Effect of Prostaglandin E₁ on Renin and Aldosterone in Hypertensive Patients

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Synopsis

The effect of prostaglandin E₁ (PGE₁) on plasma renin activity (PRA) and plasma aldosterone concentration (PAC) was studied in the hypertensive subjects treated with or without 75 mg indomethacin or 60 mg propranolol for a week. Subsequent to the treatment with indomethacin for a week, PRA and PAC levels were decreased as compared to the control, without changes in the blood pressure and heart rate. During the infusion of PGE₁, the blood pressure was decreased and the pulse rate was increased. PRA and PAC levels were also elevated. These changes of parameters were not different between the control and the indomethacin-treated subjects. PRA and PAC were suppressed after the treatment with propranolol. With the infusion of PGE₁, the level of PRA was not significantly elevated, while, PAC was significantly increased by the infusion of 100 ng/Kg/min of PGE₁. During the infusion of PGE₁, the blood pressure was decreased while the pulse rate was increased in the subjects treated with propranolol. However, the elevation of the pulse rate was less remarkable than the control. These data indicate that PGE₁ have important roles in the regulation of the release of renin and aldosterone. These findings also suggest that PGE₁ may act to stimulate the secretion of aldosterone in man.

Prostaglandins of E series (PGEs) cause vasodilatation and natriuresis and these factors may play important roles in the regulation of blood pressure. The vasodilating effect of PGEs may be mediated by the changes in circulating blood levels of the hormones or by alterations in concentration of PGEs in vascular walls (Anderson et al., 1976). It is believed that PGEs have an important role in the regulation of the renin-angiotensin-aldosterone system. Many investigations have been reported about the effect of exogenous PGEs on renin and aldosterone, and also about the effect of an inhibitor of PGs synthesis on renin and aldosterone (Fichman et al., 1972; Fölich et al., 1976; Golub et al., 1976).

These investigations indicate that endogenous PGEs may act to stimulate the release of renin. Similarly many studies examining the effect of PGs on aldosterone secretion have been performed. As aldosterone secretion is regulated by the trophic stimuli of angiotensin II (A II) and ACTH and also by potassium and a decreased serum sodium, it is hard to estimate the single factor that stimulates aldosterone secretion during the administration of PGEs. Fichman et al., (1972) demonstrated that nonvasodepressor doses of prostaglandin A₁ (PGA₁) increased plasma aldosterone concentration (PAC) in the absence of a rise in plasma renin activity (PRA) in

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man. On the contrary, Blair-West et al., (1971) could not observe consistent aldosterone stimulation with PGE$_1$ in sheep. Therefore, there is insufficient evidence to establish conclusively that PGs may participate in the physiological regulation of aldosterone secretion.

Consequently, we have designed the following studies, using subjects with essential hypertension to show the effect of PGE$_1$ on PRA and PAC under the treatment of indomethacin or propranolol which is known to suppress PRA.

**Materials and Methods**

**Subjects**

Fourteen subjects with essential hypertension participated in the study. In all, diastolic blood pressure was elevated to a level above 96 mm Hg at least in two separate outpatient visits. Antihypertensive medications were discontinued for at least 2 weeks prior to study. Nine subjects (four female and five male) who ranged in age from 31 to 62 years were under hospital admission, and five subjects (three female and two male) who ranged in age 41 to 58 years were on an outpatient basis. The hospital admitted patients were restricted to a daily intake of sodium (85 mEq/day), while the outpatients were not on a salt restricted diet.

**Experimental Protocol**

In the morning while in a fasting state, the subjects were kept recumbent, while their blood pressure and pulse were monitored every 2 min with an automatic blood pressure measuring apparatus (Ueda Electronics Works).

After an infusion of 5% glucose solution for 30 min a blood sample was drawn. PGE$_1$ was infused in a dose of 50 ng/Kg/min for 30 min. Then the dose of PGE$_1$ was doubled to 100 ng/Kg/min for 30 min. Blood specimens were obtained at 30 min after each dosage. PGE$_1$ was diluted with 5% glucose solution. After the infusion study as the control, 75 mg indomethacin was administered to six subjects, and 60 mg propranolol was administered to six subjects for a week. After the treatment with indomethacin or propranolol for a week, the PGE$_1$ infusion and blood sampling were performed in the same way as previously described.

**Laboratory studies**

PRA was measured by radioimmunoassay using a modification of the technique described by Haber et al. (1969). PAC was measured by radioimmunoassay using the procedure of a nonchromatographic non-extraction radioimmunoassay (Ogihara et al. 1977). The data from the paired experiments were compared using a paired t test.

**Results**

**Effect of indomethacin on PRA and PAC**

After the treatment with indomethacin, PRA level was significantly ($P<0.01$) decreased in the subjects with essential hypertension as shown in Fig. 1. The blood pressure and pulse rate did not change remarkably before or after the treatment with indomethacin.

**Effect of PGE$_1$ on PRA and PAC**

The effect of PGE$_1$ on PRA and PAC levels, with or without indomethacin treat-
ment, is demonstrated in Fig. 2. As described previously, the reduction of PRA and PAC levels was observed after the treatment with indomethacin. The infusion of PGE\textsubscript{1} induced a significant increase in PRA (P<0.05) and PAC (P<0.05 and 0.01) levels.

The effect of PGE\textsubscript{1} on PRA and PAC levels, with propranolol treatment, is illustrated in Fig. 3. A decrease of PRA and PAC levels was observed after the treatment with propranolol. The level of PRA treated with propranolol was not increased significantly even after the infusion of PGE\textsubscript{1}. The level of PAC was not increased after the infusion of 50 ng/kg/min of PGE\textsubscript{1}, however it was significantly (p<0.05) increased after the infusion of 100 ng/kg/min.

**Effect of PGE\textsubscript{1} on blood pressure and pulse rate**

The blood pressure and pulse rate changes caused by the varying PGE\textsubscript{1} doses are illustrated in Fig. 4. A decrease of the mean blood pressure and an increase of pulse rate were observed statistically significantly (P<0.05) after the PGE\textsubscript{1} infusion. There was no difference of vascular response to PGE\textsubscript{1} before and after the treatment with indomethacin. Statistically significant (P<0.05) differences of pulse rates in response to PGE\textsubscript{1} were observed.

![Fig. 2. Effect of prostaglandin E\textsubscript{1} (PGE\textsubscript{1}) infusion on plasma renin activity (PRA) and plasma aldosterone concentration (PAC) (mean±SEM, n=6) in patients treated with or without indomethacin for a week. Star symbols denote differences between before and after infusion of PGE\textsubscript{1} (*: p<0.05, **: p<0.01).](image)

![Fig. 3. Effect of prostaglandin E\textsubscript{1} (PGE\textsubscript{1}) infusion on plasma renin activity (PRA) and plasma aldosterone concentration (PAC) (mean±SEM, n=6) in patients treated with or without propranolol 60 mg for a week. Star symbols denote differences between before and after infusion of PGE\textsubscript{1} (*: p<0.05, **: p<0.01).](image)
before and after treatment with propranolol. However, there was no difference in blood pressure in response to PGE₁ before and after the treatment with propranolol.

**Discussion**

PGEs may play an important role physiologically in the regulation of the renin-angiotensin-aldosterone system. The suppression of PRA and PAC after the administration of indomethacin was reported in patients with essential hypertension and in the normal volunteers, and this effect was associated with a substantial reduction in the urinary excretion of PGE (Frölich et al., 1976). Since indomethacin is the inhibitor of prostaglandin synthetase (Vane, 1971), endogenous PGE₁ has the predominant role of stimulating renin release and regulating blood pressure. In animal studies, indomethacin inhibited the renin release in rabbits (Larsson et al., 1974). In the similar ways, a significant increase of PRA was observed by the infusion of PGE₁ in dogs (Werning et al., 1971). PGE₁ stimulated the release of renin from cell suspensions of rabbit renal cortex (Dew and Michelakis, 1974). These investigations along with our results suggest that endogenous and exogenous prostaglandins may act to stimulate renin release.

The effect of PGs on the secretion of aldosterone is still obscure at present. Administration of nonvasodepressor doses of PGA₁ induced the increase of PAC in the absence of a rise of PRA in man (Fichman et al., 1972). The above result indicates that PGA₁ may act to stimulate the secretion of aldosterone. Indomethacin also suppressed the level of PAC in the present study. On the contrary, Blair-West et al., (1971) could not demonstrate the increase of aldosterone secretion with the infusion of PGE₁ in sheep. PGEs were also demonstrated to enhance the in vitro biosynthesis of aldosterone in rats (Spät and Józan, 1975). In the present study, chronic treatment with propranolol suppressed the PRA levels in hypertensive subjects, while the infusion of PGE₁ did not demonstrate an elevation of PRA, although with a high dose of PGE₁, PAC was significantly elevated. These results indicate that PGE₁ may also stimulate the secretion of aldosterone in human subjects.

The mechanism of PGEs-induced stimulation of renin release is unclear at present. Golub et al., (1976) suggested that the PGA₁-induced release of renin was not the result of natriuresis. The suppression of PRA by indomethacin is associated with some degree of the retention of sodium, however Frölich et al., (1976) found that complete suppression of PRA response to
Furosemide infusion was observed under the treatment of indomethacin and they concluded that indomethacin lowered PRA with a reduction in renal PG synthetase activity. The mechanism of PGEs-induced stimulation of aldosterone secretion is also unclear. The renin-angiotensin system is a dominant regulator of aldosterone secretion, and an increase of aldosterone secretion in sodium depletion or natriuresis is believed to be enhanced by the increase of circulating level of renin and angiotensin II (Brown et al., 1972). An increase of aldosterone due to natriuresis by the infusion of PGE1 should be considered, however no increase of renin release by PGE1 was observed under the treatment of propranolol in the present study. Therefore the direct action of PGE1 on the secretion of aldosterone may be suggested. The direct role in aldosterone secretion by PGE1 is compatible with the result of in vitro study (Spätt and Józan, 1975).

The dynamic relationship between PGEs and renin-angiotensin-aldosterone system is recognized in these studies. PGEs may also affect the vascular tone directly and modulate the response of vascular smooth muscle to other vasoactive agents (Vane and McGiff, 1975). These factors may correlate with each other for the regulation of blood pressure. After the treatment with indomethacin, blood pressure changes induced by PGE1 were not different from the control in the present study.

After the treatment with propranolol the PGE1-induced elevation of pulse rate was suppressed as compared to the control, however, the PGE1-induced reduction of blood pressure was not different from the control. Under the infusion of PGE1, blood pressure was decreased along with the elevation of PRA and PAC. After the treatment with indomethacin or propranolol, the levels of PRA and PAC were decreased. However there was no difference in blood pressure as compared with the control. These phenomena suggest that the vascular sensitivity to vasoactive agents may change with treatment with indomethacin or propranolol in association with the suppression of PRA and PAC.

In conclusion, the reduction of the PRA and PAC levels was observed after the treatment with indomethacin in hypertensive subjects. The elevation of PRA and PAC levels was also observed after the infusion of PGE1. These elevations were noticed in subjects with or without the treatment with indomethacin. PRA was also suppressed by propranolol. However the infusion of PGE1 (100 ng/Kg/min) stimulates an increased PAC level without a correspondent elevation of PRA after the treatment with propranolol. These data suggest that PGE1 has a direct affection on the secretion of aldosterone.

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References


