Pathogenesis of Essential Hypertension with Low Renin: Responses of Plasma Renin Activity to Various Stimulation Tests in Essential Hypertension

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Plasma renin activity (PRA) was measured in 14 control subjects and 27 patients with essential hypertension (EH) (low renin group: 9, normal renin group: 11, and high renin group: 7) before and after the following stimulation tests.

Test procedures:
1) Circadian rhythm (0600, 1600 and 2400h).
2) Adrenal stimulation test (ACTH: 12.5 I.U.).
3) Adrenal suppression test (Dexamethasone: 1.0 mg).
4) Metoprine test (1.5 g).
5) Angiotensin II infusion test (8 ng/kg/min).
6) Saline infusion test (1000 ml/hr).

Patients with low PRA showed significantly lower levels of PRA than those of other two groups in circadian rhythm, after 2 hours of ACTH infusion and after angiotensin II infusion. Furthermore, these patients showed significantly higher responses of PRA than other two groups after furosemide test under dexamethasone and after metoprine test.

In case of saline infusion test, patients with low and normal PRA did not show significantly decreased levels of PRA after the infusion, though all patients with high PRA and all control subjects showed significantly decreased levels of PRA.

From the present studies, it might be concluded that patients with low PRA has an unknown mineralocorticoid excess which is ACTH dependent and 11 hydroxylated and some of hypertensive patients have an abnormality in their renin-angiotensin-aldosterone volume feed back loop as a factor for hypertension.

Key Words:
ACTH
Angiotensin II
Dexamethasone
Essential hypertension
Furosemide
Metoprine
Saline

The role of plasma renin activity (PRA) in various types of hypertension has been studied by many investigators.

Recently, it has been generalized to classify patients with essential hypertension (EH) into low, normal and high PRA groups by means of renin stimulation test.1-3 And it has been discus-

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Table I.

Test procedures:

All subjects when studied were on a diet containing 5–8 g NaCl daily. Blood samples for baseline PRA determinations were drawn between 0800 and 0900h after overnight recumbency.

All hypertensive patients had been studied according to the following test procedures.

1) Circadian rhythm: Blood samples for circadian rhythm were drawn at 0600, 1600 and 2400h on recumbency.

2) Adrenal stimulation test: Immediately after the baseline sample was drawn, a 4-hour infusion of 12.5 IU of ACTH (Acthar, Armour Pharmaceutical Co.) in 500 ml of 5% dextrose was begun and two other samples were collected 2 and 4 hours later. The subjects remained recumbent throughout the study.

3) Adrenal suppression test: One mg of dexamethasone was administered at 2100h orally and on the next day, the baseline sample was drawn. Immediately afterwards, furosemide (0.7 mg/kg) was administered intravenously and after 2 hours, another blood sample was collected.

4) Metopirone test: One and half gram of metopirone was administered at 2100h orally and on the next morning, another plasma sample was drawn between 0800 and 0900h.

5) Angiotensin II infusion test: Immediately after the baseline sample was drawn between 1200 and 1300h, angiotensin II (8 ng/kg/min, Hypertensin Ciba) was infused intravenously for 30 minutes and plasma samples were collected at 15, 30 and 45 minutes later.

6) Saline infusion test: Immediately after the baseline sample was drawn, 1000 ml of saline was infused for one hour and another blood sample was collected.

The hypertensive patients with low PRA were on average older than those with normal and high PRA. The mean systolic and diastolic blood pressure were slightly but not significantly higher in the low renin group compared to other two groups. The patients with low PRA presented significantly ($P < 0.01$) higher plasma sodium levels than those of high renin group and slightly lower plasma potassium levels than other two groups.

The circadian levels (ng/ml/hr) or PRA (Fig. 1) were $1.1 \pm 0.6$ (S.D.) at 0600, $0.7 \pm 0.7$ at 1600 and $0.8 \pm 0.5$ at 2400h in patients with low PRA and $2.5 \pm 0.8$ at 0600, $2.7 \pm 0.9$ at 1600 and $2.1 \pm 1.1$ at 2400h in patients with normal PRA and $6.1 \pm 1.5$ at 0600, $5.3 \pm 2.8$ at 1600 and $4.7 \pm 2.3$ at 2400h in patients with high PRA. Patients with low PRA showed significantly lower PRA levels ($P < 0.02$) than those with normal or high PRA.

The mean levels of PRA before and after 2 and 4 hours of ACTH infusion (Fig. 2) were $0.9 \pm 0.6$ (S.D.) (ng/ml/hr), $0.5 \pm 0.5$ and $0.75 \pm 0.7$ in patients with low PRA ($n = 8$), $2.6 \pm 1.4$, $3.7 \pm 1.8$ and $1.5 \pm 0.8$ in patients with normal PRA ($n = 8$) and $5.7 \pm 1.8$, $4.2 \pm 1.7$ and $4.4 \pm 1.4$ in patients with high PRA ($n = 6$), respectively. In the patients with low PRA, the mean level of PRA after 2 hours of ACTH infusion was significantly lower ($P < 0.01$) than the baseline level of PRA. In the patients with normal PRA, the mean level after 4 hours of ACTH infusion was

PRA was measured by the use of kit of LE COMMISSARIAT A L ENERGIE ATOMIQUE, France.

Plasma renin substrate was measured by the modified method of Katz et al.

Statistical comparisons were made by the use of Student's t test.

RESULTS

Table I contains the ages, blood pressure and serum electrolyte concentrations for patients with EH.

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There was no significant difference in the plasma levels of PRA between before and after dexamethasone.

The mean levels of PRA after furosemide and 2 hours of upright posture without and with dexamethasone were 0.7 ± 0.1 and 2.9 ± 0.8 in the low PRA group (n=7), 6.4 ± 0.8 and 7.8 ± 1.5 in the normal PRA group (n=6) and 11.8 ± 1.9 and 12.8 ± 1.6 in the high PRA group (n=6). There was a significant (P < 0.02) difference between the levels of PRA after furosemide test without and with dexamethasone in the low renin group but there was no significant difference in other two groups.

In order to clarify the increased responses of PRA in the low renin group, the excretion of urinary sodium for 2 hours before and after the stimulation test, the effect of dexamethasone on renin release by using dog renal cortical cell suspension and plasma levels of renin substrate before and after the administration of dexamethasone were investigated.

i) The urinary sodium excretions (Fig. 4) for two hours before and after furosemide test without dexamethasone were 89.1 ± 25.4 (S.E.) (mEq/day) and 1096 ± 122.1 in the low renin group (n=5), 81.6 ± 15.6 and 858.2 ± 66.0 in the normal renin group (n=4) and 68.3 ± 7.9 and 780.9 ± 171.6 in the high renin group (n=4).

In case of the administration of dexamethasone, the urinary sodium excretion for 2 hours before and after furosemide test were 129.5 ± 35.5 (S.E.) (mEq/day) and 980.7 ± 189.4 in the low renin group, 1063 ± 47.0 and 569.1 ± 79.4 in the normal renin group and 79.7 ± 28.7 and

significantly (P < 0.05) lower than the mean levels before and after 2 hours of ACTH infusion. In the patients with high PRA, the mean levels after 2 and 4 hours of ACTH infusion were significantly (P < 0.01) lower than the baseline level.

In the study of adrenal suppression test (Fig. 3), the mean levels of PRA before and after the administration of dexamethasone were 0.6 ± 0.2 (S.E.) (ng/ml/hr) and 1.2 ± 0.3 in the low renin group (n=7), 2.9 ± 0.5 and 3.4 ± 0.8 in the normal renin group (n=6) and 4.6 ± 0.3 and 5.0 ± 0.8 in the high renin group (n=6), respectively.

Fig. 6. The effect of dexamethasone (0.1 µg and 0.2 µg) on renin secretion from dog renal cortical cell suspension.

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1047.6 ± 206.8 in the high renin group.

ii) In the study of plasma levels of renin substrate (Fig. 5), the mean level in 14 normal male subjects at 0900h was 969 ± 115 (S.D.) (ng/ml) on a diet containing 5–8 g of NaCl/day.

In the hypertensive patients, the plasma levels before and after dexamethasone were 932 ± 255 and 1112 ± 302 in patients with low PRA (n=5) and 1240 ± 428 and 900 ± 265 in patients with normal PRA (n=6). There was no significant difference between plasma levels of renin substrate before and after dexamethasone in these two groups.

iii) In the study of the effect of dexamethasone on renin release (Fig. 6), a dog renal cell suspension made by the method of Michaelakis et al. was used in this experiment. The mean percent increase of PRA after incubation was 357.4% (n=4), while the mean percent increase of PRA after incubation with dexamethasone (0.1 μg and 0.2 μg, n=4) were 360.5% and 356.5%. There was no significant difference between plasma levels of PRA after incubation without and with dexamethasone.

In the study of plasma levels of PRA before and after metopirone (Fig. 7), patients with low PRA (n=8) showed 0.5 ± 0.2 (S.E.) (ng/ml/hr) and 1.68 ± 0.62, patients with normal PRA (n=8) 3.3 ± 0.7 and 1.8 ± 0.3 and patients with high PRA (n=6) 4.6 ± 0.3 and 4.9 ± 1.1, respectively. Patients with low PRA showed a tendency of increase in the responses of PRA after metopirone (P < 0.1).

In the responses of PRA to angiotensin II (Fig. 8), patients with low PRA (n=5) showed 0.7 ± 0.1 (S.E.) (ng/ml/hr), 0.5 ± 0.1, 0.6 ± 0.1 and 0.5 ± 0.1 before and 15, 30, and 45 minutes after the beginning of the infusion and patients with normal PRA (n=6) showed 2.6 ± 0.8, 2.0 ± 0.7, 1.7 ± 0.5 and 1.8 ± 0.5 and patients with high PRA (n=6) showed 2.7 ± 0.5, 3.0 ± 0.9, 1.7 ± 0.3 and 3.6 ± 1.0, respectively. In the patients with low PRA, the mean level of PRA after 15 minutes of angiotensin II infusion was significantly (P < 0.05) lower than the mean baseline level. In the patients with normal PRA, the mean levels of PRA after 15 and 30 minutes of the infusion were significantly (P < 0.01 and P < 0.05, respectively) lower than the mean baseline level. In the patients with high PRA, the mean level of PRA after 30 minutes of the infusion was significantly (P < 0.02) lower than the baseline level.
In the study of the saline infusion test (Fig. 9), the levels of PRA before and after the infusion were $1.23 \pm 0.7$ (S.E.) (ng/ml/hr) and $0.7 \pm 0.4$ in normal subjects (n=6), $1.5 \pm 0.5$ and $1.3 \pm 0.4$ in patients with low PRA (n=8), $3.4 \pm 0.7$ and $2.7 \pm 0.6$ in patients with normal PRA (n=10) and $5.5 \pm 0.9$ and $3.2 \pm 0.5$ in patients with high PRA (n=7). All control subjects and all patients with high PRA showed significant ($P < 0.05$ and $P < 0.01$, respectively) lower levels of PRA than the baseline levels. On the other hand, 4 of 8 patients with low PRA and 3 of 10 patients with normal PRA did not show lower levels of PRA than their baseline levels.

**DISCUSSION**

In the study of circadian rhythms of PRA, patients with low PRA showed significantly lower levels of PRA than those of other two groups. Up to the present time, circadian rhythm of PRA have not been previously reported in patients with low renin hypertension except Grim's report. Grim et al. reported that the mean PRA was always lower in patients with low PRA as compared to normal subjects but at midnight, the mean PRA was not significantly lower in patients with low PRA. The discrepancy between their and our results would be due, at least to some extent, to dietary sodium content or a classification of patients with low, normal and high renin groups.

In the responses of PRA to ACTH infusion, patients with low PRA showed significantly lower levels after 2 hours of ACTH infusion than their baseline levels, while patients with normal PRA showed slightly increased levels of PRA after 2 hours of ACTH infusion compared to their baseline levels. In the patients with high PRA, the levels of PRA after 2 and 4 hours of ACTH infusion were lower than the baseline levels. Generally, it is believed that ACTH increases the secretion rate and plasma concentration of the minor mineralocorticoids but has only a small effect on aldosterone. With regard to the study of the effect of ACTH on PRA, several investigators have reported that ACTH stimulates renin release directly. From this report, it is suggested that in patients with normal PRA, ACTH increased PRA after 2 hours of ACTH infusion and after 4 hours of ACTH infusion, the increased levels of several mineralocorticoids induced by ACTH stimulation suppressed PRA. On the other hand, it is probable that in patients with low and high PRA, ACTH increased initially the secretion of several mineralocorticoids and these increased steroids suppressed PRA. In the study of dexamethasone treatment, only low renin group showed a significantly increased response to furosemide and 2 hour ambulation test under dexamethasone. Therefore, several additional experiments were performed, in order to clarify the increased responses of PRA. However, it was found that the administration of dexamethasone did not increase the urinary excretion of sodium, the concentration of renin substrate and renin release from renal cortical cell suspension. Haynes et al. reported that cortisone increased plasma renin substrate in animal experiments. On the other hand, Newton et al. reported that the treatment of dexamethasone decreased levels of PRA in human experiments. Recently, Otokiya et al. presented that PRA increased with the administration of dexamethasone (2 mg/day) with and without Bumetamide administration in normal subjects.

In this study, the evidence for the increased PRA after dexamethasone and furosemide test in low renin group was not found clearly. Probably, it might depend on the several problems that the time for the collection of urine was too short and the dose of dexamethasone added to renal cortical cell suspension was too little and the method of renin substrate was not so sensitive.

Up to the present time, it is reported that several known mineralocorticoids were not increased in low renin hypertension. Therefore, it might be thought that patients with low PRA have an excessive unknown mineralocorticoid secretion which was ACTH dependent and hydroxylated at the position of 11 in steroid structure. On the other hand, it might be thought that two other groups also have this steroid secretion but the secretion of this steroid is less than the low renin group. Recently, several investigators reported that hypertensive patients with low PRA have an unknown mineralocorticoid activity.

In the study of the negative feed back system of renin-angiotensin-aldosterone loop, angiotensin II infusion test and saline infusion test were performed in the three groups of EH. In the responses of PRA to angiotensin II infusion, patients with low, normal and high PRA showed the decreased levels of PRA after the infusion. Therefore, it is suggested that a short feed back system between PRA and angiotensin II works normally in EH. In the responses of PRA to

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saline infusion, all of normal subjects and patients with high PRA showed significantly lower levels of PRA after saline infusion than their baseline levels. However, the levels of PRA after the infusion did not decrease significantly in patients with low and normal PRA, because 4 of 8 patients with low PRA and 3 of 10 patients with normal PRA did not show the decreased levels of PRA.

From the above results, it is suggested that renin-angiotensin-aldosterone volume feed back loop does not work in some part of patients with EH and a disorder in this loop might be a factor causing hypertension. Recently, Tuck et al reported a similar result.

Finally, it might be concluded that in the study of responses of PRA to various stimulation test, there are possibilities that patients with low PRA have an excess of unknown mineralocorticoid secretion which is ACTH dependent and 11 hydroxylated and some of hypertensive patients have an abnormality in their renin-angiotensin-aldosterone volume back loop as a factor for hypertension.

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REFERENCES