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Effects of Indomethacin on Plasma Renin Activity, Plasma Aldosterone Concentration, Urinary Prostaglandin E Excretion and Blood Pressure in Patients with Essential Hypertension

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YASUJIMA, M., ABE, K., CHIBA, S., SATO, M., IROKAWA, N., IMAI, Y., SAITO, K., SAKURAI, Y., ITO, T., RITSU, K., HARUYAMA, T., OTSUKA, Y. and YOSHINAGA, K. *Effects of Indomethacin on Plasma Renin Activity, Plasma Aldosterone Concentration, Urinary Prostaglandin E Excretion and Blood Pressure in Patients with Essential Hypertension.* Tohoku J. exp. Med., 1979, **128** (1), 31-37 —— To investigate the interrelationship between the renin-angiotensin-aldosterone system and prostaglandin system, plasma renin activity, plasma aldosterone concentration, urinary sodium excretion, urinary prostaglandin E excretion and blood pressure were determined before and after administration of indomethacin, a prostaglandin synthetase inhibitor, during sodium depletion with furosemide administration and low sodium diets in 11 patients with essential hypertension. With the addition of indomethacin, plasma renin activity decreased from 52.9±8.6 ng/ml to 8.5±1.3 ng/ml, plasma aldosterone concentration from 20.4±3.7 ng/100 ml to 5.4±1.3 ng/100 ml, and urinary prostaglandin E excretion from 330.1±58.8 ng/day to 168.8±32.8 ng/day. Significant positive correlation was found between the change of plasma renin activity and that of urinary prostaglandin E excretion ($r=0.73$, $p<0.01$). The addition of indomethacin did not produce any significant change in urinary sodium excretion (from 78.0± 10.6 mEq/day to 61.2±11.6 mEq/day); whereas indomethacin administration diminished the hypotensive effects of furosemide administration and low sodium diets. The present results show that renal prostaglandin E may be one of the regulators of renal renin release, and that the use of indomethacin, an anti-inflammatory drug frequently prescribed in recent years, may diminish the hypotensive effects of furosemide and other diuretics. ——— indomethacin; sodium depletion; renal prostaglandin system; renin-angiotensin-aldosterone system; essential hypertension

It has been proposed that the renin-angiotensin-aldosterone system and the prostaglandin system interact in a complicated manner to regulate systemic blood pressure and water electrolyte homeostasis. It is well known that release of renin is stimulated by furosemide administration as well as by low sodium diets (Davis and Freeman 1976). Recent studies show that the increase in plasma

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renin activity, natriuresis and hypotensive effect of furosemide administration may be mediated, at least in part, by the renal prostaglandins (Patak et al. 1975; Romero et al. 1976). Furthermore, many reports suggest that prostaglandins may play a role in aldosterone secretion (Fichman et al. 1972; Saruta and Kaplan 1972).

The present study was designed to investigate the interrelationship between the renin-angiotensin-aldosterone system and renal prostaglandin system. To achieve the purpose described above, the effects of indomethacin, a prostaglandin synthetase inhibitor, on plasma renin activity, plasma aldosterone concentration, urinary sodium excretion, urinary prostaglandin E excretion and blood pressure were studied during the activation of renin-angiotensin-aldosterone system by two stimuli, furosemide administration and low sodium diets, in patients with essential hypertension.

Patients and Methods

Eleven patients with essential hypertension who had normal renal function were studied in Tohoku University Hospital. They consisted of 5 men and 6 women, aged from 22 to 59 with an average of 37.

All medications were stopped for at least 2 weeks prior to the study. Subjects were given 200 mEq/day of sodium for 7 days to achieve equilibration with this diet. This period was used as a control. Then, diets containing 100 mEq/day of sodium and furosemide, 40 mg orally every 12 hr, were given for 6 days, and indomethacin, 50 mg orally every 8 hr, was added for 3 days in the latter half of this period.

Sampling of peripheral vein blood for plasma renin activity and plasma aldosterone concentration was done from fasting subjects the next morning of the last day of each period. Collection of 24 hr urine for urinary sodium excretion and urinary prostaglandin E excretion was done on the last day of each period. Blood pressures were monitored with a sphygnomanometer immediately before the sampling of peripheral vein blood.

Plasma renin activity was measured by our modified method of Haber et al. using radioimmunoassay of angiotensin I (Abe et al. 1972). This procedure consisted of 6 hr incubation of 1 ml of plasma, at pH 5.5, with disodium ethylene-tetraacetic acid and diisopropyl fluorophosphate, and the radioimmunoassay of angiotensin I generated during the incubation. Plasma aldosterone concentration was also determined by radioimmunoassay with commercial kits after extracted with ethyl acetate. Urinary prostaglandin E excretion was determined as described previously (Abe et al. 1977; Yasujima et al. 1978).

Results

The effects of indomethacin on plasma renin activity, plasma aldosterone concentration, urinary sodium excretion and urinary prostaglandin E excretion during sodium depletion

In all subjects, plasma renin activity and plasma aldosterone concentration increased during furosemide administration and low sodium diets and reduced to the control level following the administration of indomethacin. Plasma renin activity increased from 8.1 ± 3.0 ng/ml (mean$\pm$S.E.) to 52.9 ± 8.6 ng/ml, and plasma aldosterone concentration also increased from 5.7 ± 1.0 ng/100 ml to 20.4 ± 3.7 ng/100 ml by the two procedures of provocation. The addition of indomethacin

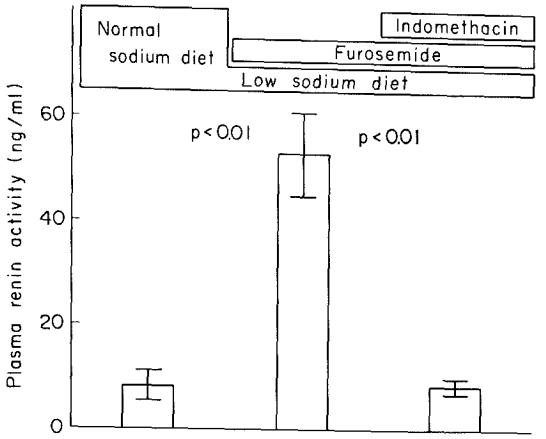

Fig. 1. Changes in plasma renin activity during sodium depletion and during indomethacin treatment with sodium depletion in 11 patients with essential hypertension.

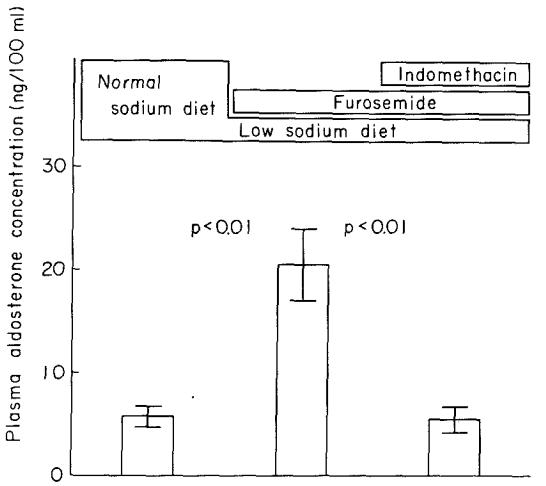

Fig. 2. Changes in plasma aldosterone concentration during sodium depletion and during indomethacin treatment with sodium depletion in 11 patients with essential hypertension.

produced significant reductions of plasma renin activity to 8.5±1.3 ng/ml and of plasma aldosterone concentration to 5.4±1.3 ng/100 ml, respectively (Figs. 1, 2).

With furosemide administration and low sodium diets, urinary prostaglandin E excretion did not change significantly (from 301.0±62.3 to 330.1±58.8 ng/day). But urinary prostaglandin E excretion significantly decreased to 168.8±32.8 ng/day after the administration of indomethacin (Fig. 3).

During furosemide administration and low sodium diets, the addition of indomethacin did not produce any significant change in urinary sodium excretion (from 78.0±10.6 to 61.2±11.6 mEq/day).

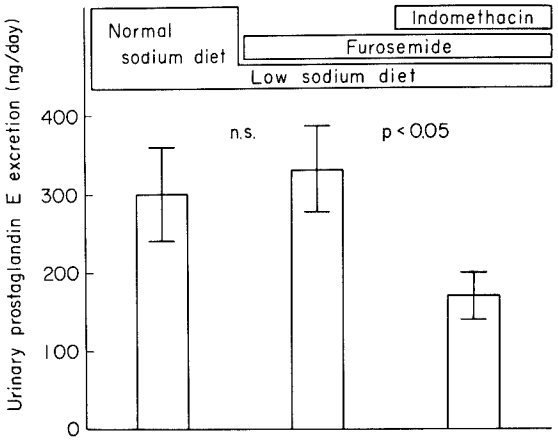

Fig. 3. Changes in urinary prostaglandin E excretion during sodium depletion and during indomethacin treatment with sodium depletion in 11 patients with essential hypertension.

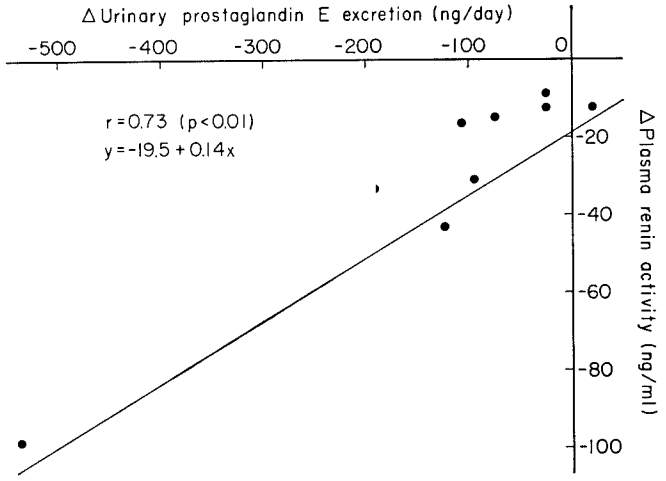

Fig. 4. Relationship between the change in plasma renin activity and that in urinary prostaglandin E excretion after indomethacin treatment in 11 patients with essential hypertension.

Fig. 4 shows the correlation between the changes of plasma renin activity and of urinary prostaglandin E excretion after the addition of indomethacin. Significant positive correlation was found between them. There was no correlation between the changes of plasma aldosterone concentration and of urinary prostaglandin E excretion. No significant correlation was found between the changes in urinary sodium excretion and in plasma renin activity, in plasma aldosterone concentration, or in urinary prostaglandin E excretion after the administration of indomethacin.

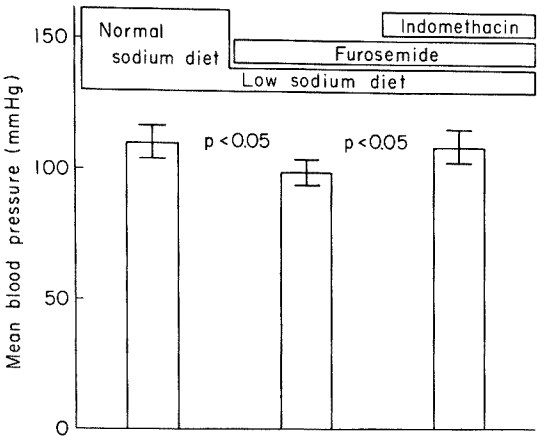

Fig. 5. Changes in blood pressure during sodium depletion and during indomethacin treatment in 11 patients with essential hypertension.

Blood pressure response to indomethacin during sodium depletion

In 6 out of 11 subjects, blood pressure lowered after furosemide administration and low sodium diets and returned to the control level with the addition of indomethacin. In the remaining 5, blood pressure did not change significantly after furosemide administration and low sodium diets. The addition of indomethacin had no effect on their blood pressures. Mean blood pressure dropped from 108.3 $\pm$6.6 mmHg to 100.8$\pm$5.2 mmHg after furosemide administration and low sodium diets. When indomethacin was added, mean blood pressure elevated to the control level of 107.8$\pm$6.1 mmHg. With indomethacin administration, the hypotensive effect of sodium depletion with furosemide administration and low sodium diets was diminished (Fig. 5).

Discussion

The important observation in the present study is the inhibition of the effects of sodium depletion with furosemide administration and low sodium diets on plasma renin activity, plasma aldosterone concentration and blood pressure by treatment with indomethacin.

In our previous report, we showed that the injection of furosemide as a bolus induced increases in urine volume and urinary sodium excretion together with an increase in urinary prostaglandin E excretion in normal subjects and essential hypertensives (Abe et al. 1977). It had been known that furosemide might modify the catabolism of the prostaglandin system through the effects on 15-hydroxy dehydrogenase and 9-ketoreductase (Hansen 1976; Stone and Hart 1976). Weber et al. (1976) also reported that furosemide induced an increase in arachidonic acid, known as a precursor of prostaglandin. Therefore, we proposed that diuretic and natriuretic effects of furosemide might be mediated in part by renal

prostaglandin. On the other hand, we observed a reduction in the excretion of urinary prostaglandin E in the face of an increase in renin-angiotensin-aldosterone system after sodium depletion (Yasujima et al. 1978). The failure of the increase in the excretion of urinary prostaglandin E during furosemide administration and low sodium diets in this experiment may be explained by the opposing effects of sodium and furosemide.

Though urinary prostaglandin E excretion did not exhibit the significant change after furosemide administration and low sodium diets, the present result might not necessarily rule out the correlation between renin-angiotensin-aldosterone and renal prostaglandin systems, because the effects of furosemide administration on urinary prostaglandin E excretion may be masked with low sodium diets, and because indomethacin, a prostaglandin synthetase inhibitor, induced a decrease in plasma renin activity and plasma aldosterone concentration. After the administration of indomethacin, the relationship between the changes in plasma aldosterone concentration and in urinary prostaglandin E excretion was lost, while there was a close correlation between the changes in plasma renin activity and in urinary prostaglandin E excretion. Indomethacin did not effect on urinary sodium excretion. The present data suggest that renal prostaglandin E plays a role in the regulation of renin release during furosemide administration and low sodium diets and that the decrease in plasma aldosterone concentration after the indomethacin treatment is secondary to the decrease in plasma renin activity.

The depressor effects of sodium depletion with furosemide administration and low sodium diets cannot be explained only by acute volume depletion. Though a decrease in body weight of about 1.5 kg was observed in all subjects, the addition of indomethacin during furosemide administration and low sodium diets induced an elevation of blood pressure without any changes in urinary sodium excretion or body weight. It is well known that prostaglandin in vascular wall may modulate the effects of pressor substances, angiotensin II and noradrenaline (Vane and McGiff 1975). The pressor effect of indomethacin may be due to the inhibition of prostaglandin synthesis in the vascular wall. To understand the hypotensive effects of furosemide administration and low sodium diets, it is necessary to know the role of prostaglandin in the vascular wall.

The present results show that renal prostaglandin E may play a role in the secretion and release of renin. Furthermore, the present experience suggests that the use of indomethacin, as an anti-inflammatory drug, may impair the hypotensive effects of furosemide and other diuretics.

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