PARTICIPATION OF THE SYMPATHETIC NERVOUS SYSTEM IN SPONTANEOUSLY HYPERTENSIVE RATS

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HYPERTENSION, a main cause of heart failure and an accelerating factor of arteriosclerosis, is of essential type in more than 80% of cases. Enormous studies have so far been made on its aetiology, and they are still being continued from various points or views. Its hereditary factors were analyzed by *Weitz*,¹ *Alexander*² and *Platt*.^{3,4} The present author made studies on the aetiological mechanism of hypertension in spontaneously hypertensive rats (SHR)⁵ which were specially brought up by Okamoto, Aoki as models surely developing hereditary hypertension — hypertension quite resembling hypertension in human beings, through investigations into various organs, especially the cardiovascular system, would show changes in their modes of metabolic and hemodynamic responses to the administration of catecholamine (CA), which is clinically used as endogenous pressor substance and the antagonist of which is used as anti-hypertensive agent.

METHODS

The SHR used as experimental animals were male F₁₅–F₂₀, with ages of 3 weeks, 3 months, and 6–8 months. The controls were male Wistar-strain KOBE rats with normal blood pressure (NR) and the same ages as above. All of these rats were fed from generation to generation under the same conditions in the experimental animal house of Kobe University School of Medicine. They were given solid feeds NMF available from Oriental Ferment Industry K.K. Both of the SHR and NR were given Tyramine, as a pressoramine and Reserpine, as a CA

releaser. Observations were made on the CA level in the various organs, that is, heart, adrenal gland, lung, liver and kidney, as well as on pressor responses after administration of the drugs.

Tyramine hydrochloride was mingled with the Ringer solution at a rate of 2 mg per ml. Blood pressure was measured on the surgically exposed left carotid artery periodically without anesthesia but under confinement, while Tyramine was injected by intravenous infusion through the right jugular vein at a rate of 1.5 mg/kg/min until the raised pressure returned to the previous normal level. Meanwhile, Reserpine, 0.02 mg/kg, was intramuscularly administered 24 hours before measurement.

The salt loading for both of the SHR and NR was begun from the first month of their birth to be continued for the following 7 months by the use of 1% NaCl solution which was given to them as drinking water.

Immediately after each animal was sacrificed through decapitation, every organ was extracted and divided into two parts for determination of the CA content; one part served as materials for the fluorescent determination according to the modified Fujiwara's method⁶ and the other part was homogenated with 5% trichloroacetate according to the modified Crout's method⁷ to be absorbed with active alumina and then subjected to quantitative analysis with Hitachi's spectrophotometer (MPF-2) after development of fluorescent coloring with THI method.

But the rats treated with Tyramine were decapitated after blood pressure was measured, and then the quantitative analysis of the CA content in the tissues was similarly made.

Blood pressure was measured on the caudal artery 3 to 4 days before decapitation by the use of Blood Pressure Measuring Unit FK-A 93

Key Words:

Catecholamine
Spontaneously Hypertensive Rats (SHR)

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TABLE I CATECHOLAMINE CONTENTS IN VARIOUS ORGANS OF NR AND SHR IN PROPORTION TO THE AGING PROCESS

Age		No. of cases	Heart*	Lung*	Liver*	Kidney*	Spleen*	Adrenal gl.**
3 Weeks	NR	14	0.94 ± 0.04	0.11 ± 0.02	0.10 ± 0.01	0.20 ± 0.02	0.66 ± 0.06	428 ± 17
	SHR	14	0.89 ± 0.05	0.10 ± 0.01	0.12 ± 0.02	0.21 ± 0.02	0.64 ± 0.06	445 ± 22
3 Months	NR	14	1.46 ± 0.05	0.14 ± 0.02	0.12 ± 0.01	0.32 ± 0.02	0.68 ± 0.08	580 ± 17
	SHR	14	0.62 ± 0.03	0.15 ± 0.02	0.15 ± 0.02	0.30 ± 0.03	0.66 ± 0.06	572 ± 18
6-8 Months	NR	14	1.66 ± 0.06	0.20 ± 0.02	0.13 ± 0.01	0.37 ± 0.04	0.65 ± 0.04	717 ± 57
	SHR	14	0.71 ± 0.04	0.26 ± 0.02	0.16 ± 0.01	0.32 ± 0.02	0.63 ± 0.04	756 ± 51

Values are the means $\pm$ S.D. *: calculated as noradrenaline (mcg/g) **: calculated as adrenaline (mcg/g)

Fig.1. Catecholamine fluorescence in the adventitia and interspace of myocardial fibers in NR.

Fig.2. Catecholamine fluorescence in the myocardium of SHR. The fluorescent density due to catecholamine was significantly decreased compared with Fig.1 of NR.

(developed by Kyoto University) except for the rats treated with Tyramine.

RESULTS

1) CA content in the tissues of adult rats

As shown in Table I, the CA content of the heart was 1.66 ± 0.06 mcg/g for the NR aged 6-8 months, while 0.71 ± 0.04 mcg/g for the SHR corresponding in age, the latter count being significantly decreased.

When distribution of CA within the tissues was determined by means of the tissue fluorescent method, it was found that CA in the heart of the NR was found distributing most predominantly at the adventitia of vessels and occasionally between the myocardial fibers, as shown in Fig. 1. As compared with the samples of the NR, those of the SHR gave evidence of a definite decrease, as seen in Fig. 2.

The CA content in the other organs were as

follows; in the lung, 0.20 ± 0.02 mcg/g for the NR and 0.26 ± 0.02 mcg/g for the SHR; in the liver, 0.13 ± 0.01 mcg/g and 0.16 ± 0.01 mcg/g, respectively; in the kidney, 0.37 ± 0.04 mcg/g and 0.32 ± 0.02 mcg/g, respectively; in the spleen 0.65 ± 0.04 mcg/g and 0.63 ± 0.04 mcg/g, respectively. As shown by these figures, there was no significant difference between the two groups of rats.

Meanwhile, the CA content of the adrenal gland was 717 ± 57 mcg/g for the NR, and 756 ± 51 mcg/g for the SHR, with no significant difference between the two.

2) Changes in the CA content of various organs with aging process

In view of the fact that the SHR show increases in blood pressure with aging process, the present author determined the CA content in various organs as in the same way as above in

Fig.3. Catecholamine contents of the myocardium in NR and SHR. at 3 weeks, 3 months and 6-8 months of age.

order to see the differences, if any, between the SHR and NR which were in the stage of normal blood pressure (3 weeks after birth), in the stage of increased blood pressure with a systolic blood pressure of about 180 – 200 mmHg (3 months after birth), and in the stage of established hypertension (6 – 8 months after birth).

The CA content in the heart after 3 weeks of life was 0.89 ± 0.05 mcg/g for the SHR and 0.94 ± 0.04 mcg/g for the NR with no significant difference between the two. However, after 3 months of life when there occur differences in blood pressure, the CA content was 0.62 ± 0.03 mcg/g for the SHR, and 1.46 ± 0.05 mcg/g for NR, the difference being significant. This difference was practically equal to the above mentioned difference in the CA content of the heart between the SHR and NR aged 6-8 months. (Fig. 3)

The CA content of the adrenal gland in various stages of life was as follows; after 3 weeks of life, 445 ± 22 mcg/g for the SHR, and 428 ± 17 mcg/g for the NR; after 3 months of life, 572 ± 18 mcg/g for the SHR, and 580 ± 17 mcg/g for the NR; and after 6 – 8 months of life, 756 ± 51 mcg/g for the SHR, and 717 ± 57 mcg/g for the NR. The difference between the two groups was not significant in any stage of life.

The CA content of the other organs, lung, liver, kidney and spleen in each stage of life was not significantly different between the SHR and NR, either. (Table I)

Fig.4. Effect of Tyramine on blood pressure in NR and SHR.

3) Changes in blood pressure and the CA content of various organs following administration of Tyramine

As shown in Fig. 4, both of the SHR and NR showed a rapid increase in blood pressure after administration of Tyramine, followed by maintenance after a while, and then return to the previous level of blood pressure. A blood pressure of 120/80 mmHg, for example, in the NR was increased up to 190/140 mmHg after administration of Tyramine, namely an increase by 70 mmHg for the systolic pressure and by 60 mmHg for the diastolic pressure. A blood pressure of 200/130 mmHg, for example, in the

TABLE II CHANGES IN CATECHOLAMINE CONTENTS OF VARIOUS ORGANS FOLLOWING ADMINISTRATION OF TYRAMINE AND RESERPINE

		No. of cases	Heart*	Lung*	Liver*	Kidney*	Adrenal gl.**
	non treated	14	1.66 ± 0.06	0.20 ± 0.02	0.13 ± 0.01	0.37 ± 0.04	717 ± 57
NR	TYRAMINE treated	14	0.69 ± 0.04	0.13 ± 0.01	0.08 ± 0.01	0.17 ± 0.01	580 ± 36
	RESERPINE treated	14	0.37 ± 0.03	0.07 ± 0.01	0.07 ± 0.01	0.12 ± 0.01	588 ± 29
	non treated	14	0.71 ± 0.04	0.26 ± 0.02	0.16 ± 0.01	0.32 ± 0.02	756 ± 51
SHR	TYRAMINE treated	14	0.57 ± 0.03	0.22 ± 0.01	0.13 ± 0.01	0.21 ± 0.01	718 ± 37
	RESERPINE treated	14	0.35 ± 0.03	0.16 ± 0.01	0.09 ± 0.01	0.16 ± 0.01	714 ± 13

*: calculated as noradrenaline (mcg/g $\pm$ S.D.) **: calculated as adrenaline (mcg/g $\pm$ S.D.)

SHR was remarkably increased up to 360/220 mmHg an increase by 160 mmHg for the systolic pressure and 90 mmHg for the diastolic pressure, accompanied by a prominent increase in the pulse pressure.

Table II shows the CA content in various organs which were extracted from the rats which had been decapitated immediately after administration of Tyramine. As apparently seen from the table, the CA content of the heart was found prominently decreased from 1.66 ± 0.06 mcg/g to 0.69 ± 0.04 mcg/g in the NR, while the SHR showed a far less prominent decrease from 0.71 ± 0.04 mcg/g only to 0.57 ± 0.03 mcg/g. The CA content of the adrenal gland, on the other hand, was slightly decreased from 717 ± 57 mcg/g to 580 ± 36 mcg/g in the NR, and from 756 ± 51 mcg/g to 718 ± 37 mcg/g in the SHR. The release of CA in the other organs (lung, liver, and kidney) following administration of Tyramine was nearly equal in the SHR and NR, too.

4) Changes in the CA content of various organs after administration of Reserpine

The SHR and NR aged 6–8 months were intramuscularly pre-treated with Reserpine (0.02 mg/kg), 24 hours prior to decapitation in order to see fluctuations in the CA content of various organs. (Table II)

The CA content of the heart was decreased from 1.66 ± 0.06 mcg/g to 0.37 ± 0.03 mcg/g in the NR, while from 0.71 ± 0.04 mcg/g to 0.35 ± 0.03 mcg/g in the SHR; the NR showed a greater reduction in the CA content than the SHR as seen after administration of Tyramine,

and the determined amount after administration of Reserpine were nearly equal in both groups.

The adrenal gland, on the other hand, which is important as a catecholamine source, reacted to the administration of Reserpine almost in a similar way as the other organs in both of the NR and SHR groups.

5) Fluctuations in blood pressure and the CA content of various organs due to salt loading

The SHR and NR were fed on 1% NaCl solution as drinking water for 7 months from the first month of life, and observations were made on fluctuations in blood pressure and the CA content. It was found that blood pressure was not remarkably different between the salt-loaded

Fig.5. Changes in blood pressure on physiological saline solution from 5 weeks to 8 months after birth. Vertical lines indicate standard deviations of the means.

TABLE III CHANGES IN CATECHOLAMINE CONTENTS OF VARIOUS ORGANS FOLLOWING SALT LOADING

	No. of cases	Heart*	Lung*	Liver*	Kidney*	Spleen*	Adrenal gl.**
NR	8	1.32 ± 0.06	0.19 ± 0.02	0.12 ± 0.02	0.31 ± 0.05	0.66 ± 0.06	729 ± 71
SHR	5	0.69 ± 0.09	0.25 ± 0.05	0.17 ± 0.03	0.27 ± 0.03	0.64 ± 0.09	737 ± 153

*: calculated as noradrenaline (mcg/g±S.D.)

**: calculated as adrenaline (mcg/g±S.D.)

rats and non-loaded rats of both groups (Fig. 5), but that there were significant differences in the CA content of some organs, as shown in Table III.

To be concrete the CA content of the heart was moderately decreased from 1.32 ± 0.06 mcg/g in the NR loaded with salt, while 0.69 ± 0.09 mcg/g in the SHR loaded with salt, which was not significantly different from the amount of 0.71 ± 0.04 mcg/g in the group of rats not loaded with salt. The CA content of the kidney was 0.27 ± 0.03 mcg/g for the salt loaded SHR, and 0.31 ± 0.05 mcg/g for the salt-loaded NR.

The CA content of the other organs, lung, liver, and adrenal gland, was not significantly different between the salt-loaded rats and non-loaded rats in both of the NR and SHR.

DISCUSSION

Physical and mental excitement in the organism may result in hypertension which is associated with a hyperactivity of the sympathetic nervous system.⁸⁻¹⁰ It is reported, on the other hand, that the incidence of hypertension is greater among people who are more frequently and severely subject to stress in everyday living.¹¹ Experimentally, it has been demonstrated that ischemic condition in the brain stem¹² or electrical stimulation of the diencephalon¹³ may induce hypertension associated with central changes in which the sympathetic nervous system is supposed to take part. Yamori^{14,15} noticed that there were changes in the CA metabolism at the brain stem (hypothalamus), that reduction in the CA content had a great influence, and that the depression of blood pressure induced by injection of Noradrenaline into the ventricles of the brain was greater in the SHR than in the NR. He presumed from these findings that impaired Noradrenaline metabolism in the central nervous system might participate in the occurrence of hypertension. It is reported that injection of

Noradrenaline into the ventricles of the brain induces hypotensive response in rabbits, whereas it is increased by intraventricular injection of Veratrin¹⁶ which is known to stimulate the vagus at the peripheral application to induce hypotensive effect. The fact that CA or Veratrin injected into the ventricles of the brain takes an action reverse to that following intravenous injection¹⁷ may be supposed to give a clue to elucidation of the etiological mechanism of hypertension. If changes in the CA metabolism at the central nervous system are connected with hypertension, it may be naturally supposed that the modification of the CA metabolism at the peripheral side or in the major circulatory system are also involved. On the basis of this supposition, the present author determined the CA content of the heart and other organs in the SHR aged 6-8 months when hypertension has already been fixed. As shown in Table I, the SHR showed a significant decrease in the CA content of the heart as compared with the NR. Such a decrease in the CA content of the heart has been noted in heart failure¹⁸⁻²⁰ due to the valvular disease, hyperkalemia or coronary insufficiency in which the CA content of the heart decrease in proportion to its increase in blood and urine. Similarly, the decrease is seen in animals with experimentally induced heart failure^{21,22} thereby demonstrating that CA contributes to improvement of heart failure.

Histochemical studies also demonstrated that the myocardium of the SHR was poorly stained with CA-fluorescence as compared with that of the NR. According to Tabei and Creveling, the increase of MAO activity²³ is simultaneously seen with the occurrence of hypertension in the SHR, and a similar tendency may also be noted with COMT.²⁴ This fact indicates that CA, which is secreted at the end of the sympathetic nerve, is rapidly metabolized by those two enzymes. It is also reported that experimental hyperthyroidism²⁵ is associated with the lowered CA content

TABLE IV INFLUENCE OF RESTRAINT AND ANANESTHESIA ON CATECHOLAMINE CONTENTS OF VARIOUS ORGANS IN NR. THE VALUES OF CATHCHOLAMINE CONTENTS IN THE CONTROL GROUP AND THE GROUP THAT WAS SUBJECTED TO THEIR OPERATION UNDER ANANESTHESIA AND RESTRAINT

	No. of cases	Heart*	Kidney*	Adrenal gl.**
Sham operated group	4	1.52 ± 0.09	0.30 ± 0.07	704 ± 86
Control group	14	1.66 ± 0.06	0.37 ± 0.04	717 ± 57

*: calculated as noradrenaline (mcg/g±S.D.) **: calculated as adrenaline (mcg/g±S.D.)

of the heart and increased MAO activity as noticed in the hyperactivity of the sympathetic nerve. It may be understood from these findings that the accelerated secretion of CA in the heart has simultaneously induced the increased activity of the catabolic enzymes from the metabolic system corresponding to it. The decrease of CA in the myocardium following the overloading of the cardiovascular system is also the same with hyperthyroidism which presents symptoms closely resembling those of hyperactivity of sympathetic nervous system. The decrease of the CA content in the SHR may be supposed to suggest a participation of the sympathetic nervous system under the overloading of maintenance of hypertension.

However, further studies seem to be necessary on the question as to whether the quantitative fluctuations in the CA content are the cause or consequence of hypertension, since the present author made no investigations on the CA metabolism in the peripheral vascular system. Since the other organ, that is, the adrenal medulla is a CA reservoir as well as a supplier of CA into blood, it was supposed that there would be some abnormal changes in that organ of the SHR, but there were, as shown in Table I, no significant differences as compared with the NR.

However, the reports have so far been variable on the CA content of various organs in the SHR, some reports^{26,27} describe no quantitative differences in the CA content of the myocardium, while others describe an increase in the CA content of the adrenal gland.

The function of various organs in the organism is naturally supposed to undergo changes with aging process, and those functional changes may not be uniform with all organs. It is not difficult to imagine that, as a result of such changes, the autonomic nervous system and

endocrine system may also have changes in their activity to maintain the homeostasis. In fact, there is a report²⁸ describing that there occur changes in irritability of the autonomic nervous center or sensitivity of the peripheral receptor as the age advances. Tomomatsu *et al.*²⁹ made studies on the CA content of the heart and adrenal gland in rabbits at various stages of life, to find that there were quantitative changes in the CA content mutually contrary to each of the two organs. As for the heart of rats, there were no significant differences between the SHR and NR after 3 weeks of life, as shown in Table I and Fig. 3. After that period of life, however, the NR showed, as rabbits did, an increase in the CA content of the heart, whereas the SHR began to have a decrease in that content concurrently with the development of hypertension. It may be questionable to conclude that there is directly a causative relation between blood pressure and the CA content of the myocardium, but in view of changes in the CA metabolism in various circulatory disturbances, it would not be difficult to presume that the CA content is a causative factor or a factor to promote the development of hypertension.

The use of Wistar-strain KOBE rats by the present author may have taken a unreliable subject in the finding that the SHR showed a significant difference in the CA content from the NR. In other words, the Wistar-strain KOBE rats are perhaps originally different from Wistar-strain KYOTO rats. However, at the beginning of life, the SHR and NR showed similar CA contents of the heart and adrenal gland, but as they grew older that is, the SHR approached the stage of increased blood pressure leading to the stage of perfect hypertension, both groups showed different contents.

Experimental results with the conventional

urethane anesthesia indicate no great influences on the CA content of tissues.³⁰ However, injection of urethane into the abdominal cavity may occasionally induce the depression of blood pressure and finally apnea. It is unthinkable that such hemodynamic changes do not give any influence to the activity of the sympathetic nervous system at all. In the present experiment, therefore, the rats were treated under fastening and restraint but not anesthesia. It is fully possible, however, that the stress originating from fastening and surgical operation may accelerate the activity of the sympathetic nerve, thus inducing changes in the CA content of various organs. Actually, it is reported that peptic ulcer can be experimentally induced in rats with 24-hour restraint, complicated by an accelerated activity of the sympathetic nerve.^{31,32} Therefore, the present author made studies on influences of experimental conditions on the myocardium and other organs through so-called sham operation in rats which were put under the same conditions but not treated with Tyramine. It was found, as shown in Table IV, that the CA content of the heart showed a decreasing tendency, which was not considered significant on the basis of sampling. It may be concluded from this that the decrease of the CA content in various organs of the rats treated with Tyramine under those conditions is mostly attributable to the CA release from the end of the sympathetic nerve by Tyramine. The releasing action by Tyramine is variable with different organs; it is said that the release from the adrenal gland is mild.^{33,34} The decrease in CA of the heart following administration of Tyramine appears in Table II. It is apparent that the NR showed a remarkable decrease, while the SHR only a mild decrease. As for the adrenal gland, no significant differences could be established between the two groups. This agrees with the report³³ that the CA content of the adrenal gland scarcely showed a decrease in rabbits treated with Tyramine. At any rate, it is apparent that the SHR have a smaller amount of CA released from the sympathetic nerve endings by Tyramine than the NR. This released CA is supposed to be subject to metabolic degradation by MAO and COMT. In spite of this, blood pressure reacted to the administration of Tyramine more greatly in the SHR than the NR, inducing prominent hypertension. To understand this phenomenon, the conception of the hypersensitivity in adrenergic receptor must be taken into account. There are not a few reports³⁵

pointing out that hemodynamic changes induced by exogenous CA are due to hypersensitivity of the peripheral blood vessels. In contrast with this, some other reports³⁶ indicate lowering of their sensitivity or no remarkable differences from the control. The reason for the employment of Tyramine in the present as a releasing agent for endogenous CA was that the use of the drug was more physiologically than coinciding with the phenomena in the organism as compared with the administration of exogenous CA. As mentioned above the decrease of CA following administration of Tyramine is variable with different organs. In this connection, the present author next investigated into the question as to what differences would be observed between the SHR and NR after pretreatment with Reserpine, an extremely potent releaser of CA. It was found that there were no differences between the SHR and NR in the CA content not released by intramuscular administration of Reserpine in a dose of 0.02 mg/kg. (Table II)

On the other hand, the decrease in the CA content of the heart following administration of Tyramine was markedly different from that after administration of Reserpine. In contrast with this, there was no significant decrease confirmed in the CA content of the adrenal gland irrespective of the groups or drugs administered. *Strömblad*³³ could not demonstrate the CA release from the adrenal gland by perfusion of a solution containing 100 mcg/ml of Tyramine, while *Stjärne*³⁷ observed a decrease in the CA concentration of the adrenal venous blood after 0.5–1.0 mg/kg of Tyramine intravenously in cats. *Weiner*³⁴ observed similar results in dogs. When *Stjärne*³⁷ perfused the bovine adrenal gland with a larger amount of Tyramine (10 mg/min for 10 minutes), he could not confirm any release of the CA, but *Haag*³⁸ reported on an increase. As an explanation for these phenomena, *Trendelenburg*³⁹ suggested that there might be two different modes of storage at the end of the sympathetic nerve and adrenal gland. According to *Neff*⁴⁰ and *Gutman*,⁴¹ repeated administration of Tyramine in large doses could release as much CA as Reserpine, which they presumed might be attributable to the rapid metabolic destruction of Tyramine and the different speed of the CA release from the organs.

The above are the discussion on the participation of the sympathetic nervous system in the development of hypertension in the SHR as

evidenced from the CA release by Tyramine. Studies on fluctuations in the CA content of various organs in the SHR and NR following pretreatment of Reserpine revealed that was a prominent decrease of the CA content except for the adrenal gland, — a decrease being significantly different between the SHR and NR, as seen in Table II, but that there was almost no significant difference in the residual CA content between the two groups, as mentioned above.

On the other hand, the CA content of the adrenal gland was mildly decreased by pretreatment of Reserpine, but there was no significant difference between the SHR and NR. Regarding this point, *Muscholl*⁴² *Stjärne*⁴³ and *Iversen*⁴⁴ reported that a decrease in the CA content of the adrenal gland was observed after large doses of Reserpine. Their doses were greatly different from those used in the present study. Of course, various organs are said to have different reactivity to or affinity for such a CA-releaser.⁴¹ However, as pointed out in the previous reports, Reserpine, unlike Tyramine, scarcely increased the blood level of CA or changed the hemodynamic changes. Thereby, the slow and moderate changes in the blood CA level following administration of Reserpine would have an important meaning. The pre-treatment with Reserpine in the present study did not induce significant differences in the reaction of the sympathetic nervous system between the SHR and NR.

Salt plays an important role in the development of hypertension. In order to make studies on essential hypertension epidemiologically and also on the development of experimental hypertension by means of salt loading and its likeness to the decrease in the CA content of the myocardium in rats with hypertension induced by the combined administration of DOCA and salt, observations were made on the changes in the CA content of various organs in the NR and SHR following salt loading. According to the previous reports,^{46,47} loading of hypertonic saline solution (1.5–2.5%) is more requisite for the development of hypertension than administration of physiological saline solution. If the administration of hypertonic saline solution is begun from around 4th week of life, animals show only a poor weight gain, which often leads them to death. In anticipation of such an ill effect of the hypertonic saline solution in the comparative studies in animals aged 6 to 8 months, the present author decided on the

administration of physiological saline solution. The results are shown in Fig. 5. No definite hypertension could be induced in the NR. Even in the SHR there was no significant difference in the increase of blood pressure between the animals treated with salt and those not treated with it. As far as the CA content of the myocardium was concerned, there was no significant difference in that content of the SHR treated with salt; only their kidney showed an appreciable change in the CA content (Table III). The significance of this finding is not yet established, but further studies should be made on this point, since the kidney is the most important organ for control of the electrolytes in the organism with a wide-spread distribution of the sympathetic nerve which has a great role in the functional control of the organ. The NR group, on the other hand, showed a decrease of the CA content in the heart and kidney. This decreasing tendency may be taken as a fundamental factor for development of hypertension suggesting influences of cardiovascular overloading resulting from changes in the circulatory blood volume and peripheral vascular resistance due to the salt loading, although hypertension did not occur. However this fact seems to be significant in showing that the animals lie between the rats with hypertension induced by administration of DOCA + NaCl and SHR.

SUMMARY

In order to study the participation of the sympathetic nervous system in development of hypertension in the SHR, the present author made comparative observations on fluctuations in blood pressure and the CA content of various organs at various stages of life. The author also made studies on fluctuations in blood pressure and the CA content of various organs following administration of Tyramine, Reserpine and salt. 1) In the 3rd week of life when hypertension is not yet established, the SHR and NR showed nearly equal contents of CA in the myocardium. 2) According to the aging process thereafter, the NR showed an increasing tendency in the CA content of the myocardium irrespective of blood pressure, whereas the SHR showed a decreasing tendency in that CA amount in the stages of increased blood pressure and established hypertension; the difference was significant between the two groups. There was no significant difference between the two groups in the CA content of the adrenal gland, lung, liver, kidney and

spleen.

3) The NR showed a more prominent decrease in the CA content of the heart than the SHR after administration of Tyramine. But the increase of blood pressure was more prominent in the SHR.

4) The CA content was remarkably decreased in all organs except the adrenal gland after pretreatment with Reserpine. But there were no significant differences in either of the SHR or NR.

5) The NR showed no appreciable changes in blood pressure, but a decreasing tendency of the CA content in the myocardium with salt loading. On the other hand, there were almost no influences in the SHR.

It was presumed from these findings that accelerated metabolism of CA at the sympathetic nerve ending in the heart and hypersensitivity of the peripheral adrenergic receptors might participate in the development of hypertension.

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REFERENCES

- WEITZ, W.: Zur Ätiologie der genuinen oder vasculären Hypertension. *Z. Klin. Med.* 96: 151, 1923.
- ALEXANDER, N., HINSHAW, L. B., & DRURY, D. R.: Development of a strain of spontaneously hypertensive rabbits. *Proc. Soc. Exp. Biol. Med.* 86: 855, 1954.
- PLATT, R.: The nature of essential hypertension. *Lancet*, II: 55, 1959.
- PLATT, R.: Heredity in hypertension. *Lancet*, I: 899, 1963.
- OKAMOTO, K. & AOKI, K.: Development of a strain of spontaneously hypertensive rats. *Jap. Circ. J.* 27: 282, 1963.
- FUJIWARA, M.: Histochemical detection of catecholamine and serotonin by fluorescent technique—its methods and applications. *Saishin Igaku* 22: 100, 1967. (in Japanese)
- CROUT, J. R., CREVELING, C. R., & UDENFREIND, S.: Norepinephrine metabolism in rat brain and heart. *J. Pharmacol. Exp. Ther.* 132: 269, 1961.
- LEVI, L.: The urinary output of adrenalin and noradrenalin during pleasant and unpleasant emotional states. *Psychosom. Med.* 27: 80, 1965.
- LEVI, L.: The urinary output of adrenaline and noradrenaline during experimentally induced emotional stress in clinically different groups. *Acta Psychother.* 11: 218, 1963.
- YAMAWAKI, T.: Psychophysiological study on essential hypertension. *J. Jap. Psychosom. Soc.* 7: 343, 1967. (in Japanese)
- SIMONSON, E. & BROZEK, J.: Russian research on arterial hypertension. *Ann. Intern. Med.* 50: 129, 1959.
- MARSHALL, J.: Evidence upon the neurogenic theory of hypertension. *Lancet*, II: 410, 1966.
- UEDA, H., et al.: Effect of chronic electrical stimulation of diencephalon on blood pressure in rabbits. *Jap. Heart J.* 5: 260, 1964.
- YAMORI, Y., LOVENBERG, W., & SJOERDSMA, A.: Norepinephrine metabolism in brainstem of spontaneously hypertensive rats. *Science* 170: 544, 1970.
- YAMORI, Y., LOVENBERG, W., & SJOERDSMA, A.: Catecholamine metabolism in the central and peripheral nervous system of spontaneously hypertensive rats. *Japan. J. Constitutional Med.* 34: 36, 1971.
- JARISCH, A., RICHTER, H., & THOMA, H.: Zentrogenes Lungenödem. *Klin. Wschr.* 18: 1440, 1939.
- NAKAMURA, K., GEROLD, M., & THOENEN, H.: Experimental hypertension of the rat: Reciprocal changes of norepinephrine turnover in heart and brainstem. *Naunyn-Schmiedbergs Arch. Pharmacol.* 268: 125, 1971.
- TOMOMATSU, T., UEDA, Y. et al.: Catecholamine in congestive heart failure (Report I). *Jap. Heart J.* 4: 13, 1963.
- MATSUMOTO, T.: Studies on catecholamine with special reference to congestive heart failure (Part I). The changes of urinary excretion of catecholamine in congestive heart failure. *J. Jap. Soc. Intern. Med.* 53: 7, 1964. (in Japanese)
- TOMOMATSU, T., UEDA, Y. et al.: Catecholamine in congestive heart failure (Report II). *Jap. Heart J.* 8: 242, 1967.
- ITO, Y.: The tissue catecholamine concentration of the rabbit in experimental cardiac failure. *Jap. Circ. J.* 32: 761, 1968.
- TOMOMATSU, T.: Study on myocardial content of catecholamine, with special reference to heart disease. *Jap. Circ. J.* 35: 979, 1971.
- TABEI, R.: On histochemical studies of the various organs of spontaneously hypertensive rats. *Jap. Circ. J.* 30: 717, 1966.
- CREVELING, C. R., DALGARD, N. H. & NIKODIJEVIC, B. V.: Elevated catechol-o-methyltransferase activity in spontaneously hypertensive rats. *Fed. Proc.* 28: 416, 1969.
- KOGAME, H.: The pathophysiological significance of the sympathetic nervous system in thyroid disorders. *Folia Endocr. Jap.* 48: 612, 1972. (in Japanese)
- OZAKI, M.: Metabolism of monoamines in spontaneously hypertensive rat. *Jap. J. Pharmacol.* 16: 257, 1966.
- LOUIS, W. J., SPECTOR, S., TABEI, R., & SJOERDSMA, A.: Synthesis and turnover of norepinephrine in the heart of the spontaneously hypertensive rat. *Circ. Res.* 24: 85, 1969.
- TOMOMATSU, T. & UEDA, Y.: Heart and catechol-

- amine in old age. *Jap. J. Geriat.* 7: 36, 1970. (in Japanese)
29. YAMAMOTO, Y. et al.: Studies on catechol (XXXI). Aging process and tissue catecholamine concentration. *Folia Endocr. Jap.* 45: 1540, 1970. (in Japanese)
 30. SPRIGGS, T. L. B.: The effects of anaesthesia induced by urethane or phenobarbitone upon the distribution of peripheral catechol amines in the rat. *Brit. J. Pharmacol.* 24: 752, 1965.
 31. BRODIE, D. A.: Ulceration of the stomach produced by restraint in rats. *Gastroenterology* 43: 107, 1962.
 32. BRODIE, D. A., MARSHALL, R. W., & MORENO, O. M.: Effect of restraint on gastric acidity in the rat. *Amer. J. Physiol.* 202: 812, 1962.
 33. STRÖMBLAD, B. C. R.: Effect of denervation and of cocaine on the action of sympathomimetic amines. *Brit. J. Pharmacol.* 15: 328, 1960.
 34. WEINER, N., DRASKOCZY, P. R., & BURACK, W. R.: The ability of tyramine to liberate catecholamines in vivo. *J. Pharmacol. Exp. Ther.* 137: 47, 1962.
 35. HAEUSLER, G. & HAEFELY, W.: Pre- and post-junctional supersensitivity of the mesenteric artery preparation from normotensive and hypertensive rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 266: 18, 1970.
 36. SHIBAYAMA, F., MIZOGAMI, S., & SOKABE, H.: Cardiovascular reactivity in hypertensive rats. *Jap. Heart J.* 12: 68, 1971.
 37. STJÄRNE, L.: Tyramine effects on catecholamine release from spleen and adrenals in the cat. *Acta Physiol. Scand.* 51: 224, 1961.
 38. HAAG, H. W., PHILIPPU, A., & SCHÜMANN, H. J.: Liberation of pyrocatechol amines from the isolated perfused adrenal gland by tyramine and betaphenylethylamine. *Experientia* 17: 187, 1961.
 39. TRENDLENBURG, U.: Modification of the effect of tyramine by various agents and procedures. *J. Pharmacol. Exp. Ther.* 134: 8, 1961.
 40. NEFF, N. H., TOZER, T. N., HAMMER, W., & BRODIE, B. B.: Kinetics of release of norepinephrine by tyramine. *Life Sci.* 4: 1869, 1965.
 41. GUTMAN, Y. & WEIL-MALHERBE, H.: Kinetics of catecholamine release by tyramine in rat heart, spleen and uterus. *Life Sci.* 5: 1293, 1966.
 42. MUSCHOLL, E. & VOGT, M.: The action of reserpine on the peripheral sympathetic system. *J. Physiol.* 141: 132, 1958.
 43. STJÄRNE, L. & SCHAPIRO, S.: Effects of reserpine of secretion from the denervated adrenal medulla. *Nature* 184: 2023, 1959.
 44. IVERSEN, L. L., GLOWINSKI, J., & AXELROD, J.: The uptake and storage of H^3 -norepinephrine in the reserpine-pretreated rat heart. *J. Pharmacol. Exp. Ther.* 150: 173, 1965.
 45. MIALL, W. E.: Follow-up study of arterial pressure in the population of a Welsh mining valley. *Brit. Med. J.* II: 1204, 1959.
 46. SAPIRSTEIN, L. A., BRANDT, W. L., & DRURY, D. R.: Production of hypertension in rat by substituting hypertonic sodium chloride solutions for drinking water. *Proc. Soc. Exp. Biol. Med.* 73: 82, 1950.
 47. YAMAGUCHI, Y.: Experimental study on hypertension and salt metabolism. (Part I) Hypertension due to common salt. *Kobe J. Med. Sci.* 10: 169, 1964.
 48. de CHAMPLAIN, J., KRAKOFF, L. R., & AXELROD, J.: Catecholamine metabolism in experimental hypertension in the rat. *Circ. Res.* 20: 137, 1966.
 49. de CHAMPLAIN, J., MUELLER, R. A., & AXELROD, J.: Turnover and synthesis of norepinephrine in experimental hypertension in rats. *Circ. Res.* 25: 285, 1969.