequency of vascular lesions was evaluated as follows. For each paraffin block of four parts of the mesentery and pancreas, one section was examined for the number of small arteries and arterioles as well as medium-size arteries with mild vascular lesion, moderate vascular lesion and no vascular lesion. The number of arteries with mild, moderate and no vascular lesion counted in four sections from four blocks of each organ was totalled as classified by artery and severity of vascular lesion. The sum of small arteries and arterioles and medium-size arteries in the mesentery and pancreas of a rat was calculated for each group. Then the percentage of injured arteries against the entire arteries seen in each organ of a rat was calculated and the mean value of frequency of vascular lesion was evaluated for each experimental group. The difference of mean values was examined statistically and vascular necrotizing effects were compared among various fractions.

RESULTS

1. Pressor activity of renal extracts

SHR F_3 and WR F_3 showed no pressor effect. SHR F_4 and WR F_4 almost equally had remarkable pressor effect (SHR F_4: 24 ± 4 mmHg, WR F_4: 25 ± 3). SHR F_{3+4} also showed pressor effect (SHR F_{3+4}: 12 ± 2, WR F_{3+4}: 13 ± 4). However, the pressor effect of F_{3+4} was lower than that of F_4.

2. Macroscopic findings

At the time of sacrifice, ascites was noted in almost all cases and pleural fluid in more than a half of the cases. The kidney showed mild hydronephrosis and swelling in almost all rats. The mesentery contained petechial hemorrhage in 2 cases each of group 1 and group 3. However, hemorrhage was not observed in the brain, pancreas and other organs in any rat.

3. Light microscopic findings

The findings of vascular changes were similar among various experimental groups.

Small arteries and arterioles showed edematous cytoplasm of smooth muscle cells, fibrinoid necrosis of individual cells, invasion of erythrocytes into the vascular wall, and infiltration of neutrophils and lymphocytes in the perivascular area. Medium-size arteries showed degeneration and necrosis of smooth muscle cells as seen in small arteries, and invasion of fibrin-like materials and erythrocytes into the intercellular matrix of the media. The invasion of fibrin-like materials and erythrocytes was more frequent in the outer media (Figure 2 and 3).

4. Electron microscopic findings

(1) Endothelial cells and subendothelial space: Endothelial cells were denuded and platelets adhered to that region. In the cytoplasm of endothelial cell, dilatation of rough endoplasmic reticulum and formation of vacuoles were observed. The subendothelial space was invaded by plasma components and leukocytes, and endothelial cells of this area protruded towards the lumen and formed blebs (Figure 4 and 5).

(2) Media: Smooth muscle cells had large lysosomes and containing electron dense

Table 2 Mild Vascular Lesions produced by Renal Cortical Extracts*

Experimental group	Mesentery		Pancreas	
	small arteries and arterioles	medium-size arteries	small arteries and arterioles	medium-size arteries
SHR F_3 (5mg)	21.9±11.7	25.2±11.9	23.0±10.7	17.7±16.9
SHR F_3 (2mg)	38.3± 2.7	30.1±13.1	28.6± 4.7	12.4±14.1
SHR F_{3+4} (5mg)	24.0±14.6	24.9±13.8	18.1± 7.5	22.8±17.0
SHR F_4 (2mg)	26.4± 2.7	27.2±12.0	28.8± 8.1	23.1±14.7
WR F_3 (5mg)	22.1±15.7	14.1±14.7	16.8±15.1	10.3±19.5
WR F_{3+4} (5mg)	26.6± 2.6	33.5±19.7	30.0± 7.8	25.2±13.0
WR F_4 (2mg)	18.5±14.7	17.4±13.2	17.8±15.5	11.8±13.9

* Percentage of the number of arteries with mild vascular lesions against the total number of arteries examined in a rat of each experimental group

± standard deviation

Table 3 Moderate Vascular Lesions produced by Renal Cortical Extracts*

Experimental group	Mesentery		Pancreas	
	small arteries and arterioles	medium-size arteries	small arteries and arterioles	medium-size arteries
SHR F_3 (5mg)	17.1±16.3	21.3±30.4	10.6±10.5	4.0± 9.9
SHR F_3 (2mg)	23.9±12.6	12.1±15.0	14.6±10.2	3.3± 7.4
SHR F_{3+4} (5mg)	17.5±16.3	14.6±22.1	6.6± 8.1	3.5± 5.0
SHR F_4 (2mg)	28.8± 7.3	2.0± 3.9	13.2± 9.4	3.5± 6.9
WR F_3 (5mg)	10.7± 9.0	27.4± 1.8	1.8± 4.7	0
WR F_{3+4} (5mg)	33.0±19.7	14.0±21.2	26.7± 5.1	1.4± 3.4
WR F_4 (2mg)	11.5±12.1	3.8± 6.1	6.8± 5.4	0

* Percentage of the number of arteries with moderate vascular lesions againstthe total number of arteries examined in a rat of each experimental group

± standard deviation

materials. The intercellular matrix showed accumlation of cell debris and fibrin. In the cytoplasm of smooth muscle cells adjacent to degenerated or necrotized cells, rough endoplasmic reticulum and mitochondria increased (Figure 4 and 5).

5. Frequency of vascular lesions by renal extracts

Mean values of the frequency of mild vascular lesions, moderate vascular lesions and mild and moderate vascular lesions in all experimental groups are showen in Table 2, 3 and 4. The comparison of vascular necrotizing effects of various fractions is showen in Table 5. In summary, F_3 and F_4 were more intensive in SHR than in WR and then F_{3+4} showed no difference between SHR and WR. In SHR, F_3, F_4 and F_{3+4} were of the same intensity of effect.

Table 4 Total of mild and moderate Vascular Lesions produced by Renal Cortical Extracts*

Experimental group	Mesentery		Pancreas	
	small arteries and arterioles	medium-size arteries	small arteries and arterioles	medium-size arteries
SHR F_3 (5mg)	39.0±23.0	46.5±24.7	33.4±14.8	21.7±22.6
SHR F_3 (2mg)	62.3±11.5	42.3±20.6	43.2±10.4	15.7±19.3
SHR F_{3+4} (5mg)	41.5±19.7	39.5±26.4	24.7±14.1	26.2±20.9
SHR F_4 (2mg)	55.2± 7.2	29.4±12.6	42.0±13.2	26.6±11.8
WR F_3 (5mg)	32.9±26.4	14.8±14.9	18.6±17.4	10.3±19.5
WR F_{3+4} (5mg)	60.0±19.6	47.5±29.9	57.9± 9.6	26.6±11.8
WR F_4 (2mg)	23.6±23.0	21.1±15.9	23.7±20.4	11.9±13.9

* Percentage of the number of arteries with mild and moderate vascular lesions against the total number of arteries examined in a rat of each experimental group

± standard deviation

Table 5 Comparison of percentage of number of injured arteries in each experimental group ($p<0.05$)

		mild vasular lesions	moderate vascular lesions	mild and modeate vascular lesions
F_3	Mesentery	SHR=WR	SHR=WR	SHR=WR
	Pancreas	SHR=WR	SHR>WR	SHR=WR
F_4	Mesentery (small art.)	SHR=WR	SHR>WR	SHR>WR
	Pancreas (medium)	SHR=WR	SHR>WR	SHR>WR
F_{3+4}	Mesentery	SHR=WR	SHR=WR	SHR=WR
Fractions of SHR	Mesentery and Pancreas	F_3 (2mg) = F_4	F_3 (2mg) = F_4	F_3 (2mg) = F_4
		F_3 (5mg) = F_{3+4}	F_3 (5mg) = F_{3+4}	F_3 (5mg) = F_{3+4}

DISCUSSION

After it was first clarified by the experiment of WINTERNITZ et al.[20] that renal extracts have vascular necrotizing effects, various experiments on the effects of renal extracts on vessels have been performed by ASSCHER and ANSON[1], MASSON et al.[9], MURAKAMI[10], KINOSHITA[8] and many other investigators.

ASSCHER and ANSON[1] took into consideration the relation between the increase of vascular permeability by renal extracts and hypertension and considered renal extracts play an important role in the pathogenesis of hypertensive vascular lesion. MASSON et al.[9] and ONOYAMA et al.[16],[17] thought that the vascular necrotizing factor contained in the kidney was renin or renin-like substance. On the other hand, MURAKAMI[10] reported that the vascular permeability factor of renal extracts had nothing to do with renin, and NAKAO et al.[12] and YAMAGUCHI[21] reported that the vascular necrotizing factor of renal extracts was in the non-pressor fraction. Several experiments have been reported in our laboratory, that the non-pressor fraction of renal extracts of normal rats has intensive vascular necrotizing effects.[4],[13],[18],[19]

Also in experiments using renal extracts of animals with experimental hypertension, controversive reports have been made. MASSON et al.[9] sampled renal extracts from rats with experimental hypertension by constriction of the aorta and indicated that the vascular necrotizing factor in the renal extracts was renin. ONOYAMA et al.[16] divided into subcellular fractions the renal cortex of rats with renovascular hypertension produced by renal artery constriction and indicated that the lysosomal fraction had high renin activity and intensive vascular necrotizing effects. On the other hand, YAMAGUCHI[21] indicated that the non-pressor fraction of renal cortical extracts of rabbits with renal artery constriction had more intensive vascular necrotizing effects than the non-pressor fraction of normal renal cortical extracts and that the vascular necrotizing effects of the pressor fraction were weak. SHIMOMURA[18], having produced renal extracts of rats with adrenal regeneration hypertension, reported that pressor effect was somewhat weaker in the pressor fraction of hypertensive renal extracts than in the pressor fraction of normotensive renal extracts, and that the vascular necrotizing effect of the pressor fraction was weak in both hypertensive and normotensive renal extracts.

There has been no report on the vascular necrotizing effect of renal extracts of SHR. In the present study, the fraction without pressor effect but with vascular necrotizing effect (F_3) and the fraction with pressor effect (F_4) isolated from renal cortical extracts of SHR showed more intensive vascular necrotizing effect than renal cortical extracts of normal rats. Since renin activity is not observed in F_3, the vascular necrotizing effect of F_3 has nothing to do with renin. With respect to F_4, the pressor effect was hardly different between SHR F_4 and F_4 of normal rats. However, the vascular necrotizing effect was intensive in SHR than in normal rats. In other words, there was no correlation between pressor effect and vascular necrotizing effect. Consequentry, it is seemed that F_4 of SHR has some vascular necrotizing substance which is unrelated to pressor effect.

Concerning the vascular necrotizing effect of the pressor fraction, NAKAMURA et al.[11] conducted an interesting experiment. They demonstrated that the lysosomal fraction of the renal cortex of rats had pressor effect and vascular necrotizing effect but it still had "mild but significant" vascular necrotizing effect even after losing renin activity by being heated at 60°C for 30 minutes, and consequently it had some vascular necrotizing substance which was different from renin. It is suggested by the present study also that F_4 of SHR has some vascular necrotizing substance which is different from renin. F_4 of SHR showed more intensive vascular necrotizing effect than renal extracts of normal rats. F_4 and F_3 of SHR were equal in vascular necrotizing effect.

According to a report by SHIMOMURA[18] with respect to renal extracts of normal rats, the vascular necrotizing effect was much weaker in the pressor fraction (F_4) than in the non-pressor fraction (F_3). In consideration of his experimental results, the vascular nectotizing substance was contained more in F_3 in case of normal kidney but equally in F_3 and F_4 in case of the kidney of SHR. In other words, the ratio of the vascular necrotizing substance contained in F_3 and F_4 may possibly be different between normal kidney and SHR kidney. This phenomenon may be explained by the presumption that the components of the kidney of SHR became different from normal kidney because of pathologic state and consequently the fraction of SHR kidney and normal kidney were different despite the same method of fractionation. The reason why SHR kidney has more intensive vascular necrotizing substance than normal kidney is unknown. There are two possibilities to cause this phenomenon. One is that SHR kidney has much vascular necrotizing factor congenitally, and the other is that persisting hypertension resulted in injury of renal tissue and increase of vascular necrotizing substance. The pathogenesis of SHR has been studied by many investigators. OKAMOTO et al.[15] and YAMORI[22] regarded the hypertension of SHR as a disease due to some genetical disorders and indicated various biochemical abnormalities in SHR. From this fact, it is possible that SHR kidney originally has more intensive vascular necrotizing factor than normal kidney. However, the confirmation of the possibility requires examination of vascular necrotizing effect by renal extracts of SHR prior to the occurrence of hypertension, and therefore further studies are awaited.

On the other hand, NAKAO et al.[12] and YAMAGUCHI[21] demonstrated that the non-pressor fraction of the renal cortex injured by ischemia increased more intensive vascular necrotizing effect than normal kidney. In view of this, it may be considered that the kidney of SHR with persisting hypertension contains much vascular necrotizing substance abundantly. However, since the nature and origin of vascular necrotizing substance of renal extracts have not been clarified, it is difficult to explain the increased vascular necrotizing effect of SHR. The histological findings of vascular lesion caused by renal extracts of SHR were light microscopically the same as those of vascular lesion caused by renal extracts of normal rats.

In the present experiment, the vascular lesions caused by renal extracts of SHR were examined electron microscopically, and changes were observed in the endothelium and

media. Detailed electrom microscopic observation of vascular lesions caused by renal extracts of normal rats has already been performed by SHIROMA[19] in this laboratory. He examined electron microscopically the early vascular lesions within 24 hours after intravenous injection of the non-pressor fraction of normal renal cortex to rats. In that study, he observed that vascular lesions occured first in the endothelial cells and then in the media. The electron microscopic findings of the media in his study resembled the findings of the media caused by renal extracts of SHR but the findings of the endothelium in this experiment showed some difference in his experiment. The denudation of endothelial cells and the adherence of platelets to that area observed in the present experiment were also seen in his experiment, but there is no description in his experiment concerning the vacuolar formation of endothelial cells and the bleb-shaped protrusion. The vacuolar formation of endothelial cells was observed by HOFF and GOTTLOB[7] when the aorta of rabbit was perfused with epinephrine, nor-epinephrine, bradykinin and hypertonic glucose of high concentration and when the rabbit was placed in the state of shock. GERTZ et al.[5] in their experiment to produce ischemia in the common carotid arteries of monkey and rabbit observed vacuoles and blebs in endothelial cells but stated that the origin was uncertain. CONSTANTINIDE and ROBINSON[3] observed that endothelial cells bulged into the lumen after dopamine was injected into the common iliac artery of rat. These experiments and the present experiment are different in experimental animals, region of arteries obsorved, size of arteries, and methods of experiment, and the vascular lesions observed in those experiments and the vascular lesions observed in the present experiment cannot be compared directly and therefore it is difficult to speculate the genesis of the vascular lesions observed in the present experiment from the results of those experiment. Yet, it is possibly considered that the vacuoles and protrusions of endothelial cells were caused by the stimuli of renal extracts. However, the question as to whether these findings are peculiar to the injection of renal extracts of SHR or they are not seen when renal extracts of normal rats are injected cannot be ascertained at this stage, and further studies are required.

Macroscopic, light microscopic and electron microscopic observation of rats sacrificed 24 hours after unilateral nephrectomy and contralateral urethral ligation without injection of renal extracts have been conducted by NISHIMORI et al.[13] and FUKAZAWA[4] of this laboratory. They reported that only mild hydronephrosis was noted macroscopically, and the mesentery and pancreas showed no vascular change light microscopically and electron microscopically.

CONCLUSION

From the renal cortex of spontaneously hypertensive rats (SHR) with persisting hypertension, a fraction with non-pressor but vascular necrotizing effect (F_3), a pressor fraction (F_4), and an extract without separation of F_3 and F_4 (F_{3+4}) were extracted, and they were compared with renal cortical extracts of normal Wistar rats (WR) for pressor

activity and vascular necrotizing effect.

1. Pressor activity was not seen in F_3 of SHR and F_3 of WR. Remarkable pressor activity was seen in both F_4 of SHR and F_4 of WR at the same degree. F_{3+4} of SHR and F_{3+4} of WR showed slight pressor activity.

2. Rats with right nephrectomy and left urethral ligation were sacrificed 24 hours after intravenous injection of renal extracts, and the arteries of the mesentery and pancreas were examined light and electron microscopically for comparison of vascular lesions caused by renal extracts of SHR and WR.

(1) Light microscopically, the main finding of vascular lesions caused by any fraction was fibrinoid necrosis histomorphologically.

(2) Electron microscopic examination of vascular lesions caused by renal extracts of SHR revealed, in the endothelium, denudation of endothelial cells, adherence of platelets, vacuolar formation in the cytoplasm of endothelial cells, invasion of leukocytes into the subendothelial space and bleb formation of endothelial cells; and in the media, degeneration and necrosis of smooth muscle cells, increase of rough endoplasmic reticulum and mitochondria in the cytoplasm of smooth muscle cells adjadent to these degenerative and necrotic cells, and accumulation of cell debris and fibrin in the intercellular matrix.

(3) Vascular lesions caused by renal extracts were classified into mild vascular lesion and moderate vascular lesion and frequency of mild and moderate lesions was each calculated for small arteries and medium-size arteries, and the frequency was compared statistically among various experimental groups, and following results were obtained.

$SHR \cdot F_3 \geqq WR \cdot F_3$, $SHR \cdot F_4 > WR \cdot F_4$

$SHR \cdot F_{3+4} = WR \cdot F_{3+4}$, $SHR \cdot F_3 = SHR \cdot F_4$, $SHR \cdot F_{3+4} = SHR \cdot F_3$

These results indicated that both F_3 and F_4 of SHR have more intensive vascular necrotizing effect, and it is speculated that F_4 of SHR has same vascular necrotizing substance which is unrelated to pressor effect.

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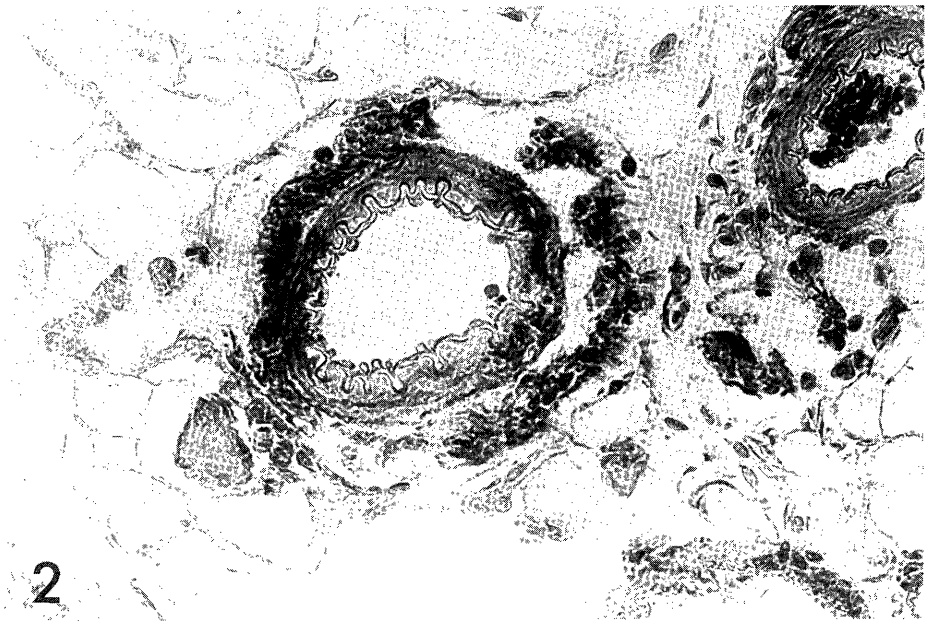

Figure 2 Small mesenteric artery with mild vascular lesion (Group 1).
The artery has less than three layers of smooth muscle cells. Fibrinoid necrosis of individual smooth muscle cells is shown, and extends less than one guarter of the circumference. Azan-Mall ory stain, x370

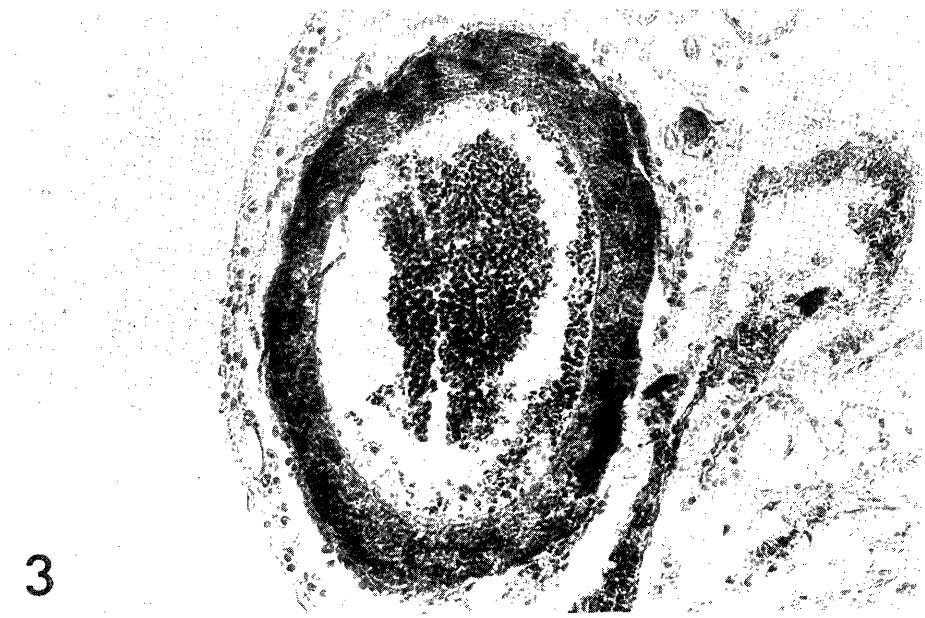

Figure 3 Medium-size mesenteric artery with moderate vascular lesion (Group3).
The artery has more than four layers of smooth muscle cells, and fibrinoid necrosis extends more than one guarter of the circumference. The invasion of fibrin-like materials and erythrocytes is prominent in the outer media. Azan-Mallory stain, x185

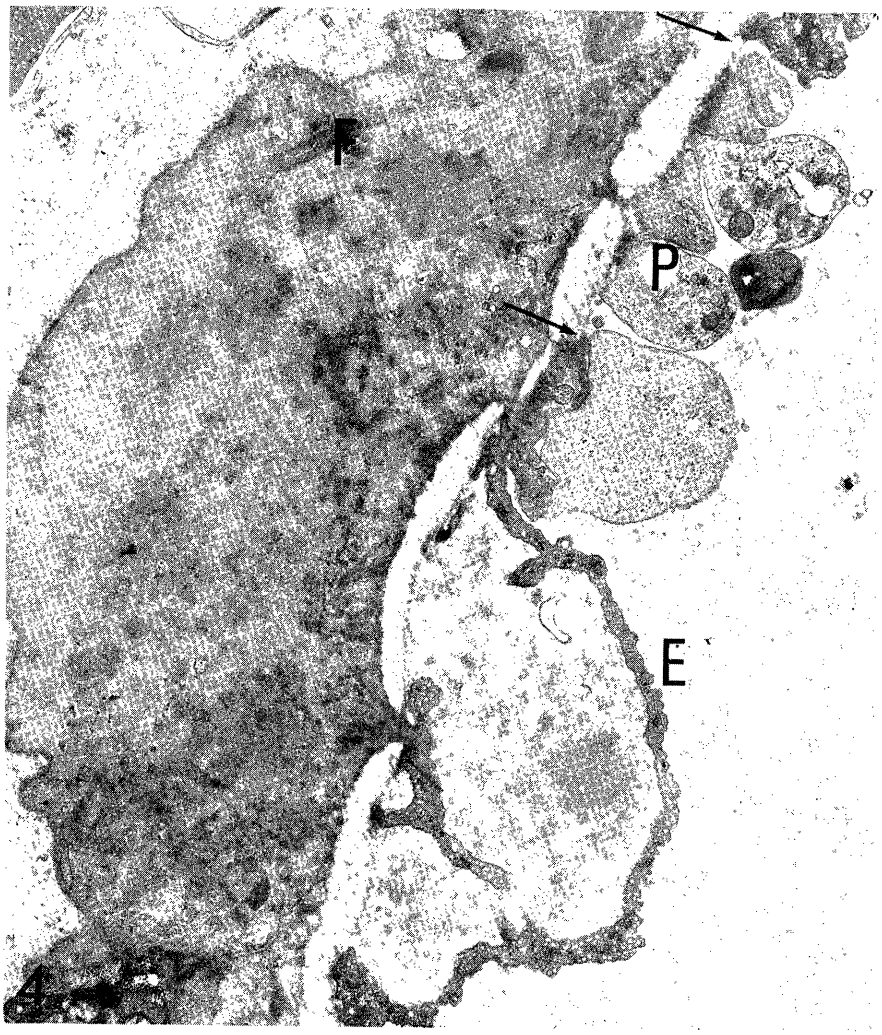

Figure 4 Electron microscopic picture of pancreatic vascular lesion (Group 1). Endothelial cells are denuded (from arrow to arrow), and platelets (P) adhere to that region. The subendothelial space is occupied by plasma components and endothelial cells (E) protrude towards the lumen and from a bleb. Smooth muscle cells of media contain electron dense materials. Fibrin (F) is seen in the intercellular matrix of media. x7,500

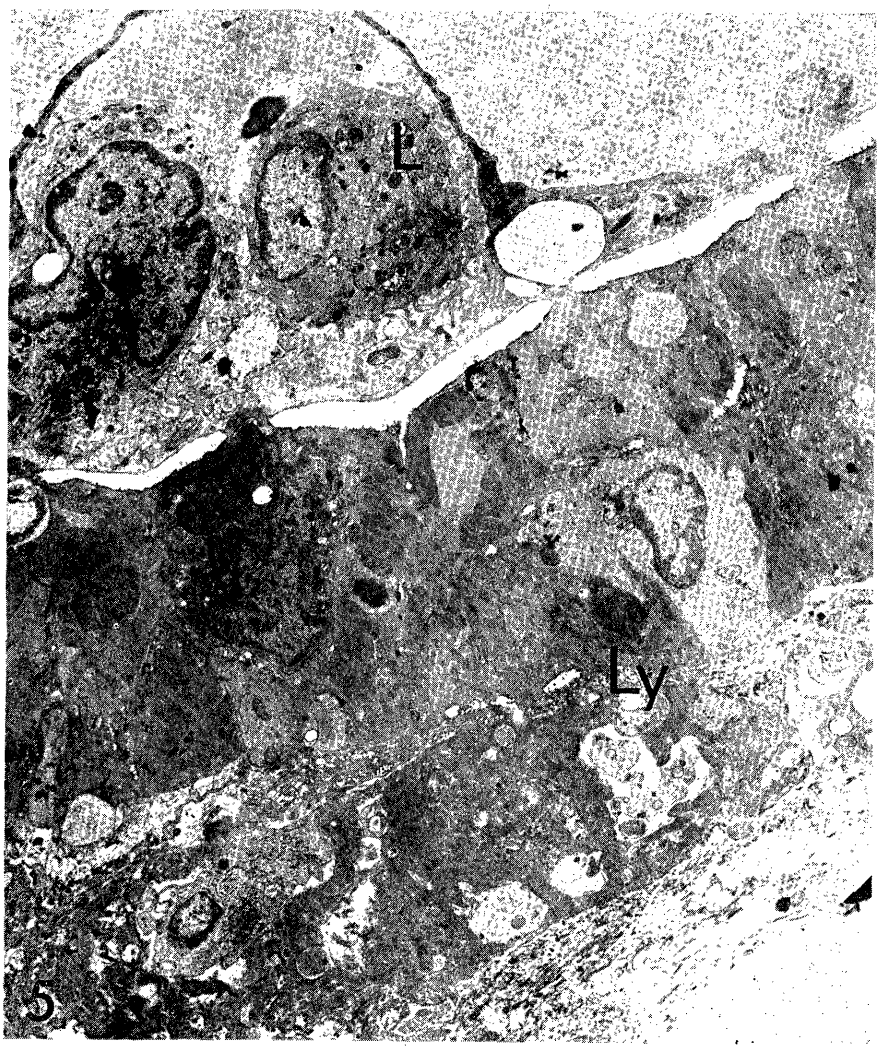

Figure 5 Electron microscopic picture of mesenteric vascular lesion (Group 3). The subendothelial space is invaded by plasma components and leukocytes (L), and endothelial cells of this area protrude towards the lumen and from a bleb. In media, smooth muscle cells have large lysosomes (Ly) and the intercellular matrix has accumulation of cell debris and fibrin. x 4,250