Symposium on the Etiology and Treatment of Hypertension*

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(1) The Interaction of Renin-Angiotensin-Aldosterone System and Renal Depressor System

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Numerous studies on hypertension have been done from the concept that the elevation in blood pressure is mediated by an activation of pressor system. However, some different approaches to the possible etiology of human essential hypertension have been undertaken during the last decades. The principle underlying this latter concept is that high blood pressure is not necessarily due solely to the overactive pressor mechanism but may be due to a deficiency in vasodilating and antihypertensive mechanisms^{1~3}).

Kinins and prostaglandins are vasodilating substances naturally generated in the kidney, vascular beds and other organs. The previous animal experiments and clinical studies have shown that there are close interrelations among kinin system, prostaglandin system and renin-angiotensin-aldosterone system^{4~7}. Thus, possibilities exist that renal PGE and kallikrein-kinin

system may regulate blood pressure by opposing the action of renin-angiotensin-aldosterone system in human subjects and that the impairment of production of renal PGE and kallikrein in essential hypertension may play some roles in the pathogenesis of this disease. To investigate these possibilities, we examined interrelationships among renal PGE, renal kallikrein-kinin system and the renin-angiotensin-aldosterone system in normal volunteers and in patients with essential hypertension.

MATERIALS AND METHODS

Healthy subjects and hypertensive patients described in protocol were included in this study. Hypertensive patients had blood pressures of 150 mmHg in systolic and 90 mmHg in diastolic or higher on repeated observations. They were allowed to be on unrestricted Na diet and anti-hypertensive medications had been discon-

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tinued at least 2 weeks before study.

Protocol

1) Low Na diet: Ten patients received firstly a diet containing 200 mEq of Na per day for a week and then 100 mEq and finally 30 mEq of Na each for 3 days, and the 24 hour's urine was collected on the last day of each period and the blood sampling was done on the next morning after overnight fasting.

2) Furosemide iv and an upright posture: Sixteen normal subjects were allowed to take an unrestricted diet for 2 weeks. They were fasted overnight, and kept supine for 1 hr on the next morning, then sampling of blood and urine was done. Then, furosemide (1 mg/kg) was injected intravenously and the subjects were asked to assume an upright posture for 120 minutes. At 30 (F30) and 120 (F120) minutes after furosemide administration, blood and urine samples were collected.

3) Administration of spironolactone: Three patients with essential hypertension were allowed to take an unrestricted diet for 2 weeks and then, spironolactone (100 mg/day) was given for a week. Sampling of blood and urine was done before and at the end of the spironolactone administration.

4) Sodium deprivation and addition of indomethacin: Thirteen hypertensive patients were given a diet containing 90 mEq/day of Na with the oral administration of furosemide (80 mg/day) for 3 days, and then, the oral administration of indomethacin (150 mg/day) was added for additional 3 days. Sampling of blood and urine was done before and at the end of each 3 days period.

5) Administration of captopril and indomethacin: Nineteen hypertensive patients who responded to captopril by 10 mmHg or greater lowering of blood pressure were given placebo 3 times daily for 2 weeks and then captopril was administered. After the administration of effective doses of captopril (75-300 mg/day) for a week, indo-

methacin (75-150 mg/day) was added for the additional 3 days. The sampling of blood and urine was done at the control period and at the end of each period of medication.

Measurement of urinary PGE: Urinary PGE was measured radioimmunologically by the method⁷⁾ already described.

Measurement of urinary kallikrein: Urinary kallikrein activity was measured as kininogenase activity using radioimmunoassay of kinin⁸⁾ and by TAME esterase activity.

Measurement of plasma renin activity: PRA was determined by means of radioimmunoassay of angiotensin I.

Measurement of aldosterone: PAC and urinary aldosterone were measured with a commercial radioimmunoassay kit (Cer Ire Sorin).

Urinary Na⁺ and K⁺ were measured with an autoanalyzer. All results were expressed as mean $\pm$ SEM. The significances between mean values were evaluated by Student's t-test.

RESULTS

1) Influence of low Na diet: PRA, PAC and urinary kallikrein excretion increased after dietary sodium depletion. On the contrary, urinary Na and PGE excretion decreased. The changes in urinary kallikrein excretion were closely related to those of renin-angiotensin-aldosterone system after sodium depletion, whereas a dissociation occurred between urinary PGE excretion and renin-angiotensin-aldosterone system or urinary kallikrein excretion.

3) Effect of furosemide: As shown in Fig. 1, PRA and PAC were continuously increased up to 120 minutes after the administration of furosemide, and maximum values were found at F120. On the other hand, urinary excretion of PGE and PGF₂ α rapidly increased during the first 30 minutes after the furosemide injection. Subsequently it decreased and returned to the control level at 120 minutes. On the contrary, urinary excretion of PGF₂ α -metabolite de-

(1) The Interaction of Renin-Angiotensin-Aldosterone System

Fig. 1. Mean changes in PRA, PAC and urinary excretion of sodium, PGE, PGE_{2α} and PGF_{2α}-main urinary metabolite (PGF_{2α} MUM) following furosemide injection (1 mg/Kg) and upright posture in 16 normal subjects. C=control period, F30=30 minutes after the furosemide injection, and F120=120 minutes after the furosemide injection. *Values significantly different from control values ($p<0.05$); ** $p<0.01$; *** $p<0.005$.

creased continuously after the furosemide administration. There were significant correlations between urinary excretion of PGE and that of kallikrein ($r=0.65$) or PGF_{2α} ($r=0.56$). However, no significant correlation was found between urinary excretion of PGE and PRA or PAC, between urinary excretion of kallikrein and PRA or PAC, and between urinary excretion of PGF_{2α} and PRA or PAC after the administration of furosemide. There were significant correlations between urinary excretion of Na and that of PGE ($r=0.71$) or kallikrein ($r=0.61$), and between urine flow and urinary excretion of PGE ($r=0.72$) or kallikrein ($r=$

0.62).

3) Effect of spironolactone: Urinary excretion of kallikrein gradually decreased while urinary excretion of PGE and Na increased on the first day of the spironolactone administration and then, decreased gradually to control level.

4) Effects of the sodium deprivation and indomethacin: PRA was markedly increased after the administration of furosemide with low Na diet in all subjects, while urinary PGE excretion was not increased. PRA was completely decreased after the addition of indomethacin in all subjects. The changes of PAC were similar to those of PRA. Urinary excretion of PGE was also significantly decreased, and that of kallikrein and Na tended to decrease, respectively, following the indomethacin administration.

As shown in Fig. 2, mean blood pressure was increased in 5 patients out of 11 with essential hypertension with average increase of 16.2 ± 3.4 mmHg after the addition of indomethacin, while less hypertensive or hypotensive response with average change of -0.5 ± 2.3 mmHg was found in the remaining 6 patients. There was a significant difference between average change of mean blood pressure in 2 groups ($p<0.01$). In indomethacin responsive hypertensive group,

Fig. 2. Changes in mean blood pressure following the sodium deprivation and the additional administration of indomethacin in 5 patients of responder and in 6 of non-responder.

mean blood pressure was decreased with average change of -17.4 ± 2.8 mmHg after the administration of furosemide associated with low sodium diet, while less hypotensive or hypertensive response with average decrease of -0.8 ± 3.0 mmHg was found in indomethacin non-responsive hypertensive group. There was a significant difference in blood pressure responses after the sodium deprivation between 2 groups ($p < 0.05$). Indomethacin responsive hypertensive patients have relatively low basal levels of PRA and significantly less decrease of PRA by indomethacin as compared with indomethacin nonresponsive hypertensive patients ($p < 0.05$).

5) Effects of captopril and indomethacin: Captopril induced an equivocal reduction in blood pressure, a significant increase in PRA and urinary PGE excretion and a significant decrease in PRA and urinary kallikrein excretion. In contrast, indomethacin induced a significant increase

in blood pressure and a significant decrease in PRA, urine flow and urinary excretion of Na, K and PGE. As shown in Fig. 3, however, all patients were divided into 2 groups according to the patterns of the response of blood pressure and plasma renin activity. In 9 patients with low renin hypertension, the antihypertensive effect of captopril was attenuated after the inhibition of the endogenous PG generation by indomethacin, while no significant change in blood pressure was found and the hypotensive effect of captopril continued in 10 patients with normal renin hypertension. The enhanced renin release induced by captopril in the latter was completely inhibited after the addition of indomethacin, while no significant change in PRA was found in the former.

DISCUSSION

In 1975, Kaizu and Margolius⁶⁾ have reported that the release of kallikrein in the rat renal cortical cell suspension is increased by aldosterone and reduced by spironolactone, indicating that the release of renal kallikrein is regulated by aldosterone or other sodium retaining steroid hormones. In the present study, changes in urinary excretion of kallikrein were closely related to those in PRA and PAC after the addition of various stimuli such as low sodium diet or the administration of furosemide, angiotensin converting enzyme inhibitor or spironolactone, indicating that renal kallikrein-kinin system may be involved in the regulation of blood pressure by opposing the action of renin-angiotensin-aldosterone in dynamic fashion.

According to the reports by McGiff and his associates⁴⁾, intrarenal arterial infusion of angiotensin II induces an augmentation of PGE release in the venous effluent in the dog, suggesting that angiotensin II may be a regulator of renal PGE release. In our data, however, urinary PGE excretion was not increased after the sodium deprivation in spite of the augmentation of the renin-angiotensin system. The changes in urinary

Fig. 3. Effects of captopril and indomethacin on mean blood pressure and plasma renin activity in 10 cases of normal renin hypertension and in 9 of low renin hypertension.

PGE excretion were closely related to those in urinary sodium output after various stimuli, suggesting that renal PGE may contribute to the regulation of blood pressure by means of renal sodium handling.

There are several papers indicating that renal PGs may be involved in the renin release mechanism in experimental animals^{9,10}. The present data that the augmented renin release induced by the sodium deprivation or the captopril administration was completely inhibited by the addition of indomethacin indicate that renal PG may contribute to the macula densa mechanism or the negative short feedback mechanism of renin release in human.

The previous animal experiments and clinical studies have shown that the orally active inhibitor of angiotensin I converting enzyme, captopril, lowered blood pressure by means of the inhibition of the renin-angiotensin-aldosterone system¹¹. However, there is a evidence that captopril lowers blood pressure in the patients with low renin hypertension¹². What is the hypotensive mechanism of captopril in low renin hypertension? The inhibition of the renin-angiotensin-aldosterone system may not contribute to the hypotensive mechanism of captopril in them, because they are non-renin dependent hypertension. In the present data, hypotensive effect of captopril was abolished after the inhibition of the endogenous PG system by indomethacin, suggesting that captopril may augment a vasodilating PG system which may contribute to hypotensive effect of captopril. In contrast, the inhibition of the renin-angiotensin system may be a prime hypotensive mechanism of captopril in normal renin hypertension. In the present data, indomethacin also induced an increase in blood pressure in some patients under the sodium depleted status, and the hypotensive effect induced by the sodium deprivation was completely abolished after the inhibition of endogenous PG system by indomethacin. In the present data, salt sensitive hypotensive patient having low basal levels of PRA

and less responses of the renin-angiotensin system after the sodium deprivation and the addition of indomethacin was included in the patient who showed hypertensive response to indomethacin, indicating that endogenous PG system may be involved in the pathogenesis of hypertension in salt sensitive hypertensive patient. In contrast, the remaining patients having normal-high levels of basal PRA and hyperresponses of the renin-angiotensin system to the sodium deprivation or the addition of indomethacin showed no change of blood pressure in each stage, suggesting that the exaggerated responses of the renin-angiotensin system to the sodium deprivation or exaggerated inhibition of the renin-angiotensin system by the addition of indomethacin may manipulate no change of blood pressure. The present data indicate that the maintenance mechanism of hypertension was different in low renin hypertension and in normal-high renin hypertension.

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(2) Recent Advances in Clinical Application of Blockers of Renin-Angiotensin System

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The development of specific inhibitors of the renin-angiotensin system had led to great advances in clinical investigation of hypertension. Many inhibitors have been introduced in the clinical area. In the present symposium we present our results on angiotensin II antagonists (AIIA) and converting enzyme inhibitors (CEI).

I. Advances in renin-angiotensin inhibitors

Inhibitors of renin-angiotensin system are useful tools for the investigation of etiology or pathophysiology of hypertension in human as well as in hypertensive models. Various kinds of renin-angiotensin inhibitors are listed in Table I. Among these many inhibitors, AIIA and CEI have been applied for clinical use. AIIAs have used as diagnostic drugs for renin-dependent hypertension and captopril, an orally active CEI, has been used as antihypertensive agent. The usefulness of both drugs have been demonstrated, however, limitations or

adverse reactions have been also shown. New potential agents which blocks renin-angiotensin system have been under development.

II. Clinical application of AIIA

a) Effects of AIIA and sodium balances: Since 1973, two AIIAs, [Sar¹, Ala⁸]AII (saralasin) and [Sar¹, Ile⁸]AII, have been widely used clinically¹³. We have shown that [Sar¹, Ile⁸]AII, acts as antagonist when the patient's renin-angiotensin system is activated and as agonist when its system is suppressed at AII receptors in vasculature, adrenal cortex and juxta-glomerular apparatus. Antagonistic and agonistic effects of both two analogues are affected by sodium balances of the subject. Sodium depletion potentiated the antagonistic effects of both compounds²⁹.

b) Diagnosis of renin-dependent hypertension by AIIA: AIIA is mainly used as a tool for the screening of renin-dependent hypertension especially renovascular hyper-