A Comparative Study on (Des-Aspartyl¹)-Angiotensin II and Angiotensin II in Patients with Essential Hypertension

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SUMMARY

Twenty-one patients with essential hypertension received a constant infusion of angiotensin II and des-aspartyl¹-angiotensin II for 45 min on 2 consecutive days during normal sodium intake. Des-aspartyl¹-angiotensin II increased mean blood pressure from 127.5 ± 17.7 to 142.3 ± 18.8 mmHg and plasma aldosterone concentration from 12.1 ± 7.8 to 18.8 ± 11.4 ng/100 ml. Although plasma aldosterone concentration elevation was positively correlated with pre-infusion levels of plasma renin activity ($r=0.862$, $p<0.001$), mean blood pressure elevation was inversely correlated with the values of renin activity ($r=-0.599$, $p<0.01$). In contrast, elevations of both plasma aldosterone concentration and mean blood pressure were inversely correlated with pre-infusion levels of plasma renin activity in angiotensin II infusion. Des-aspartyl¹-angiotensin II and angiotensin II were equally effective in suppressing renin release. These data demonstrate that des-aspartyl¹-angiotensin II rather than angiotensin II plays an important role in aldosterone production in essential hypertension.

Additional Indexing Words:

Angiotensin II-(2-8)-heptapeptide Blood pressure Aldosterone
production Renin activity

SINCE angiotensin II is a potent stimulator of aldosterone secretion in man, the renin-angiotensin-aldosterone system has been accepted as a coordinated system acting simultaneously to regulate blood pressure and sodium or potassium balance.¹⁾⁻³⁾ Angiotensin II is degraded into supposedly inactive fragments by action of some kinds of enzymes; endopeptidases, aminopeptidases or carboxypeptidases.⁴⁾ However, the C-terminal heptapeptide fragment of angiotensin II, des-aspartyl¹-angiotensin II was recently found to be an important substance in that it has high affinity for adrenal receptor and stimulates biosynthesis of aldosterone in man.⁵⁾⁻⁷⁾ This heptapeptide, so call-

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ed angiotensin III, has been isolated and measured in plasma of several species.⁸⁾

On the other hand, role of the heptapeptide in the regulation of blood pressure and aldosterone production in hypertensive patients has not been concluded. In addition, interaction between angiotensin II and III has been scarcely reported. The present study was undertaken to seek a role of the heptapeptide by examining the effects on blood pressure and aldosterone production in patients with essential hypertension on normal sodium intake.

MATERIALS AND METHODS

Subjects (Table I):

Twenty-one patients with essential hypertension, whose ages ranged from 24 to 59 years, were studied. The diagnosis was established by the following criteria; supine diastolic blood pressure of 90 mmHg or higher on at least 5 different occasions after admission, absence of papilledema or rapidly accelerating retinopathy, blood urea nitrogen below 20 mg/100 ml, and absence of any known causes of hypertension. The patients had normal intravenous pyelogram, and normal urinary 17-OHCS and 17-KS. In 7 (No. 1, 4, 5, 12, 15, 20, and 21), renal arteriography was done and showed normal. One patient (No. 13) had intermittent hypertension, and was studied when diastolic blood pressure was normal.

Study procedure:

The patients were given a constant diet containing approximately 150 mEq of sodium for at least 20 days, and consecutive 24-h urine samples were collected and analyzed for sodium and potassium. No food was given after 7:00 p.m. before the study day when the patients assumed supine position until completion of the study. At 8:00 a.m. of the study day, an intravenous administration was begun with 5% dextrose in water at a rate of 0.2 ml/min and continued for 15 min until the blood pressure became stable. Without disturbing the patients, the infusion was then changed to solution containing 1.0 ng of angiotensin III in each ml of dextrose in water. This was started at a constant speed of 25.0 ng/Kg/min for 45 min. Serial measurements of blood pressure were done every 3 min over the brachial artery with a sphygmomanometer and blood was drawn for determination of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) before and after the infusion.

After completion of the study, the patients were continued on the constant diet, and on the next day, an identical protocol as the previous day was followed except that, instead of angiotensin III, angiotensin II was administered intravenously at a constant rate of 10.0 ng/Kg/min for 45 min.

The blood pressures are expressed as the mean values obtained during the infusions. PRA and PAC were determined by radioimmunoassay as previously reported.^{13),14)} Synthetic angiotensin III was provided by Protein Research Foundation, Osaka, Japan, and synthetic angiotensin II was courteously given from Ciba Pharmaceutical Co, Tokyo, Japan. The results are expressed as mean $\pm$ 1 SE. Statistical analysis was carried out with Student's t-test.

RESULTS

I. Effects of angiotensin III on blood pressure, PRA, and PAC

Results obtained by angiotensin III infusion are summarized in Table I. In the first 15 min of the control period, blood pressure was 173.8 ± 26.5 mm of mercury systolic and 104.3 ± 14.9 mm of mercury diastolic. Angiotensin III administration resulted in a rise to 191.9 ± 30.6 mm of mercury in systolic and to 116.5 ± 16.6 mm of mercury in diastolic blood pressure. Both the systolic and the diastolic blood pressures began to elevate within 5 to 7 min after the infusion and reached zenith within about 10 min, and held a steady state of elevation until cessation of the infusion.

A negative correlation ($r = -0.599$, $p < 0.01$) was observed between the changes of mean blood pressure and the values of PRA obtained at the end of control period (Fig. 1).

Table I. Effects of (Des-asp¹)-Angiotensin II on Blood Pressure, Plasma Renin Activity, and Plasma Aldosterone Concentration

No.	Age (y.o.)	Control			(des-asp ¹)-angiotensin II		
		B.P. mmHg	PRA ng/ml/h	PAC ng/100 ml	B.P. mmHg	PRA ng/ml/h	PAC ng/100 ml
1	30	164/93	3.6	13.1	160/94	2.0	20.9
2	41	151/95	0.7	9.5	187/121	0.6	14.1
3	42	248/140	0.3	8.7	270/156	0.3	11.9
4	45	201/110	1.5	5.2	228/118	1.1	9.1
5	34	155/92	2.0	13.3	172/104	1.5	19.1
6	54	170/94	0.3	6.4	198/112	0.4	6.8
7	40	210/118	0.5	5.1	233/128	0.4	10.1
8	28	148/100	2.0	14.4	150/106	1.4	24.7
9	34	209/117	0.5	7.2	226/125	0.4	11.3
10	46	201/106	0.3	6.2	219/115	0.1	12.1
11	50	154/97	1.0	11.5	166/122	1.4	20.1
12	42	152/98	3.2	9.7	155/101	3.0	19.8
13	43	160/78	0.5	5.3	172/90	0.5	7.1
14	59	156/100	1.9	11.2	188/120	1.9	21.0
15	55	178/114	2.8	7.9	189/126	1.3	19.9
16	27	187/132	4.9	18.5	194/141	3.2	34.8
17	30	170/120	0.1	8.5	204/144	0.1	9.8
18	24	162/97	1.1	9.8	190/104	0.9	14.1
19	47	162/88	0.1	14.1	201/104	0.0	17.7
20	30	170/104	8.1	36.5	172/110	7.1	54.7
21	46	142/98	3.3	29.9	155/106	1.8	35.9

B.P., PRA, and PAC mean blood pressure, plasma renin activity, and plasma aldosterone concentration, respectively.

Fig. 1. Relation between changes of mean blood pressure and pre-infusion levels of PRA in angiotensin III infusion. A significant correlation ($r = -0.599$, $p < 0.01$) is observed.

Fig. 2. Relation between changes of PAC and pre-infusion values of PRA in angiotensin III infusion. A high correlation ($r = 0.862$, $p < 0.001$) is observed.

PAC was 12.1 ± 7.9 ng/100 ml at the end of control period and significantly increased to 18.8 ± 11.4 ng/100 ml ($p < 0.05$) after the infusion. There was a significant positive correlation ($r = 0.862$, $p < 0.001$) between the changes of PAC and the levels of PRA before the angiotensin III infusion (Fig. 2).

PRA was 1.84 ± 1.97 ng/ml/h and was slightly decreased to 1.40 ± 1.59 ng/ml/h at the end of angiotensin III infusion.

II. Effects of angiotensin II on blood pressure, PRA, and PAC

Results obtained by angiotensin II infusion are summarized in Table II. In the first 15 min of the control period, blood pressure was 173.0 ± 22.7 mm of mercury systolic and 105.7 ± 12.0 mm of mercury diastolic. Angiotensin II administration resulted in a rise to 191.3 ± 26.2 mm of mercury in systolic and to 122.3 ± 13.0 mm of mercury in diastolic blood pressure.

Table II. Effects of Angiotension II on Blood Pressure, Plasma Renin Activity, and Plasma Aldosterone Concentration

No.	Age (y.o.)	Control			Angiotensin II		
		B.P. mmHg	PRA ng/ml/h	PAC ng/100 ml	B.P. mmHg	PRA ng/ml/h	PAC ng/100 ml
1	30	171/100	3.1	14.2	184/112	2.5	19.2
2	41	160/91	0.5	10.1	184/122	0.6	20.6
3	42	234/134	0.3	9.1	254/148	0.1	19.7
4	45	198/100	1.1	5.5	212/121	1.1	12.8
5	34	161/94	2.2	13.1	174/108	0.8	16.4
6	54	158/100	0.4	6.7	174/127	0.3	19.4
7	40	204/114	0.4	5.5	234/134	0.5	20.1
8	28	152/94	2.2	13.4	168/108	2.1	16.6
9	34	200/109	1.7	7.1	214/124	1.6	12.4
10	46	204/112	0.3	6.5	242/136	0.5	20.7
11	50	148/107	1.1	12.9	162/124	1.1	19.8
12	42	150/106	3.4	10.4	162/108	2.9	16.1
13	43	160/84	0.9	6.2	178/102	0.9	16.9
14	59	162/112	1.7	14.1	187/129	0.9	20.3
15	55	170/114	2.4	8.6	191/122	2.1	12.1
16	27	186/124	4.7	20.1	192/131	4.5	22.7
17	30	164/122	0.1	10.1	180/147	0.1	26.1
18	24	162/100	1.4	7.8	180/126	1.3	15.9
19	47	162/94	0.0	12.4	204/125	0.1	15.8
20	30	172/104	7.7	33.7	178/103	7.4	36.7
21	46	154/104	2.9	24.5	164/112	2.7	29.8

B.P., PRA, and PAC mean blood pressure, plasma renin activity, and plasma aldosterone concentration, respectively.

Fig. 3. Relation between changes of mean blood pressure and pre-infusion levels of PRA in angiotensin II infusion. A negative correlation ($r = -0.893$, $p < 0.001$) is observed.

Fig. 4. Relation between changes of PAC and pre-infusion levels of PRA in angiotensin II infusion. A significant negative correlation ($r = -0.754$, $p < 0.001$) is found.

A significant negative correlation ($r = -0.893$, $p < 0.001$) was observed between the changes of mean blood pressure and the values of PRA at the end of control period (Fig. 3).

PAC was increased from 12.0 ± 6.9 to 19.5 ± 5.8 ng/100 ml ($p < 0.01$) after the infusion. There was a high significant correlation ($r = -0.754$, $p < 0.001$) between the changes of PAC and pre-infusion values of PRA (Fig. 4).

PRA was slightly decreased from 1.83 ± 1.84 to 1.62 ± 1.74 ng/ml/h after the infusion.

DISCUSSION

We have previously shown that specific receptor for angiotensin II exists in both the vascular smooth muscle and the adrenal cortex in experiments using angiotensin II and its competitive antagonist.^{15),16)} Recent studies, however, have demonstrated the presence of specific receptor for angiotensin III in the adrenal cortex in rat¹⁷⁾ and in aorta in rabbit.¹⁸⁾ The present studies have elucidated that angiotensin III has biologic activity, suggesting existence of the vascular and the adrenocortical receptors for angiotensin III in man. Our experiments indicate that the effect of the heptapeptide upon aldosterone production is superior to that upon vasoconstriction, when compared with angiotensin II activity. These results are similar to those preliminarily demonstrated by several investigators.^{19),20)}

Dietary sodium deprivation is followed by enhanced activity of the renin-angiotensin-aldosterone system as manifested by increased plasma renin activity and aldosterone secretion.²¹⁾ In the present study, vascular and adreno-

cortical sensitivities to injected angiotensin II on normal sodium intake were low in the patients with high levels of renin activity. On the other hand, the responses were heightened in the patients with low renin activity. To explain this phenomena, one can speculate that, when amount of endogenous angiotensin II is low, these vascular and adrenal receptors are less occupied, and that, therefore, it may result in amplifying the sensitivities to angiotensin II injections since the peptide exogenously given could bind to the unoccupied receptors in larger quantities.⁹⁾⁻¹¹⁾ Conversely, it may be also possible that, when amount of angiotensin II endogenously formed increases, unoccupied receptors decrease; therefore, the lessened sensitivities are caused because of decrease of receptors available to respond to exogenous angiotensin II. This speculation may be supported by the recent noteworthy reports of Marks et al²²⁾ and Wisgerhof and colleagues,²³⁾ in which they elucidated that patients with essential hypertension who had decreased levels of circulating angiotensin II had increased adrenocortical and vascular sensitivities to angiotensin II injection than patients with high levels of angiotensin II. It has been believed that angiotensin III may be derived from angiotensin II by the action of some kinds of peptidases,⁴⁾ and from this, one can predict that the more active the renin-angiotensin system, the higher levels of the heptapeptide originated from the octapeptide. Therefore, similar to angiotensin II injections, it is expected that the sensitivities of vascular smooth muscle and adrenal cortex to angiotensin III endogenously given are modulated by the number of unoccupied receptors available to respond to exogenous angiotensin III, that is, the lessened sensitivities should be observed when the renin-angiotensin system is active. Nevertheless, our results are contrary to those anticipated from the aldosterone response. This suggests that angiotensin-induced aldosterone production in patients with essential hypertension, especially, when their renin systems are active, depends not so much upon angiotensin II as upon angiotensin III via its receptor, and the possibility that angiotensin II and III act upon different receptor sites in the adrenal cortex. Recent studies in normal man have shown that dose-response curves for the 2 peptides with regard to aldosterone secretion were not parallel,¹²⁾ which was taken as evidence that the 2 peptides acted upon different adrenocortical receptors. Furthermore, angiotensin III has been reported to have higher affinity than angiotensin II for the adrenal receptor in rat.¹⁷⁾ On the other hand, circulating angiotensin III concentration in normal human arterial blood is reported to be lower than that of angiotensin II; the concentration is physiologically only about 20% of angiotensin II, while angiotensin III has almost equal aldosterone stimulating property to angiotensin II.²⁴⁾ These suggest a significant role of the heptapeptide in aldosterone production.

In the present study, both peptides equivalently suppressed renin release. This confirms the results of Steele et al⁵⁾ in the rabbit and Carey and colleagues in normal man.¹²⁾ The mechanism of the inhibitory effect on renin secretion is not clarified completely, but the data previously reported are consistent with feedback inhibition of the peptide at the juxtaglomerular apparatus.^{25), 26)} A renal hemodynamic change also may be possible to explain the mechanism of renin suppression, but the marked differences in renal vasoconstrictor effects of the 2 peptides in dog, rabbit, and perfused kidney²⁷⁾ do not account for equivalent suppression of renin release by the both peptides. However, since the present study did not assess renal hemodynamics in response to angiotensin II and III, the contribution of the mechanisms to the observed renin suppression remains to be clarified.

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