Plasma Renin and Vascular Complications in Substrains of the Spontaneously Hypertensive Rat, with a Reference to Water and Electrolyte Balance

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The stroke-prone and stroke-resistant substrains of the spontaneously hypertensive rat (SHR) were employed for an evaluation of possible role of renin-angiotensin system and of water and electrolyte balances in inducing hypertensive vascular lesions. Serial study on plasma renin level and vascular changes did not support the hypothesis that plasma renin is a major risk factor in the development of cardiovascular complications. The high plasma renin level seen in advanced stages of hypertension appeared to be a result of severe vascular damages, indicating malignant transformation of hypertension. In this state, water turnover was enhanced without any abnormality in electrolyte balances. A possible mechanism involved in the malignant course of hypertension is discussed.

In order to evaluate the hypothesis that plasma renin is a major risk factor in the development of hypertensive vascular complications, plasma renin level and vascular changes were observed in substrains of the spontaneously hypertensive rat (SHR) at various stages of hypertension. If this concept was true, the stroke-prone strain of SHR (SHRSP) should have a higher plasma renin level than the stroke-resistant strain (SHRSR) in their earlier life, since more than 80 per cent of the former is expected to develop cerebrovascular complications. Relationship between water and electrolyte balances and renin-angiotensin system was also studied, as these are believed by some investigators to be important factors in the course of malignant hypertension.

METHODS

Experiment 1
Males of SHRSP, SHRSP and normotensive Wistar-Kyoto strain (WK) of matched ages from 7 weeks to 12 months were fed a standard chow (Oriental MF) and tap water. Blood samples were taken in conscious state through an indwelled aortic catheter, and plasma renin concentration (PRC) was determined by means of radioim-
Fig. 1. Plasma renin concentration and kidney renin activity in 4-, 5-, and 7-month old rats. There is a significant correlation between the two values of SHRSP (r= 0.67, p < 0.01).

munoassay of angiotensin I. Mean arterial pressure was recorded by an electromanometer connected to the catheter. Some rats of 4-, 5-, and 7-month old groups were sacrificed to study morphological findings. Kidney renin activity (KRA) was also determined in these rats. Details of the methods employed in this experiment were described elsewhere.5,6

Experiment 2
Ten males of 5-month old SHRSP were placed in metabolic cages and fed the same diet as the above. A polyethylene catheter was indwelled in the aorta. After 10 days of adaptation, water intake, urine volume, and sodium and potassium balances were measured on daily basis. Blood samples for PRC determination were collected in conscious state between 10 A.M. and noon at weekly intervals. The period of observation in this study was 17 days.

RESULTS
1. Blood Pressure
Mean arterial pressures of both strains of SHR were significantly higher than the control WK's even at the youngest age (7 weeks) studied in experiment 1 (SP 114 ± 7, SR 126 ± 5 vs. WK 91 ± 4)*. Later the blood pressure seemed to rise more rapidly in SHRSP than in SHRSR, though the difference between the two were not statistically significant (SP 182 ± 14 vs. SR 157 ± 16 at 5 months)*. No relationship was found between the blood pressure and PRC levels.
2. Plasma Renin Level and Morphological Findings
SHRSR:
Plasma renin concentrations of this strain showed no significant differences from the
controls in any age groups. No pathological lesions were found in the kidney and the brain when autopsied at 4–7 months of age. However, some of 7-month old rats had myocardial fibrosis while their PRCs were normal. A few individuals of 10- and 12-month old groups showed higher PRC values.

**SHRSP:**

In 7-week old groups, i.e. in an early stage of hypertension, PRC of this strain was significantly lower than that of SHRSP. Later it showed no significant differences from those of WK and SHRSP up to 5 months. None of 4-month old rats showed high PRC values or macroscopic vascular complications, while abnormally high PRCs were seen in some of 5-month old rats. Plasma renin levels in 7-month and older groups of SHRSP were significantly higher than the control values. Cerebral hemorrhage and/or softening accompanied by edema as well as nephrosclerosis were found in 5- and 7-month old SP rats which showed high PRC values. In all of these rats, angionecrosis of renal arterioles together with perivascular hemorrhage and fibrosis was revealed by histological observations. Renal arterioles of the other SP rats with normal PRC values, autopsied at 4–7 months, showed some proliferative changes with occasional hyalinization and fibrosis. Myocardial fibrosis was found in some of 7-month old rats irrespective of plasma renin level.

3. Renal Renin Content (Figure 1)

Both strains of 4 to 7-month old SHR had lower KRA as compared with normotensive WK. No significant difference was found between the two substrains of SHR. Although SHRSP with the higher PRC tended to have the higher KRA,
there was no correlation between PRC and KRA of SHRSP or of WK.

4. Water and Electrolyte Balance and Plasma Renin Level (Figure 2)

The rats in experiment 2 could be divided into two groups on the basis of water turnover rate. Four rats classified as group A showed more than 2.0 ml of water intake per gram of food intake throughout the observation period, while that of six rats in group B was less than this value. Both of water intake and urine volume were significantly greater in group A than in group B. However, no difference between the two groups was detected in either of sodium balance or potassium balance or in the difference between water intake and urinary output. Only minor fluctuations were seen in these values during the observation. In addition to the enhanced water turnover, group A rats showed consistently high PRC, while most of PRC values in group B remained within the normal range. Nephrosclerosis was found in group A rats, when autopsied at the end of this experiment. Two of them had cerebrovascular lesions as well.

**DISCUSSION**

The results obtained in experiment 1 did not support the view of Brunner et al. Plasma renin level of the stroke-prone SHR was lower than that of stroke-resistant strain in an early stage of hypertension. Some vascular lesions were found in SHRSP prior to the rise of plasma renin level. And no evidence indicated that a higher plasma renin preceded the development of vascular lesions. On the other hand, high plasma renin was always associated with severe vascular lesions. Therefore it would be reasonable to consider the high plasma renin level as a result rather than the cause of vascular complications.

Renal renin content of SHR was lower than that of normotensive animals in spite of similar or higher plasma renin level. This suggests that SHR would release its renal renin into the circulation more readily than the normotensive control. It may be attributed either to hyperresponsiveness to minor stresses or to an accelerated turnover of renal renin in SHR.

Some investigators, employing renovascular or DOCA-salt hypertension model, suspected a major role of an accelerated sodium loss in inducing malignant phase of hypertension. However, our study on the stroke-prone SHR with malignant feature of hypertension could not find any abnormal electrolyte balance. Instead, only abnormalities detected in these rats were accelerated turnover of water and high plasma renin level. This discrepancy between the other reports and our findings may be derived from the difference between acute and chronic course of hypertension. The mechanism of changes observed in the present study could be interpreted as follows. As a result of hypertensive vascular lesions in the kidney and/or in the brain, circulating renin level was elevated, leading to an increased production of angiotensin. The latter would have stimulated the thirst center, and hence increased water intake which resulted in water diuresis. The increased angiotensin, on the other hand, is expected to stimulate adrenal aldosterone secretion. And one may assume that any excessive filtration of sodium due to the high blood pressure or diminished glomerular capacity might have been counterbalanced by an increased tubular reabsorption promoted by the high aldosterone level. However, no evidence for the effect of hyperaldosteronism was obtained in this study, since no increase in potassium loss was detected. More evidence should be collected for elucidating the mechanism involved in malignant hypertension.

**REFERENCES**


DISCUSSION

Chairman: Dr. JUN FUJII, Institute for Adult Diseases Asahi Life Foundation, Tokyo

CHAIRMAN: I would like to confirm your interpretation on the results. Do you suppose that the increase of PRC results from hypertensive vascular lesions?

Dr. MATSUNAGA: The increase of PRC was observed so simultaneously with malignant phase of hypertension that it is difficult to decide which was the primary. However, I suppose that angionecrosis precedes the increase of PRC, because other investigators have indicated that angionecrosis can develop without any increase of PRC.

Dr. SARUTA (Keio Univ.): Have you observed JG cells which contain renin granules?

Dr. MATSUNAGA: Yes, I have. The JG index was parallel to the renin content of the kidney.

Dr. SARUTA: Your slide showed that angionecrosis developed in the afferent arteriole of the kidney. Do you suppose that the vascular lesion is attributed to high intravascular pressure?

Dr. MATSUNAGA: Although high blood pressure greatly contributes to the lesion, it remains uncertain that other factors are involved in the development of the lesion.

Dr. SARUTA: Hyperplasia of the afferent arterioles is observed in both renovascular and malignant hypertension. However, the intravascular pressure in this portion is quite different in the two conditions. The pressure is low in the renovascular and is very high in the malignant hypertension. In spite of the difference in blood pressure, why does the similar change develop in the afferent arteriolar cells?

Dr. MATSUNAGA: The question is difficult to answer.

Dr. EBIHARA (Jichi Med. Coll.): Did you measure kidney renin? Was the renin content of the kidney parallel to PRC?

Dr. MATSUNAGA: The renin content of the kidney was not always parallel to PRC. The kidney renin was measured after sacrifice and not simultaneously with PRC.

Dr. IGARASHI (Hokkaido Univ.): We have studied prognostic significance of plasma renin activity that is casually measured in a population survey. The results show that cardiocerebral complications develop in the high renin group more than in the age, sex, and blood pressure-matched control group with normal renin. Was the incidence of stroke related with PRC? Did stroke develop in the stroke prone SHRs with normal renin?

Dr. MATSUNAGA: No severe vascular lesions were found in animals with normal renin. But it is possible that these animals may suffer from stroke in the later stage.

Dr. YAMORI (Kyoto Univ.): Exudative arterial changes such as angionecrosis developed predominantly in the brain and kidney of the stroke prone SHRs. Angionecrosis was always found in those with high renin. Benign vascular lesions such as medial hypertrophy or hyperplasia of arterial wall developed not only in the stroke prone but also in the stroke resistant SHRs.

Dr. KANeko (Yokohama City Univ.): Many studies have been reported on the relationship between plasma renin and hypertensive complications. However, retrospective studies can not give us correct answers on this problem. Plasma renin activity increases after cardiac attack or stroke. Only prospective studies will be able to give us correct answer for this problem. Did you measure PRC during the pre-stroke period?

Dr. MATSUNAGA: Yes, I did. Angionecrosis was found in the kidney in animals with high PRC that had not yet suffer from stroke.

Dr. KANeko: There is not sufficient evidence to decide whether the increase of PRC is cause of the hypertensive vascular complications or result of them.

Dr. Saito (Kyoto Univ.): I would like to present additional results. There was a slight correlation between plasma renin and kidney renin in the stroke prone SHRs.

Dr. TAKEDA (Tokyo Univ.): You showed that water intake was greater in animals with high renin than in those with normal renin. Was the water intake increased parallel to the increase of PRC.

Dr. MATSUNAGA: I have not yet enough data of serial observation to answer precisely.

Dr. SEKI (Inst. Adult Dis. Asahi Life Fdn.): Haven't you observed a transient rise of PRC? How much did PRC fluctuate in individual animals?

Dr. MATSUNAGA: It slightly fluctuated but remained within a certain range.

Dr. SEKI: Without a continuous monitoring it cannot exclude the possibility that a transient rise
of PRC which is not always measured contributes
the development of the vascular lesions.
Dr. ONOYAMA (Kyushu Univ.): You have sug-
gested that high PRC is not responsible for the
development of angionecrosis. What kind of

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factors are responsible for it?
Dr. MATSUNAGA: The high blood pressure
itself may be the most important factor.
However, I cannot mention from the present
data whether any other factors are involved in it.