STUDIES ON SODIUM AND CALCIUM CONTENTS OF CARDIOVASCULAR TISSUE IN EXPERIMENTAL HYPERTENSION

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Sodium and calcium contents of cardiovascular tissue in spontaneously hypertensive rats (SHR) and DOCA hypertensive rats were investigated. The effect of salt loading on these contents of SHR and control Wistar rats was also investigated. Calcium content increased with the development of hypertension, but not sodium content particularly in salt loading rats and at the sustained stage of DOCA hypertensive rats. These results suggest that calcium rather than sodium is more intimately related to the increase in blood pressure.

THE PATHOGENESIS of essential hypertension has not been clarified because many factors are involved in the mechanism of causing and maintaining high blood pressure. But the major factor of raising blood pressure in essential hypertension is the enhancement of peripheral vascular resistance, which is thought to be the result of the narrowing of the vascular lumen due to swelling of the vascular wall or active vascular contraction. In many experiments and clinical observations, sodium plays an important role in the rise of blood pressure. Recent studies demonstrated that calcium also plays an essential role. One of the most important vasoconstrictive substance is thought to be catecholamines, which can change permeability of various ions across membranes of vascular smooth muscle. Among them, catecholamine-induced alteration in calcium ion permeability of the membrane is considered to play an essential role in the cardiovascular function. *Haddy*¹ observed that infusion of calcium salt into a dog's limb artery increased the vascular resistance. These studies

suggest that calcium plays a major part in contraction of vascular smooth muscle.

In this study, spontaneously hypertensive rats (SHR),² DOCA hypertensive rats, salt loading SHR and salt loading Wistar rats were used. Measurement of sodium and calcium contents of cardiovascular tissues in those animals were made and its significance of their quantitative changes was investigated.

MATERIALS AND METHODS

Seven month old SHR (F₂₂ male N:28) and 7 month old control Wistar rats (Kobe strain male N:28) were used. Half of them were used as salt loading SHR (N:14) and Wistar rats (N:14) by giving 1% NaCl as drinking water for 4.5 months from 2.5 months old. DOCA hypertensive rats (acute stage N:9, sustained stage N:7 as described later) were also used in this experiment. Sodium and calcium contents of cardiovascular tissues and femoral muscle in those animals were determined. Furthermore, SHR (F_{22, 23} male) and control male Wistar rats were used at the age of 1, 3, 7, 12, and 19 months to observe the changes of sodium and calcium contents of the aorta with aging. In this experiment one group consisted of 14 rats, except 19 month old SHR group which consisted of 10 rats. SHR (F_{25, 26, 27} N:143) and Wistar rats (N:72) were also used

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to observe changes of blood pressure with growth.

Blood pressure was measured mostly under no anesthesia by tail cuff method (Narco Bio System programmed sphygmomanometer), except in some experiments measured under α -chloralose (40 mg/kg body weight) anesthesia by catheterization to the iliac artery.

DOCA hypertensive rats were prepared by the following procedure. Using male Wistar rats weighing 140–150 g, after they underwent uninephrectomy, they were divided into 3 groups. Group A (N:9) was maintained on tap water for 15 weeks and used as DOCA control rats. Group B (N:9) was maintained under same condition as Group A for the first 11 weeks, and thereafter, the tap water was replaced by 1% NaCl and simultaneously desoxycorticosterone acetate (DOCA 10 mg/kg body weight) was injected subcutaneously at weekly intervals to the end of the fifteenth week.

Group C (N:7) was maintained on 1% NaCl as drinking water all the 15 weeks, but DOCA was administered for the first 6 weeks in the same way as for Group B. Group B was used as an acute stage of DOCA hypertension and Group C was used as a sustained stage of it.

All rats were killed by decapitation and the blood was drawn on the spot for the determination of serum sodium and calcium concentration. Cardiovascular tissue (left ventricle, aorta and cortex of kidney) and femoral muscle were taken immediately after death. The aorta from the ascending portion to the bifurcation was used and the adhered fat tissue and blood were eliminated as much as possible. The removed wet tissues were cut into about 100 mg pieces. When the tissue weight was less than 100 mg, then the total tissue removed was used. These

tissues were dried for 72 hours at 80°C and weighed after fat was deprived by ethyl ether for 4 hours. The water content was calculated by wet tissue weight at 100% minus the percentage of dry tissue weight. Sodium was determined by Collman flame photometer after treatment by boiled nitric acid. Calcium was determined atomic absorption photometer (Hitachi 207 type) after treatment by boiled mixture of trichloroacetic acid and glacial acetic acid.³

To observe the effect of calcium antagonist (Nifedipine) on blood pressure in SHR and DOCA hypertensive rat, SHR (F₂₅ 6 months old N:5) and DOCA hypertensive rats (N:5) with the same level of blood pressure (about 200 mmHg) and body weight (about 300 g) were chosen, and changes of blood pressure were investigated before and after the intraperitoneal injection of Nifedipine (0.5 mg/kg body weight) at 15 minutes intervals for one hour by tail cuff method.

RESULTS

Average mean arterial blood pressure (measured by catheterization mean $\pm$ SE), serum sodium and calcium concentration (mean $\pm$ SE) in SHR (male 7 months old N:14) and control Wistar rats (male 7 months old N:14) were as follows. Blood pressure of SHR and control Wistar rats were 124 ± 4 mmHg and 91 ± 3 mmHg respectively. Serum sodium concentration was 143.3 ± 0.6 mEq/L and 144.3 ± 0.6 mEq/L, respectively. Serum calcium concentration was 10.3 ± 0.1 mg/dl and 10.2 ± 0.1 mg/dl, respectively. No difference was seen in serum sodium and calcium concentration between SHR and control Wistar rats.

Table I shows the water content of cardiovascular tissue and femoral muscle. No difference was seen except that the left ventricle

TABLE I WATER CONTENT OF CARDIOVASCULAR TISSUE AND FEMORAL MUSCLE IN SHR AND CONTROL WISTAR RAT (KOE)

	<i>L-Ventricle</i>	<i>R-Ventricle</i>	<i>L-Atrium</i>	<i>R-Atrium</i>	<i>Aorta</i>	<i>C. of Kidney</i>	<i>F-Muscle</i>
<i>Control WR</i> (<i>N</i> = 14)	71.9 ± 0.3	67.1 ± 0.4	64.2 ± 1.8	60.7 ± 2.1	55.8 ± 1.1	67.3 ± 0.5	71.0 ± 0.5
<i>SHR</i> (<i>N</i> = 14)	72.9 ± 0.2	67.2 ± 0.5	63.8 ± 1.7	64.1 ± 0.8	56.7 ± 1.0	68.9 ± 0.5	70.2 ± 0.5
<i>p Value</i>	0.02	ns	ns	ns	ns	0.05	ns

Water content was calculated by wet tissue weight at 100% minus the percentage of dry tissue weight. Data expressed as means $\pm$ SE.

WR: Wistar Rat, L: Left, R: Right, C: Cortex, F: Femoral.

Fig.1. Changes in calcium and sodium contents of aorta with growth.

Fig.2. Changes in blood pressure of SHR (F₂₅, 26, 27) and Wistar Rat with the month's age.

TABLE II SODIUM AND CALCIUM CONTENTS OF CARDIOVASCULAR TISSUE AND FEMORAL MUSCLE IN 7 MONTH OLD AND CONTROL WISTAR RAT

	L-Ventricle	R-Ventricle	L-Atrium	R-Atrium	Aorta	C. of Kidney	F-Muscle
Na mEq/kg dry tissue weight	Control WR (N = 7) 174.8 ± 1.2	200.5 ± 3.0	372.3 ± 5.3	387.2 ± 10.5	282.1 ± 9.8	221.6 ± 4.8	101.7 ± 2.7
	SHR (N = 7) 194.0 ± 3.6	224.8 ± 4.4	441.4 ± 14.8	323.3 ± 12.4	340.8 ± 9.8	269.3 ± 9.7	106.8 ± 4.9
p Value	0.001	0.001	0.001	0.001	0.001	0.001	ns
Ca mg/kg dry tissue weight	Control WR (N = 7) 168.9 ± 4.5	186.2 ± 5.2	527.7 ± 39.1	484.9 ± 11.2	494.8 ± 24.0	314.8 ± 6.3	251.0 ± 8.3
	SHR (N = 7) 181.5 ± 3.2	192.1 ± 5.9	670.1 ± 29.5	592.4 ± 32.5	532.8 ± 22.2	333.4 ± 9.2	260.1 ± 5.2
p Value	0.1	ns	0.05	0.02	ns	ns	ns

Data expressed as means ± SE.

and cortex of the kidney showed slightly higher water content in SHR.

Table II shows sodium and calcium contents of cardiovascular tissue and femoral muscle in 7 month old and control Wistar rats. Half of the 14 rats were used for sodium determination, and the other half for calcium determination. Sodium content of cardiovascular tissue in SHR was significantly higher than that of control Wistar rats, and no difference was seen in femoral muscle. Calcium content of cardiovascular tissue in SHR was not so significantly higher than that of control Wistar rats, but the level of the average calcium content in each tissue of SHR was higher than that in the corresponding tissue of control Wistar rats, suggesting that SHR had higher calcium content than control Wistar rats.

Fig. 1 shows changes of sodium and calcium contents of aorta in SHR and control Wistar rats with growth. Sodium content of the aorta decreased gradually with growth from one month to 12 months old, and thereafter, it increased slightly in both SHR and control Wistar rats. The difference between SHR and control Wistar rats in sodium content of aorta was marked from one month to 7 months old but not so significant from 12 months to 19 months old. Calcium content of the aorta also decreased with growth from one month to 7 months old, but thereafter, increased in both SHR and control Wistar rats from 12 to 19 months old. The difference between SHR and control Wistar rats in calcium content of aorta was not seen at the age of one month but became remarkable with growth from the age of 3 months.

Fig. 2 shows changes in blood pressure of SHR and Wistar rats during growth. Though all rats used in this measurement were not the same with the rats previously used in Fig. 1, the results obtained were presumed to be similar to the changes of blood pressure of the rats used in Fig. 1. Blood pressure of SHR began to rise from 1.5 months and reached about 170 mmHg at 6 months, while that of control Wistar rats showed about 120 mmHg at 1.5 months and 130 mmHg at 7 months. The effect of long term salt loading on sodium and calcium contents of cardiovascular tissue was presented in Table III. Average mean arterial blood pressure (measured by catheterization mean ± SE) of salt loading SHR (N:14) was 132 ± 3 mmHg and 104 ± 3 mmHg, respectively. The long term salt loading increased calcium content of cardiovascular tissue in both SHR

Fig. 3. Changes in blood pressure of DOCA hypertensive rat measured at one or two weekly intervals.

Group A: DOCA control rat.

Group B: acute stage of DOCA hypertensive rat.

Group C: sustained stage of DOCA hypertensive rat.

Fig. 4. Effect of intraperitoneal administration of Nifedipine on blood pressure in SHR and DOCA hypertensive rat.

and control Wistar rats and the degree was much more remarkable in SHR. On the contrary, sodium content tended to decrease in both SHR and control Wistar rats. Though the increase or decrease was not statistically significant in some tissues, the long term salt loading increased the calcium content and decreased the sodium

content on the whole.

Fig. 3 shows changes of blood pressure (measured by tail cuff method) in acute stage of DOCA hypertensive rats (Group B), sustained stage of DOCA hypertensive rats (Group C), and DOCA control rats (Group A). The blood pressure of Group C began to rise with the administra-

TABLE III EFFECT OF LONG TERM SALT LOADING ON SODIUM AND CALCIUM CONTENTS OF CARDIOVASCULAR TISSUE IN SHR AND CONTROL WISTAR RAT

		Sodium mEq/kg dry tissue			Calcium mg/kg dry tissue		
		L-Ventricle	Aorta	C. of Kidney	L-Ventricle	Aorta	C. of Kidney
Control ^{WR} (N = 14)	no salt (N = 7)	174.8 ± 1.2	272.4 ± 13.0	230.6 ± 3.5	168.9 ± 4.5	494.8 ± 24.0	314.8 ± 6.3
	on salt (N = 7)	166.0 ± 1.1	224.3 ± 6.0	229.8 ± 1.9	184.0 ± 3.5	564.8 ± 28.1	335.8 ± 6.3
p Value		0.001	0.01	ns	0.05	ns	ns
SHR (N = 14)	no salt (N = 7)	194.0 ± 3.6	340.8 ± 12.9	269.3 ± 9.7	181.5 ± 3.2	532.8 ± 22.2	333.4 ± 9.2
	on salt (N = 7)	189.2 ± 2.7	311.9 ± 11.0	256.9 ± 9.8	213.3 ± 3.9	651.7 ± 23.1	382.3 ± 8.8
p Value		ns	ns	ns	0.001	0.01	0.005

Data expressed as means ± SE.

TABLE IV BLOOD PRESSURE HEMATOCRIT, SERUM SODIUM POTASSIUM AND CALCIUM CONCENTRATION OF GROUP A (DOCA CONTROL RAT), GROUP B (ACUTE STAGE OF DOCA HYPERTENSIVE RAT), GROUP C (SUSTAINED STAGE OF DOCA HYPERTENSIVE RAT)

	BLOOD PRESSURE mmHg	HEMATOCRIT %	SERUM Na mEq/l	SERUM K mEq/l	SERUM Ca mg/dl
Group A (N = 9)	131.0 ± 4.3	41.9 ± 0.4	142.0 ± 0.4	5.0 ± 0.1	10.4 ± 0.2
Group B (N = 9)	173.0 ± 6.3 0.001	41.1 ± 0.8 ns	148.9 ± 0.6 0.001	3.7 ± 0.2 0.001	10.3 ± 0.1 ns
Group C (N = 7)	170.0 ± 10.4 0.005	39.1 ± 0.6 0.001	141.8 ± 0.2 ns	5.3 ± 0.1 ns	10.2 ± 0.1 ns

Data expressed as means ± SE. All p values are based on Student's t test for paired variates when compared with control value.

tion of DOCA and 1% NaCl as drinking water and reached about 190 mmHg at the end of the seventh week, and slightly decreased to the level of 170 mmHg at the end of the eighth week with no addition of DOCA, and thereafter, the blood pressure was maintained about 170 mmHg to the end of fifteenth week. The blood pressure of Group B showed the same level as Group C at the end of the fifteenth week. The blood pressure of Group A showed about 130 mmHg at the end of the fifteenth week, as is seen in the natural rise of blood pressure in 6 month old Wistar rats shown in Fig. 3.

Table IV shows concentration of serum sodium, potassium, calcium, and hematocrit of

Group A, B and C. The serum sodium concentration of Group B was higher than that of Group A and C, but on the contrary, the serum potassium concentration of Group B was lower than that of Group A and C. No difference was seen in serum calcium concentration between the three Groups. From the result that no difference was seen in serum sodium and potassium between Group A and C, Group C was considered to be free from the DOCA effect at the end of the fifteenth week. Hematocrit of Group C was lower than that of Group A.

Table V shows water content of left ventricle, aorta, kidney cortex and femoral muscle in Group A, B and C. The water content of Group

TABLE V WATER CONTENT OF CARDIOVASCULAR TISSUE AND FEMORAL MUSCLE IN GROUP A (DOCA CONTROL RAT), GROUP B (ACUTE STAGE OF DOCA HYPERTENSIVE RAT). WATER CONTENT (%) WAS CALCULATED AS SHOWN TABLE I

	<i>L-Ventricle</i>	<i>Aorta</i>	<i>C. of Kidney</i>	<i>F-Muscle</i>
Group A (N = 9)	74.5 ± 0.1	59.0 ± 1.2	71.9 ± 0.4	74.9 ± 0.3
Group B (N = 9)	75.4 ± 0.2 <0.005	65.1 ± 1.0 <0.005	74.7 ± 0.9 <0.01	76.2 ± 0.7 <0.001
Group C (N = 7)	73.9 ± 0.3 ns	57.5 ± 2.2 ns	72.3 ± 0.6 ns	74.2 ± 0.3 ns

Data expressed as means ± SE. All *p* values are based on Student's *t* test for paired variates when compared with control value.

TABLE VI SODIUM AND CALCIUM CONTENTS OF CARDIOVASCULAR TISSUE AND FEMORAL MUSCLE.

		<i>L-Ventricle</i>	<i>Aorta</i>	<i>C. of Kidney</i>	<i>F-Muscle</i>
Na mEq/kg dry tissue weight	Group A (N = 9)	180 ± 5	303 ± 13	249 ± 7	96 ± 2
	Group B (N = 9)	201 ± 3 0.005	381 ± 10 0.001	315 ± 15 0.005	165 ± 10 0.001
	Group C (N = 7)	174 ± 5 ns	324 ± 15 ns	258 ± 18 ns	87 ± 2 0.01
Ca mg/kg dry tissue weight	Group A (N = 9)	208 ± 3	476 ± 14	348 ± 8	278 ± 3
	Group B (N = 9)	224 ± 5 0.01	555 ± 19 0.01	389 ± 9 0.005	285 ± 8 ns
	Group C (N = 7)	223 ± 6 0.02	543 ± 17 0.01	382 ± 8 0.005	282 ± 5 ns

Group A: DOCA Control Rat, Group B: acute stage of DOCA hypertensive Rat.
Data expressed as means ± SE. All *p* values are based on Student's *t* test for paired variates when compared with control value.

B was higher than that of Group A, but no difference was seen between Group A and C.

Table VI shows sodium and calcium contents of cardiovascular tissue and femoral muscle in Group A, B and C. Sodium content of all these tissues in Group B was higher than that of Group A and C. However, sodium content of Group C was not different from that of Group A except that it was low in the femoral muscle. Calcium content of cardiovascular tissue in Group B and C was significantly higher than that of Group A.

Fig. 4 shows the effect of calcium antagonist (Nifedipine) on blood pressure of SHR and DOCA hypertensive rats. In this experiment, DOCA hypertensive rats at the end of the seventh week in Group C were used. At 15 minutes after

the injection of Nifedipine, blood pressure fell from about 200 mmHg to 160 mmHg in SHR and from about 210 mmHg to 145 mmHg in DOCA hypertensive rats. One hour after injection blood pressure of SHR and DOCA hypertensive rats fell to about 155 mmHg and 160 mmHg, respectively.

DISCUSSION

Although various factors are involved in essential hypertension, the rise in blood pressure is caused by the increased peripheral vascular resistance as a final common pathway regardless of what particular factor participates. The increased peripheral vascular resistance is thought to be strongly related to the narrowing of

vascular lumen resulting from the swelling of vascular wall or active vascular contraction. From the clinical observation that thiazide which has a natriuretic action lowers the blood pressure and calcium antagonist is often effective for the hypertension which cannot be controlled by thiazide, sodium and calcium among various electrolytes are particularly considered to be responsible for the narrowing of the vascular lumen.

In this study, calcium antagonist (Nifedipine) showed the remarkable hypotensive effect on both SHR and DOCA hypertensive rats (Fig. 4). But daily injection of hydroflumethiazide (40 mg/kg body weight) for one week and daily oral administration of trichloromethiazide (0.12 mg and 1.2 mg/kg body weight) for one week failed to lower the blood pressure in SHR, (unpublished observations). Therefore, it was suggested that calcium was more responsible for the high blood pressure in SHR than sodium.

*Tobian and Chesley*⁵ reported that sodium and calcium contents of mesenteric artery in the hypertensive rats of Goldblatt type were increased and similar results were obtained in those of tail artery in DOCA hypertensive rats.⁶ *Sirotina*⁷ reported the increase of sodium and calcium contents of cardiovascular tissue in reflexogenic hypertensive rabbits. *Hollander et al.*⁸ demonstrated that by means of mechanical constriction of aorta in dog, the sodium content of the upper portion of the aorta was higher than the lower portion. In experiments of vasoconstrictive agents, *Tobian and Fox*⁹ observed sodium content of femoral artery in dog was increased by drip infusion of norepinephrine, and *Viramil et al.*¹⁰ also reported sodium and calcium contents of carotid artery in dog were increased by drip infusion of angiotensin II. Accordingly, it is possible to think that the procedures of causing high blood pressure could increase sodium and calcium contents of cardiovascular tissue. However, it is not clear whether the increase of both sodium and calcium is necessary for the rise of blood pressure, or the increase of calcium represents a nonspecific phenomenon followed by the increase of water content with the increase of sodium, which is considered to be responsible for the swelling of the vascular wall.

In this study, as shown in Table II, the sodium content of cardiovascular tissue in SHR was significantly higher than in control Wistar rats at the period of 7 month old. Similar results were obtained in calcium content, though the

tendency was not so remarkable as sodium. But as shown in Fig. 1 the difference of calcium content of aorta between SHR and control Wistar rat became marked with growth. On the contrary, that of sodium content became less marked with growth. Table VI shows that both sodium and calcium contents of cardiovascular tissue increased at the acute stage of DOCA hypertensive rats with the increased water content, but sodium content was unaltered and calcium content remained high at the sustained stage. Moreover, regardless of the fact that sodium loading accelerate clinically and experimentally the rise of blood pressure, long term sodium loading on SHR and Wistar rat decreased sodium content of cardiovascular tissue in both SHR and Wistar rat, but calcium content increased especially in SHR. Therefore hypertension is not always associated with the increased sodium content of cardiovascular tissue, but with the increased calcium content. *Nagaoka et al.*¹¹ reported that sodium content of aorta decreased in dexamethazone hypertensive rats in spite of the rise in blood pressure, but calcium content was not determined. *Ignacio, J., Dela Riva*¹² reported that in DOCA hypertensive rats sodium content of aorta increased during the initial 5 weeks by 10% of control rat, but decreased at the end of 15 weeks by 4% of control rat regardless of sustained high blood pressure. The increased calcium content is not always followed by the increased sodium and water content, but it could be significant by itself for the sustained hypertension. However, the problem in what space of vascular wall the extra amount of calcium or sodium is located remains unknown. *Tobian and Duke*¹³ reported in hypertensive rat produced by narrowing one renal artery and removing the opposite kidney that there was 55% more calcium per unit dry weight in the left ventricle and he estimated the intracellular calcium content of the ventricle corrected for inulin space in the hypertensive rat was in an average 68% higher per unit of dry weight than in the normotensive ones. *Friedman*,¹⁴ using lithium which could be replaced for extracellular sodium at low temperature, demonstrated that the intracellular sodium was increased in tail arteries of DOCA hypertensive rats, but no significant difference from controls was observed in one renal artery clipped hypertensive rats by the same technique. *Jones*,^{15,16} using ⁶⁰Co-EDTA, observed in SHR that there was little change in aortic water, sodium and

calcium contents, and in cell water and extracellular space, during the early hypertensive stage. Although in those reports there are controversies about the increase in sodium or calcium contents in the intracellular space in various types of experimental hypertension, and the location of the extra calcium observed in these experiments could not be clarified, the increase of calcium determined as a total was thought to be more intimately related to the development of hypertension.

It may be still questionable whether the rise of blood pressure is caused by the increase of calcium content of cardiovascular tissue or vice versa. Besides the genesis of essential hypertension may lie in the defect of vascular wall in itself, although no observation related to it has been reported. The significance of the increase of calcium content in cardiovascular tissue is complicated in the sustained stage and even in the initiation of hypertension, since high blood pressure bring about structural changes of cardiovascular wall with the increase of mucopolysaccharides which can bind with cation such as sodium and calcium.¹⁷⁻¹⁹ The observed remarkable difference in calcium content of aorta between SHR and control Wistar rats with growth may be associated with those structural changes.

McGregor and Smirk²⁰ observed that mesenteric artery of genetic and renal hypertensive rats showed stronger response to norepinephrine than that of control rats, and Hinke²¹ also observed similar increased vascular response to norepinephrine by tail artery strips of DOCA hypertensive rats, which resulted from the increase of calcium content in it, and then he suggested that the increased calcium, even if it was bound to mucopolysaccharides, could become easily available for vascular contraction, since the binding was not so tight. Therefore, calcium is thought to play the important role of the hypertension whether or not it may combine with mucopolysaccharides.

In regard to the cause of the rise of blood pressure in acute stage of DOCA hypertensive rats, Champlain²² demonstrated that positive sodium balance enhanced the activity of sympathetic nervous system which could develop hypertension. Even if the increased sodium content may play an important role in the initiation of hypertension, the decrease of sodium content in cardiovascular system in long term salt loading which accompanies sustained hyperten-

sion is the good evidence that the increase of sodium content in the cardiovascular tissue is unrelated to the sustained hypertension.

SUMMARY

1) Sodium and calcium contents of the cardiovascular tissue in SHR were higher than those in normotensive Wistar rats at the age of 7 month old. Sodium content of aorta in SHR was higher than that of control Wistar rats from 1 month to 7 months, the difference becoming less marked after 12 months. Slight but significant difference in calcium content of aorta between SHR and control Wistar rats was observed during the initial months, it becoming gradually remarkable with growth.

2) Long term salt loading on SHR and Wistar rats increased calcium content and decreased sodium content of the cardiovascular tissue in both groups.

3) In the acute stage of DOCA hypertensive rats, both sodium and calcium contents of the cardiovascular tissue increased, and in the sustained stage, calcium content remained higher than control, but sodium content was with the normal range.

Thus, in SHR as well as DOCA hypertensive rats the increase of calcium content of cardiovascular tissue is not always accompanied by that in sodium content. These results may suggest that calcium rather than sodium is closely related to the development of hypertension.

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