Studies on the Role of Sympathetic Nervous System in the Mechanism of Essential Hypertension

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In order to investigate a role of sympathetic nervous system in the mechanism of blood-pressure elevation in essential hypertension, urinary catecholamines, serum dopamine-beta-hydroxylase (DBH) activity and a pressor response to infused noradrenaline (noradrenaline response) were measured, in the patients with essential hypertension, before and 2 weeks-rest after hospitalization or following salt restriction. In addition, plasma renin activity (PRA) and water-sodium contents were determined and a correlation between these variables and noradrenaline excretion, serum DBH or noradrenaline response was observed.

A blood pressure fall after hospitalization was associated with a decrease of urinary noradrenaline and serum DBH, and there was a significantly positive correlation between the changes in blood pressure and those in urinary noradrenaline or in serum DBH. A significantly adverse correlation was found between plasma volume and the amounts of urinary noradrenaline excretion. The changes in noradrenaline response was negatively correlated with those in urinary noradrenaline excretion. In addition, noradrenaline response was correlated positively with plasma volume, extracellular fluid volume and total exchangeable sodium and negatively with PRA.

Following salt restriction, a fall of the blood pressure was associated with an elevation of urinary noradrenaline excretion. The patients with more marked blood pressure fall showed a higher increase of urinary noradrenaline, and a significant correlation was found between the changes in these two variables. Noradrenaline response was significantly reduced, although it was not correlated significantly with noradrenaline excretion.

In these experiments, adrenaline, unlike noradrenaline, did not show any obvious changes.

These findings suggested that an excessive sympathetic nerve activity caused an elevation of blood pressure in the labile type of essential hypertension. It was demonstrated that a sympathetic nervous function was dependent on sodium intake and that there exisited a close relationship between noradrenaline response and water-sodium contents or PRA.

Key Words:
Essential hypertension
Sympathetic nervous system
Urinary noradrenaline
Serum dopamine-beta-hydroxylase
Noradrenaline response
Water-sodium contents
Plasma renin activity

ALTHOUGH many studies have been published concerning urinary excretion of catecholamines, plasma levels of catecholamines or serum dopamine-bata-hydroxylase activity in the patients with essential hypertension, a role of sympathetic nervous system in the mechanism of this disease still remains obscure.

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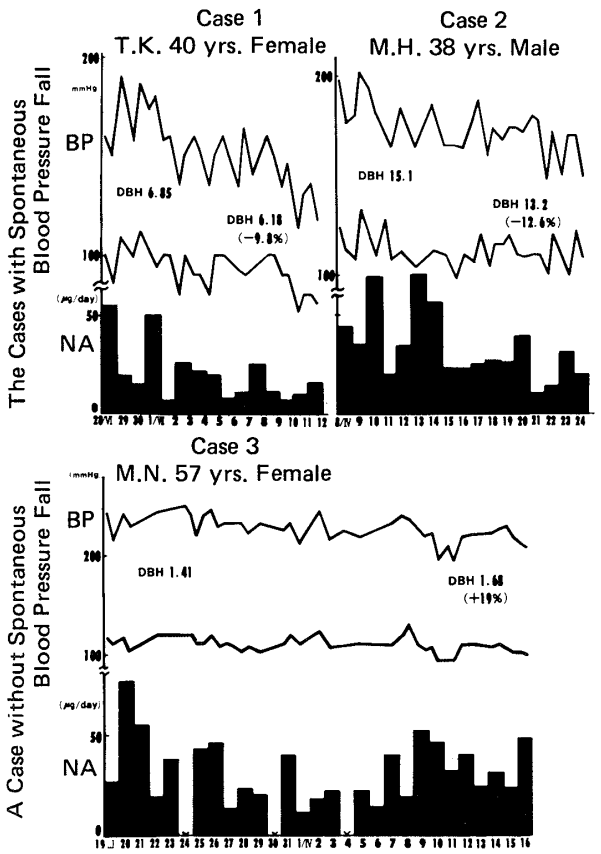

Fig.1. Changes of blood pressure (BP), urinary noradrenaline (NA), and serum dopamine-β-hydroxylase activity (DBH) after hospital admission in three essential hypertensives with (upper pannel) and without (lower pannel) spontaneous blood pressure fall.

Number in parenthesis shows percent change of DBH.

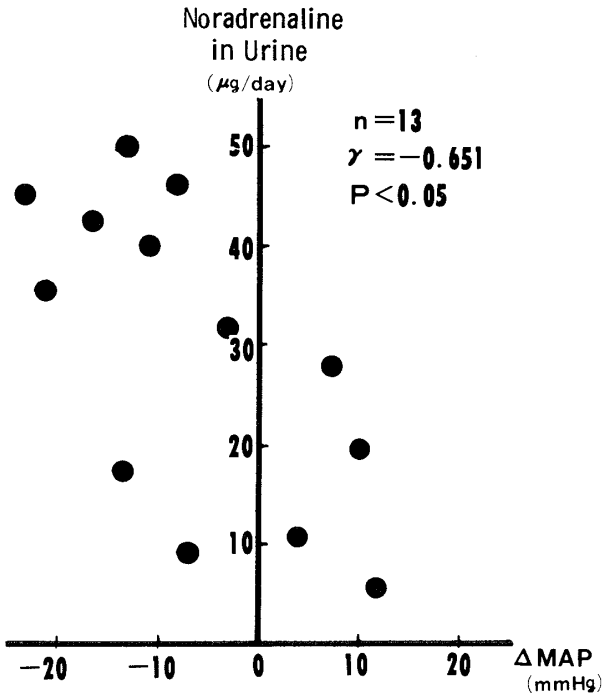

Fig.2. Correlation between the value of urinary noradrenaline in average during the first 3 days after hospital admission and the change in mean blood pressure (ΔMAP) following the 2 weeks rest.

Our previous investigation on essential hypertension[1,2] demonstrated that blood pressure fall following the hospitalization was associated with an increase of plasma volume, extracellular fluid volume, exchangeable sodium and pressor response to noradrenaline and a decrease of total peripheral resistance and hematocrit and that a pressure fall following salt restriction was associated with the oposite alteration of these variables except the reduction of total peripheral resistance. These results suggest a fluctuation of blood pressure under these conditions being related to a change in sympathetic nervous tone in this disease.

The present study, therefore, was undertaken in order to evaluate an activity of the sympathetic nervous system, employing the measurements of the changes in urinary excretion of catecholamines and plasma dopamine-beta-hyroxylase after blood pressure fall following hospitalization or salt restriction. A correlation was also determined between these changes and pressor response to noradrenaline or water-sodium contents.

MATERIALS AND METHODS

Fourty-two inpatients with essential hypertension, twenty females and twenty-two males, ranged 18–66 years of age, were studied.

At least 10 days prior to admission, all antihypertensive drugs were stopped. After admission the patients were kept at rest with a free diet for two weeks. And then, the patients whose blood pressure was still over 150/90 mmHg were placed on a low sodium diet, containing 35 mEq sodium and 75 mEq potassium for 7 days.

The investigation was performed during the first and the last 4 days of 2 weeks after hospitalization and during the last 4 days of salt restriction.

Twenty-four hours urinary excretion of catecholamines (CA : μg/day) was measured fluorometrically for 2 days before and one day after the day when a pressor response to noradrenaline (NA response) was determined, and the average value during the first and last three days was calculated. Serum dopamine-beta-hydroxylase

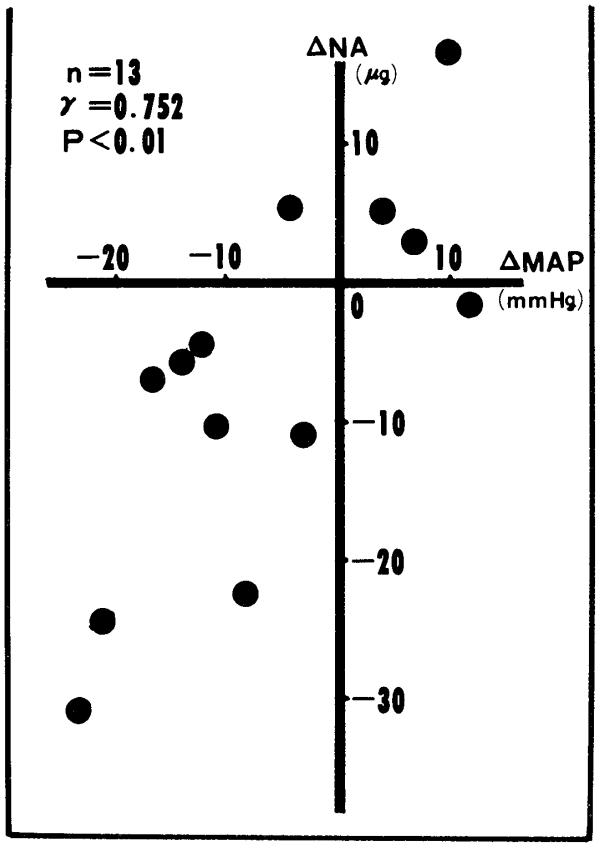

Fig.3. Correlation between the change in urinary noradrenaline (ΔNA) and that in mean blood pressure (ΔMAP) following the 2 weeks rest. The value of ΔNA or ΔMAP represents the difference between the value during the first and the last 3 days of the 2 weeks rest.

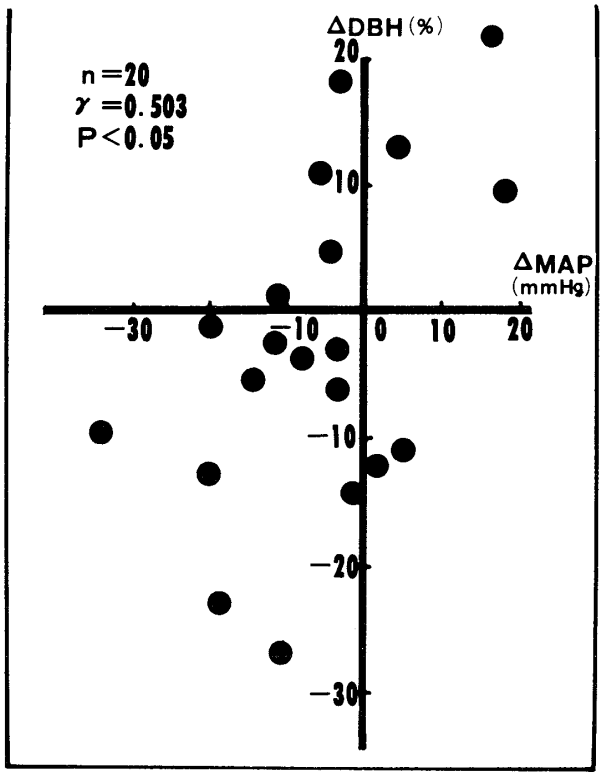

Fig.4. Correlation between the percent change in DBH and the change in mean blood pressure (ΔMAP) following the 2 weeks rest.

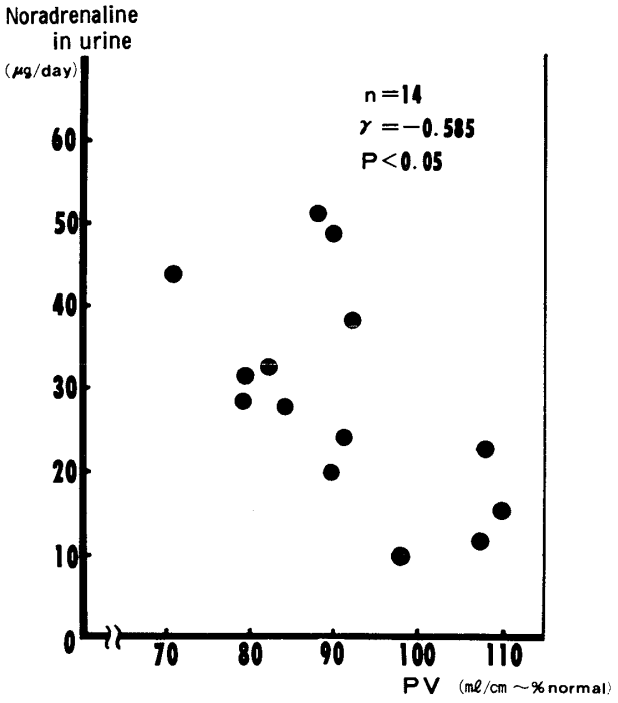

Fig.5. Correlation between urinary noradrenaline and plasma volume (PV).

activity (DBH: units) was measured by the method of Nagatsu and Udenfriend[3] NA response was estimated by the increase of mean blood pressure following an intravenous infusion of 0.3 μg/kg/min of NA after the pretreatment with intramuscular injection of 0.3 mg/kg of hexamethonium.

Plasma renin activity (PRA) was determined by radioimmunoassay, using the method of Haber. Plasma volume measured by RISA (PV) was expressed as percent of the mean value of normal men and women (ml/cm-% normal). Extracellular fluid volum (ECFV: ml/cm) and total exchangeable sodium (Nae: mEq/cm) was determined by ^{22}Na dilution method.

Mean values were expressed as standard error of the mean, and all statistical comparisons were made by Student's t-test.

RESULTS

I) The changes in urinery output of catecholamines (CA), serum DBH activity and NA response in the patients during 2 weeks rest following the hospital admission.

Fig. 1 shows time-course of blood pressure,

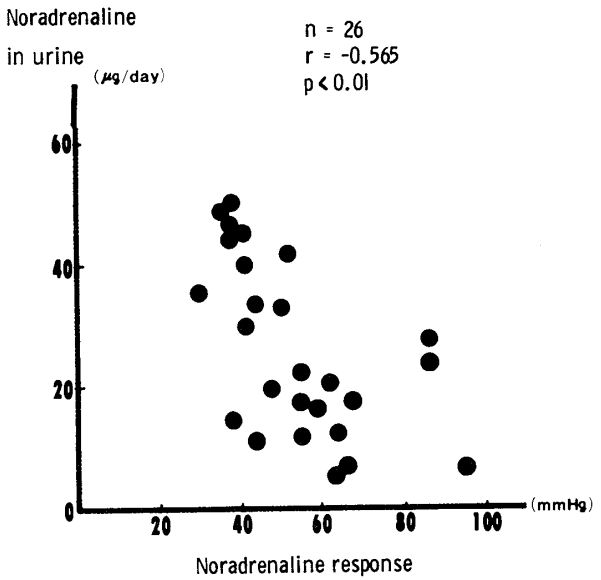

Fig.6. Correlation between the value of urinary noradrenaline and the pressor response to infused noradrenaline (Noradrenaline response).

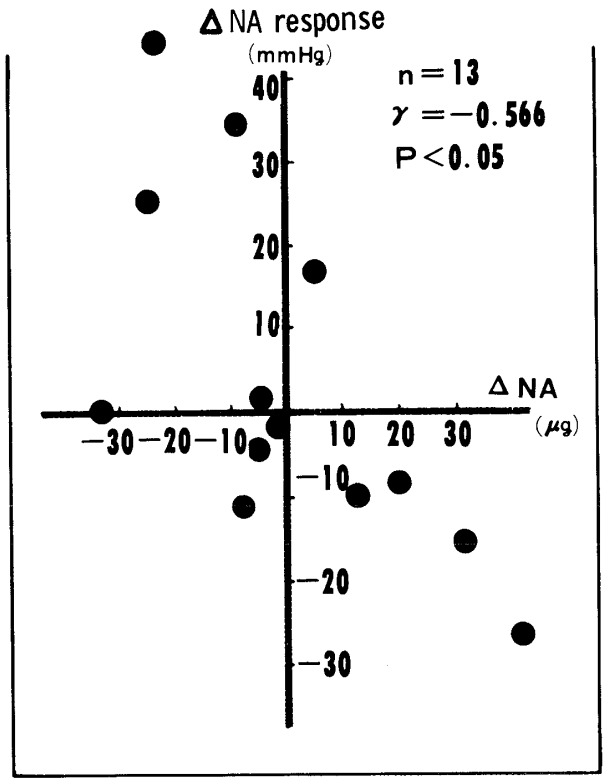

Fig.7. Correlation between the change in urinary noradrenaline (ΔNA) and that in the pressor response to infused noradrenaline (ΔNA response) following the 2 weeks rest.

urinary excretion of NA and serum DBH following the hospitalization in three typical cases. In these cases, CA were measured almost every day for more than 2 weeks, i.e. for 15 days in case 1, for 17 days in case 2 and for 29 days in case 3. Serum DBH was measured at the begining and the end of the experiment. In case 1 and 2, the blood pressure fell gradually and this fall was associated with the reduction of NA excretion and serum DBH. In case 3, in which the blood pressure level was fixed, NA excretion did not show an obvious change, while DBH was not decreased but rather increased. In these and other experiments, urinary adrenaline, unlike NA excretion, showed variable and insignificant changes.

In 13 patients including these 3 patients described above, the average of the amounts of urinary NA excretion during the first and the last 3 days of 2 weeks rest was compared. An excretion of NA was decreased in all 7 patients whose blood pressure reduced significantly, while in the remaining 6 patients the variable changes in NA excretion were observed. It was found that the patients with higher urinary NA excretion during the first 3 days showed a more marked fall of blood pressure after 2 weeks, and there was a significantly ($P < 0.05$) negative correlation between the average of the anounts of urinary NA and the changes in the mean arterial pressure (Fig. 2). It was also found that the changes in NA excretion, expressed as the difference of the average amounts of NA excretion between the first and the last 3 days of 2 weeks, were significantly ($P < 0.01$) correlated with the change in the mean arterial pressure(Fig. 3). Similary, the percent change of serum DBH was significantly ($P < 0.05$) correlated with the changes in blood pressure (Fig. 4). Plasma volume was measured in 14 patients during the first 3 days, and a significantly ($P < 0.05$) inverse correlation was established between plasma volume and the average of the amounts of NA excretion in the same period (Fig. 5).

In 13 patients, NA response was determined during the first and last 4 days of the 2 weeks rest. As shown in Fig. 6, the NA response was negatively correlated ($P < 0.01$) with the average of the amounts of NA excretion during 3 days. A significantly ($P < 0.05$) adverse correlation was also observed between the change of NA response and that of NA excretion after 2 weeks admission (Fig. 7). Apart from this experiment, NA response was measured simultaneously with water-sodium contents or PRA in 42 patients with essential hypertension. As shown in Fig. 8, NA response was correlated positively with plasma volume, extracellular fluid volume and

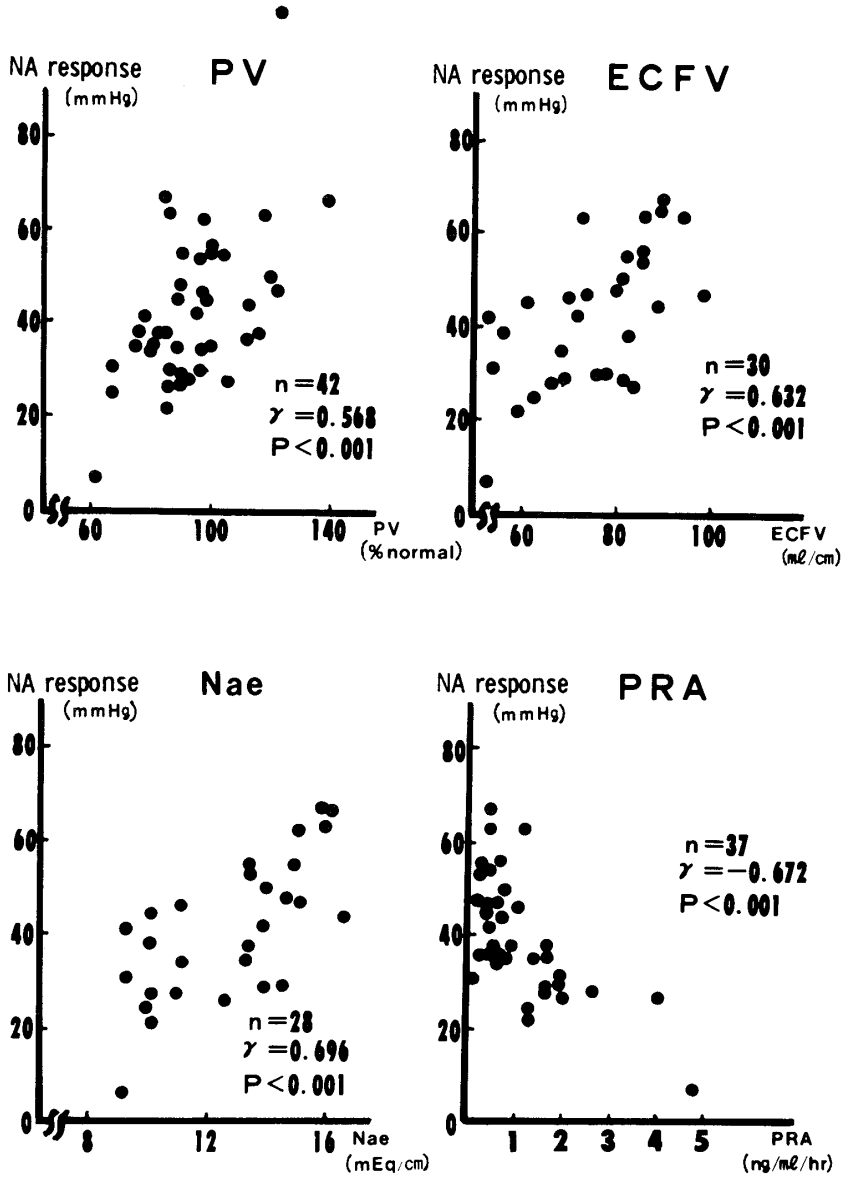

Fig.8. Correlation between the pressor response to infused noradrenaline (NA response) and the value of plasma volume (PV), extracellular fluid volume (ECFV), total exchangeable sodium (Nae), or plasma renin activity (PRA).

exchangeable sodium, and negatively with PRA (Fig. 8).

II) Urinary CA, serum DBH and NA response following salt restriction.

A salt restriction caused a rise of NA excretion in all of 14 except 2 patients, and the mean value of NA excretion after restriction was significantly ($P < 0.01$) higher than the control (Fig. 9, left pannel). In this experiment, blood pressure decreased from 166/97 to 152/92 mmHg in average, and the changes in mean arterial pressure were negatively ($P < 0.05$) correlated with those in the amounts of NA excretion (Fig. 9, right pannel). However, there was no significant correlation between the changes in blood pressure and those in serum DBH.

In contrast to the changes after hospitalization, slat restriction resulted in the significant suppression ($P < 0.01$) of NA response as shown in Fig. 10, although no significant correlation was observed between NA response and NA excretion.

Just as observed in the experiment on the changes following hospitalization, urinary adrenaline excretion did not show any obvious changes.

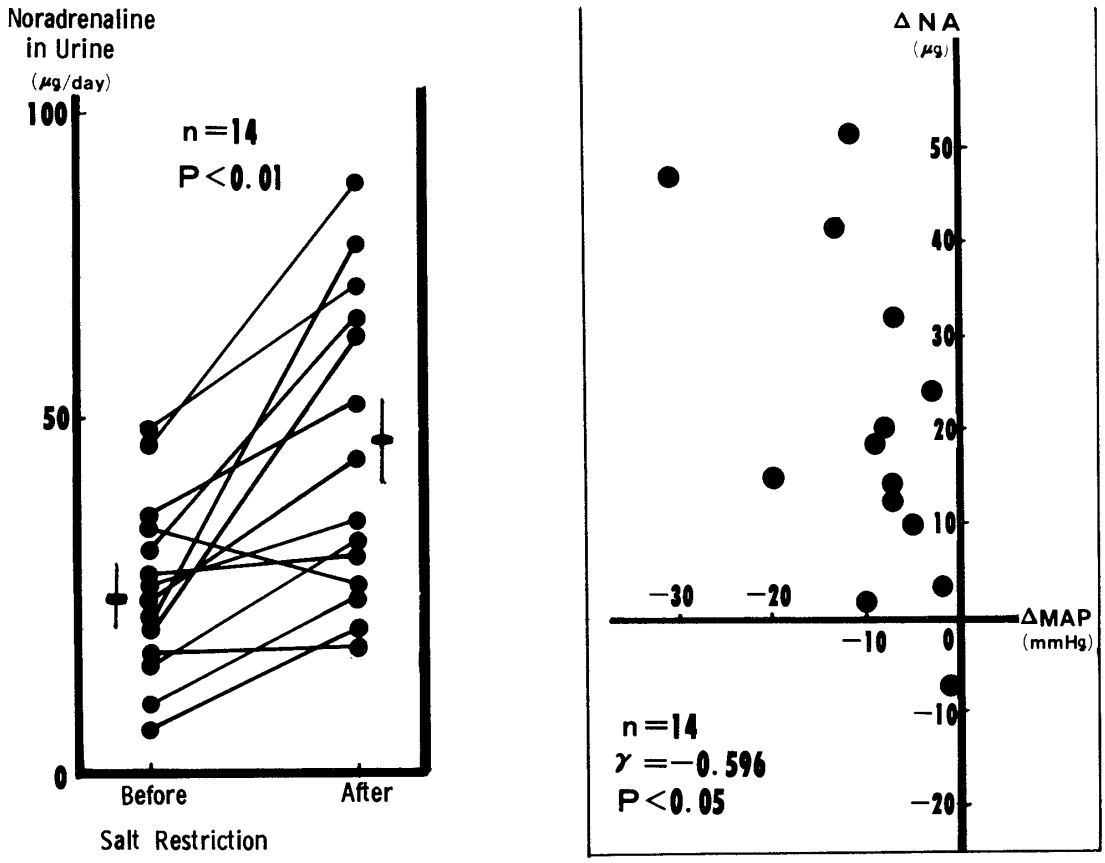

Fig.9. Changes in urinary noradrenaline (left pannel) and correlation between the change in urinary noradrenaline (ΔNA) and that in mean blood pressure (ΔMAP) (right pannel) following salt restriction.
Horizontal bar with vertical line in the left pannel indicates mean ± SEM.

DISCUSSION

Recently, plasma NA was reported to be elevated in some patients with essential hypertension[4-6] and according to Louis et al[5], there is a significantly positive correlation between the resting blood pressure and plasma level of NA. Nevertheless, most studies on the urinary excretion of catecholamines and their metabolites failed to reveal the higher values although it was found that a diurnal variation of urinary NA excretion[7] and an increment of NA excretion induced by cold pressor test[7] and mental or orthostatic stress[8] was significantly greater in the essential hypertensive group compared with the control group. In several laboratories, serum DBH which is considered to be a good index of the activity of sympathetic nervous system, has been measured in the patients with essential hypertension, and its value hitherto obtained has been in a very wide range in both normotensive and hypertensive subjects[9] Therefore, a role of the sympathetic nervous system in the mechanism of essential hypertension is still unestablished.

The purpose of the present study was to estimate the involvement of sympathetic nerve activity in the rise of blood pressure in essential hypertension, and urinary excretion of CA and serum DBH activity were measured before and after blood pressure fall induced by rest following hospitalization or salt restriction in the patients with this disease.

In the first step of the experiment, daily excretion of urinaly CA was measured continuously, and serum DBH was measured at the begining and the end of this experiment, in the patients with essential hypertension who kept a rest without medication after hospital admission. And it was found that NA excretion reduced gradually and serum DBH was decreased in the patients whose blood pressure fell obvi-

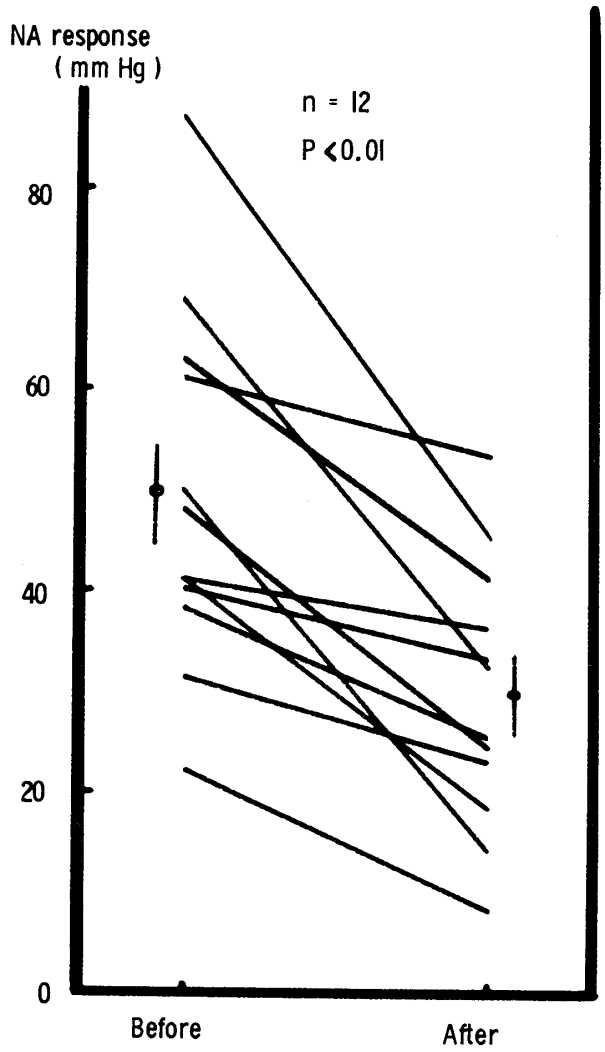

Fig.10. Changes in pressor response to infused noradrenaline (NA response) following salt restriction.
Horizontal bar with vertical line indicates mean ± SEM.

ously, while the patients whose elevated blood pressure was stable showed no decrease of both NA excretion and serum DBH. The changes in urinary excretion of adrenaline, unlike NA, were insignificant in this and other experiments.

A relation between blood pressure and NA excretion or serum DBH during 2 weeks rest after hospitalization was then estimated. It was revealed that the initial amounts of NA excretion were negatively correlated with the changes in blood pressure following the admission. It was also observed that a significant correlation existed between the alteration of blood pressure and the changes in NA excretion or the percent changes in serum DBH.

These results are summarized as follows, 1) a fall of blood pressure induced by rest following

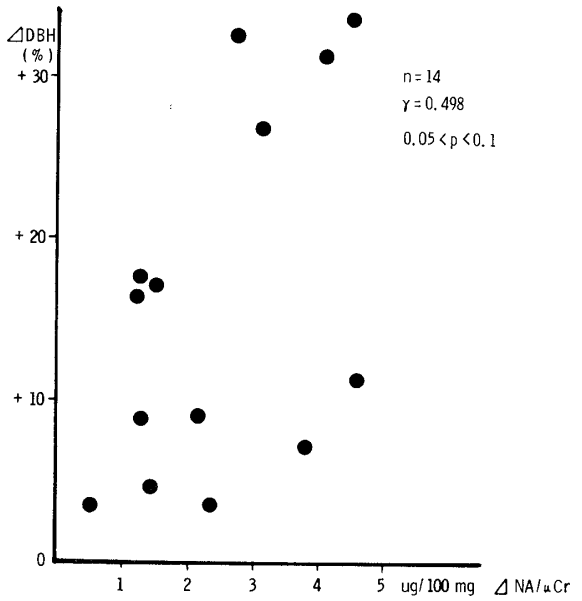

Fig.11. Correlation between percent changes in DBH (ΔDBH) and the changes of urinary noradrenaline excretion (ΔNA/Cr) following 60° tilting for two hours.

hospitalization is associated with a decrease of urinary NA excretion and of serum DBH activity and 2) this pressure fall is more remarkable when the initial amounts of NA excretion are greater and the decrease of NA excretion and DBH activity is larger.

The change in serum DBH in the same individual is considered to reflect an alteration of sympathetic nerve activity, although the changes in urinaly output of NA does not. Our other experiments, however, showed that the changes of urinary NA after 2 hours tilting was positively correlated with those of DBH as shown in Fig. 11. Therefore, it seems reasonable to conclude that a simultaneous increase or decrease in both urinary NA excretion and serum DBH reflects an augmented or reduced activity of sympathetic nerve system, respectively. And, as pointed out by Doyle et al.,[10] it is less likely that the changes in urinary NA excretion and serum DBH is caused by a disturbance in peripheral sympathetic terminal NA release or by an abnormality in NA uptake. And if this presumption is correct, the findings obtained in the present investigation suggest that a fall in blood pressure following hospitalization is caused by a reduction of sympathetic nerve activity and that an excessive sympathetic nerve activity is sufficient to account for the elevation of blood pressure in labile type of this disease. This idea is in agreement with the concept of sympathetic involvement in the

patients with labile hypertension described by Cuche et al.[11]

In contrast to the blood pressure fall following the hospitalization, the pressure fall after salt restriction was associated with an elevation of NA excretion, and the degree of this elevation was negatively correlated with the reduction of blood pressure. In the experiments of sodium depletion induced by a low sodium intake, Collins et al.[12] reported an increase of CA excretion in normal subjects and in most of hypertensive patients. In contrast, according to Alexander et al.,[13] an increase of sodium intake resulted in a reduction of urinary NA and plasma DBH. These results are in accordance with the findings obtained in the present investigation. Alexander et al.[13] suggested that salt loading might induce the changes in sympathetic activity secondary to the expansion of intra- or extra-vascular fluid volume. Our previous studies[1] demonstrated that plasma volume, extracellular fluid volume and total exchangeable sodium were decreased after salt restriction, and the present study revealed the amounts of urinary NA excretion being adversly correlated with plasma volume. Therefore, there seems to exist a close relationship between NA excretion and fluid volume or sodium in the body. The mechanism of this relationship is not clarified. However, an increased urinary NA output might be related with the greater release of NA from the tissue in sodium deficient media, as demonstrated by Bogdanski & Brodie.[14]

It has been already established that a pressor response to the vasoactive substances is augmented in the hypertensive patients.[15] The exact mechanism or significance of this augmentation, however, is still unknown. In the present study, NA response was exaggerated following hospitalization. And it was found to be adversly correlated with the amounts of NA excretion, and a negative correlation was also observed between the change in NA response and that in NA excretion. Following salt restriction, a reduction of NA response was associated with an increment of NA excretion. These results suggest that NA response is augmented when the sympathetic nerve activity is reduced and it is decreased when the sympathetic activity is accelerated. And, considering the fact that NA response is positively correlated with water-sodium contents and the fact that there exists an adverse correlation between NA excretion and plasma volume, it is reasonable to assume that NA response is dependent on sympathetic nerve function which is regulated by water-sodium contents in the body as already mentioned. However, further studies are necessary in order to elucidate whether the augmented NA response has any role in the mechanism of blood pressure rise in essential hypertension.

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