The Effect of Prostaglandin A₁ on Renin and Aldosterone in Man

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SUMMARY  Blood pressure, pulse rate, plasma aldosterone (PA), renin, and cortisol were monitored during graded intravenous infusions of prostaglandin A₁ (PGA₁), 0.075-0.6 µg/kg min⁻¹, alone and superimposed on angiotensin II (A II) administration in five normal men. The infusions of PGA₁ did not affect blood pressure, but did progressively increase the pulse rate up to 15.2 ± 2.0 (SEM) beats/min at the highest prostaglandin dose (0.6 µg/kg min⁻¹). Both PA and plasma renin activity (PRA) increased in a dose-related fashion in response to the prostaglandin infusions. Aldosterone increased from a control of 4.8 ± 0.4 to 20.7 ± 1.2 ng/dl and PRA increased from 0.9 ± 0.1 to 5.4 ± 0.4 ng/ml hr⁻¹ at the dose of 0.6 µg/kg min⁻¹. The correlation between the aldosterone and renin values was r = 0.85, P < 0.001. In separate experiments, acute volume expansion with 2 liters of saline did not affect the increase in renin activity induced by exogenous prostaglandin. A II (5 ng/kg min⁻¹) increased aldosterone and blood pressure and decreased the pulse rate. The hemodynamic effects were progressively reversed by the superimposed prostaglandin infusions, but the observed changes in renin and aldosterone concentrations were not further altered. The PA response to A II infusions was not influenced by indomethacin pretreatment. Prostaglandin A₁ (infusion) appears to have a direct effect on renin release in man.

IT HAS BEEN PROPOSED that the E or A prostaglandins may play a role in regulation of blood pressure and body fluids. The predominant vascular action of these prostaglandins is to cause vasodilation, and their administration has lowered blood pressure in hypertensive subjects. Their activities on sodium and water balance, however, are contradictory. Renal artery infusions usually have induced a natriuresis. But there also is evidence for antinatriuretic activity. Fichman et al. infused subdepressor doses of prostaglandin A₁ (PGA₁) into normal subjects and noted an increase in plasma aldosterone (PA) that was unaccompanied by changes in serum electrolytes, cortisol, or bioassayable renin activity. This increase in aldosterone represented an augmentation of the secretion rate, because the metabolic clearance of aldosterone was minimally affected by the PGA₁ infusions. This possible direct stimulation of aldosterone production by certain doses of PGA₁ is supported by results of work in vitro by SpUt and Jozan, who observed increased production of aldosterone in rat capsular adrenal glands in response to both prostaglandin E₂ (PGE₂) and prostaglandin A₂ (PGA₂). Consequently, we have proposed a dual role for prostaglandins. Their vasodilatory action could antagonize the vasoconstriction caused by angiotensin II (A II) while their adrenal action could augment the stimulation of aldosterone secretion by the peptide. To investigate this hypothesis we have evaluated the responses of aldosterone, plasma renin activity (PRA), pulse rate, and blood pressure in man to graded infusions of PGA₁, A II, and the simultaneous administration of both materials.

Methods

SUBJECTS

Healthy male volunteers ranging in age from 25 to 56 years were hospitalized in the Clinical Research Center at the University of Southern California-Los Angeles County Medical Center for the duration of the studies. The diet was kept constant and provided 150 mEq of Na⁺ and 80 mEq of K⁺ daily. The subjects were fully informed as to the nature and risks of the procedures and agreed in writing to the studies, which were approved by the hospital Human Use Committee.

LABORATORY STUDIES

Serum electrolytes were measured with the hospital AutoAnalyzer (Technicon). Subject weights and 24-hour urinary electrolytes were obtained daily. PRA was determined by radioimmunoassay of generated angiotensin I by the method of Haber et al., with minor modifications. PA and cortisol were measured by specific radioimmunoassays previously reported from our laboratories. These assays all have a precision of about 10%. Sensitivities are 0.5 ng/dl for both the angiotensin I and the aldosterone immunoassays and 0.4 µg/dl for the cortisol assay.

INFUSION PROTOCOL

All studies were performed in the morning in fasting subjects who had been kept recumbent overnight. The materials were dissolved in sterile saline and delivered by a Harvard infusion pump at a rate of 0.382-0.764 ml/min. Blood pressure was monitored every 5 minutes with a standard sphygmomanometer by one of the authors who remained in attendance throughout the procedure. Blood pressure confirmations were performed by the other author.
with each subject. Blood pressure and pulse fluctuations due to the changing doses were noted to stabilize within 10 minutes. Blood samples were drawn from an indwelling, heparinized scalp vein needle in the contralateral upper extremity.

PGA, INFUSIONS

The responses to varying doses of PGAI were measured for five subjects. After infusion of saline for 30 minutes, the control blood sample was drawn and PGAI was infused at a dose of 0.075 µg/kg min⁻¹ for 45 minutes. The dose was then doubled to 0.15 µg/kg min⁻¹ for 45 minutes. The dose was doubled twice more to give a final dose of 0.6 µg/kg min⁻¹. Previous studies in our laboratory have shown that the lowest dosage used in this study (0.075 µg/kg min⁻¹) will result in a peripheral blood concentration of PGAI, of approximately 1.0 ng/ml. Blood levels increase proportionately with the infusion rate and the blood concentration for the infusion rate of 0.6 µg/kg min⁻¹ will achieve a level of approximately 8 ng/ml in the steady state. Blood specimens were obtained at 45 minutes of each dosage schedule. On several occasions, blood also was drawn at 30 minutes. The 30- and 45-minute values for all parameters were not significantly different and indicated that a steady state had been attained.

VOLUME EXPANSION STUDY

To further evaluate the effects of PGAI on renin release, three subjects were volume-expanded with isotonic saline in addition to PGAI infusions. Each subject was given 500 ml of 0.9% saline in 30 minutes. Saline infusion then was continued at a constant rate throughout the remainder of the study so that each subject received a total of 2 liters. After infusion of 500 ml of saline, PGAI was infused at 0.15, 0.3, and 0.6 µg/kg min⁻¹ for 45-minute periods.

COMBINED A II AND PGAI

In this protocol, increasing doses of PGAI were superimposed on a continuous infusion of A II (Hypertensin, Ciba). Following a 30-minute control period, a mild pressor infusion of A II was begun at a rate of 5 ng/kg min⁻¹ and maintained to the conclusion of the study. After 45 minutes, PGAI was added at 0.075 µg/kg min⁻¹. As in the previous protocol, the PGAI dose was doubled every 45 minutes up to a rate of 0.6 µg/kg min⁻¹. This protocol was followed for five subjects, four of whom had participated in the PGAI infusions.

Because the two vasoactive materials were added sequentially in this protocol, an additional study was performed with the simultaneous administration of A II and PGAI. In four subjects, the effects of simultaneous infusion of A II (5 ng/kg min⁻¹) and PGAI (0.075 µg/kg min⁻¹) for 45 minutes was compared to the response to A II alone. The two studies were performed at the same time in the morning on two different days separated by at least 1 day of rest.

INDOMETHACIN STUDIES

In eight subjects the response to A II was tested before and after administration of a single dose of the prostaglandin synthetase inhibitor, indomethacin. A II was administered for 45 minutes at 5 ng/kg min⁻¹ at 8 a.m. on 2 days separated by at least 1 rest day. At 6 a.m. of the 2nd infusion day, the subjects were given 75 mg of indomethacin orally. For four of these subjects, the A II infusion was continued and PGAI (0.075 µg/kg min⁻¹) was added for 45 minutes.

STATISTICS

Paired analysis was used, each subject serving as his own control. A Wang taped program was used to provide the t values. Mean values are presented as ±1 SEM. A P value of less than 0.05 was considered significant. The mean blood pressure (diastolic blood pressure + 1/3 pulse pressure) was used to calculate changes in blood pressure.

PGA, INFUSIONS

The blood pressure and pulse rate changes caused by the varying PGAI doses are shown in Figure 1. There were no significant changes in blood pressure, but the pulse rate increased with each dose and was 15.2 ± 2.0 (SEM) beats/min greater than control with the 0.6 µg/kg min⁻¹ dose (P < 0.01). Serum electrolytes, including sodium and potassium, did not change during the infusions. The plasma cortisol concentrations were lower than control, probably reflecting a normal diurnal variation (Table 1).

The changes in PA and PRA are shown in Figure 2 and Table 1. The baseline aldosterone concentration was 4.8 ± 0.4 (SEM) ng/dl, and the values rose to 6.8 ± 1.1, 10.5 ± 1.1, 15.2 ± 1.3, and 20.7 ± 1.2 with the doses of 0.075, 0.15, 0.3, and 0.6 µg/kg min⁻¹, respectively. The increase from baseline was statistically significant at the dose of 0.15 µg/kg min⁻¹ and at the two subsequent doses (P < 0.01). Additionally, there was a significant increase, with each dosage doubling (P < 0.05). PRA also increased progressively from a baseline of 0.9 ± 0.1 ng/ml hr⁻¹ to 1.8 ± 0.4, 3.0 ± 0.1, 3.3 ± 0.5, and 5.3 ± 0.4 ng/ml hr⁻¹ with the four PGAI doses (Fig. 2 and Table 1). The changes from baseline were significant at the 0.15 µg/kg min⁻¹ (P < 0.001), the 0.3 µg/kg min⁻¹ (P < 0.01), and the 0.6 µg/kg min⁻¹ (P < 0.05).
TABLE 1  Plasma Renin Activity (PRA), Plasma Aldosterone (PA), and Plasma Cortisol Responses to Prostaglandin A<sub>1</sub> (PGA<sub>1</sub>) Infusions<sup>*</sup>

<table>
<thead>
<tr>
<th>Subj.</th>
<th>Control</th>
<th>0.075</th>
<th>0.15</th>
<th>0.3</th>
<th>0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRA</td>
<td>PA</td>
<td>Cortisol</td>
<td>PRA</td>
<td>PA</td>
</tr>
<tr>
<td>1</td>
<td>1.1</td>
<td>4.1</td>
<td>12.7</td>
<td>2.7</td>
<td>6.1</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>4.8</td>
<td>8.2</td>
<td>2.4</td>
<td>8.8</td>
</tr>
<tr>
<td>3</td>
<td>0.7</td>
<td>5.1</td>
<td>16.8</td>
<td>1.9</td>
<td>9.7</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>6.1</td>
<td>3.8</td>
<td>0.7</td>
<td>6.0</td>
</tr>
<tr>
<td>5</td>
<td>0.8</td>
<td>4.1</td>
<td>7.4</td>
<td>1.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Mean</td>
<td>0.9</td>
<td>4.8</td>
<td>9.8</td>
<td>1.8</td>
<td>6.8</td>
</tr>
<tr>
<td>± SE</td>
<td>±0.1</td>
<td>±0.4</td>
<td>±2.2</td>
<td>±0.4</td>
<td>±1.1</td>
</tr>
</tbody>
</table>

Probability values
- Compared to controls: NS<sup>†</sup> NS < 0.05 < 0.005 < 0.005 NS < 0.005 < 0.005 NS < 0.005 < 0.001 NS<sup>‡</sup> NS < 0.0025 < 0.0025 NS < 0.0025 < 0.0025 NS

* PRA is expressed as ng/ml hr<sup>−1</sup>; PA, as ng/dl; and cortisol, as µg/dl.
† NS = not significant.

µg/kg min<sup>−1</sup> (P < 0.005), and the 0.6 µg/kg min<sup>−1</sup> (P < 0.001) doses. When the PRA values were plotted against the corresponding aldosterone concentrations, a correlation (r) of 0.85 (P < 0.001) was found.

VOLUME EXPANSION STUDY

The renin responses to infusions of PGA<sub>1</sub>, during volume expansion (Table 2) were similar to those seen without saline administration. The mean PRA rose from 1.5 to 8.6 ng/ml hr<sup>−1</sup> with the highest PGA<sub>1</sub> dose (0.6 µg/kg min<sup>−1</sup>). This 5.7-fold increase was similar to the 5.9-fold increase seen in the previous study (0.9 to 5.3 ng/ml hr<sup>−1</sup>).

PGA<sub>1</sub> AND A II INFUSIONS

Figure 3 illustrates the effects of this protocol on mean blood pressure and pulse rate. The mean blood pressure increased by 17.4 ± 2.8 mm Hg with the infusion of A II alone at 5 µg/kg min<sup>−1</sup>. This rise in blood pressure was accompanied by a decrease in the pulse rate of 8.6 ± 1.5 beats/min (P < 0.05). The addition of the lowest PGA<sub>1</sub> dose (0.075 µg/kg min<sup>−1</sup>) to the continued angiotensin infusion produced a blood pressure fall averaging 11.3 mm Hg (P < 0.05) and the pulse increased by an average of 7.4 beats/min (P < 0.05). Further increments in the PGA<sub>1</sub> dosage continued this trend. With the highest dose of added PGA<sub>1</sub> (0.6 µg/kg min<sup>−1</sup>) the blood pressure was not significantly different from the baseline, but the pulse had increased by 12.8 ± 2.1 beats/min (P < 0.05).

The responses of PA and PRA are shown in Figure 4 and Table 3. Baseline PA (3.8 ± 1.3 ng/dl) more than tripled to 13.4 ± 1.5 (P < 0.001) with the angiotensin infusion. Additional increases in the PGA<sub>1</sub> infusions did not further increase PA. Baseline PRA levels (0.9 ± 0.3 ng/ml hr<sup>−1</sup>) were low in these supine subjects on a 150-mEq diet. The infusions of A II and PGA<sub>1</sub> did not alter the suppressed PRA values.

In four subjects the aldosterone responses to a 45-minute infusion of A II (5 ng/kg min<sup>−1</sup>) was compared with the 45-minute combined infusion of A II (5 ng/kg min<sup>−1</sup>) and PGA<sub>1</sub> (0.075 µg/kg min<sup>−1</sup>). A II alone raised the PA from 6.0 ± 1.7 to 14.5 ± 3.4 ng/dl, whereas the combined infusion increased the aldosterone from 5.2 ± 2.0 to 16.7 ± 2.3. These responses were not significantly different.

![Figure 2](https://example.com/figure2.png)

**Figure 2** Plasma aldosterone (PA) (solid line) and plasma renin activity (PRA) (dashed line) in response to prostaglandin A<sub>1</sub> (PGA<sub>1</sub>) infusions (doses in µg/kg min<sup>−1</sup> indicated by height of open bars). Means ± SE are shown. 1P < 0.01, compared to control values.

**Table 2** Plasma Renin Activity (PRA) Responses to Prostaglandin A<sub>1</sub> (PGA<sub>1</sub>) during Volume Expansion

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>0.15</th>
<th>0.3</th>
<th>0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRA (ng/ml hr&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.0</td>
<td>2.9</td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td>2</td>
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<td>7.4</td>
<td>8.7</td>
<td>9.2</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>4.5</td>
<td>7.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>1.5 ± 0.4</td>
<td>4.9 ± 1.3</td>
<td>7.1 ± 1.1</td>
<td>8.6 ± 1.8</td>
</tr>
</tbody>
</table>
INDOMETHACIN ADMINISTRATION

Forty-five minute infusions of A II with and without preadministration of 75 mg of indomethacin were compared for eight subjects. The baseline blood pressures and pulse rates were not significantly changed by indomethacin. The rise in blood pressure induced by angiotensin (15.2 ± 1.3 mm Hg) was slightly, but not significantly, greater in the subjects after indomethacin (18.6 ± 2.3). The difference in rise in blood pressure induced by angiotensin (15.2 ± 1.3 mm Hg) was slightly, but not significantly, greater in the subjects after indomethacin (18.6 ± 2.3). The difference in pulse rate was not significant. Without indomethacin, A II increased aldosterone from 4.7 ± 0.7 to 19.7 ± 3.2 ng/dl. With indomethacin pretreatment, A II increased aldosterone from 5.0 ± 1.0 to 17.8 ± 2.4. In the four subjects who received additional PGA, administration, PA rose slightly, but not significantly, from 22.6 ± 2.1 to 25.9 ± 2.1 ng/dl.

TABLE 3 Plasma Renin Activity (PRA), Plasma Aldosterone (PA), and Plasma Cortisol Responses to Prostaglandin A₁ (PGA₁) and Angiotensin II (A II) Infusions

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control PRA</th>
<th>Control PA</th>
<th>Control Cortisol</th>
<th>A II (5 ng/kg min⁻¹)</th>
<th>0.075</th>
<th>0.15</th>
<th>0.3</th>
<th>0.6</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0.6</td>
<td>2.0</td>
<td>3.1</td>
<td>0.6</td>
<td>11.7</td>
<td>3.3</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>3.7</td>
<td>10.9</td>
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<td>12.1</td>
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<tr>
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<td>3.8</td>
<td>4.5</td>
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<td>16.8</td>
<td>2.9</td>
<td>1.1</td>
<td>1.2</td>
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<tr>
<td>4</td>
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<td>0.7</td>
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<td>0.5</td>
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<tr>
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<td>8.7</td>
<td>14.9</td>
<td>0.8</td>
<td>17.1</td>
<td>11.5</td>
<td>11.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Mean 0.9 3.8 8.4 0.9 13.4 6.1 1.2 15.8 5.5 1.0 15.7 7.4 1.3 13.2 8.3 1.8 16.0 8.2
± SE 0.2 1.3 2.1 0.1 1.5 1.7 0.1 2.4 1.2 0.1 1.3 1.7 0.3 0.9 1.7 0.4 1.4 1.7

Probability values

Compared to control NS <0.001 <0.01 NS <0.025 NS NS <0.005 NS NS <0.005 NS
Compared to A II NS NS NS NS NS NS NS NS NS NS NS NS NS
Compared to previous dosage NS NS NS NS NS NS NS NS NS NS NS NS NS

* PRA is expressed as ng/ml hr⁻¹; PA, as ng/dl; and cortisol, as µg/dl.
† NS = not significant.

Discussion

A II, ACTH, potassium, and a decreased serum sodium concentration are direct trophic stimuli for aldosterone secretion. Although the renin-angiotensin system appears to regulate most physiological changes in aldosterone, there are several pathological and experimental conditions in which the regulation of aldosterone is not explained fully by the known stimuli. In the present experiments, the possibility that A prostaglandins play such a role was addressed. This was suggested by the findings of Fichman et al., who noted that infusions of PGA, increased aldosterone concentrations without causing significant changes in the other known stimulators. Zusman et al. have reported that radioimmunoassayable prostaglandin A concentrations rise...
with sodium restriction and fall with a high salt intake, changes compatible with an antinatriuretic function.

The results of our present studies indicate that PGA, infusions increased both the peripheral aldosterone concentrations, and the pulse rate in a dose-related manner. There was no significant change in the blood pressure. However, there was a significant dose-related rise in the PRA which correlated highly with aldosterone. This difference from the results of previous work cited1 may be due to the use of a more precise radioimmunoassay method for measuring PRA rather than the bioassay technique.

When PGA, was added to an ongoing infusion of A II, there was no additive or synergistic effect on PA. Also, the aldosterone response to the simultaneous infusion of A II and PGA, gave similar results. Both the pulse and blood pressure effects of A II were antagonized by the PGA, infusions. However, A II has been demonstrated to liberate prostaglandins from the kidney.17 Findings in our laboratory have shown that nearly all of PGA and a significant fraction of PGE escape pulmonary degradation in man.12 Thus, the endogenous release of prostaglandins due to the A II infusions could have masked the additional effect of exogenous prostaglandin.

To investigate this possibility, the subjects were pretreated with indomethacin, an inhibitor of prostaglandin synthesis. Oral indomethacin is quickly absorbed and reaches peak levels 2 hours after administration.18 The aldosterone response to A II was not significantly different in these subjects when they received indomethacin. The subsequent addition of PGA, to the A II only minimally increased aldosterone. In this protocol, indomethacin was given as a single oral dose. Chronic effects of indomethacin on renin and aldosterone currently are under investigation.

Thus, these studies do not provide evidence for a direct role of prostaglandin A on the human adrenal cortex in vivo. Our study suggests that the major stimulation of aldosterone by PGA, is via activation of the renin-angiotensin system. It should be noted that these studies were limited to the use of PGA, as the available prostaglandin for human use and do not necessarily exclude effects of other prostaglandins, although Blair-West et al.19 could not demonstrate consistent aldosterone stimulation with PGE, in the sheep.

Receptors for E prostaglandins in the adrenal and complex interactions with ACTH in vitro have suggested that prostaglandins might play a role in steroidogenesis.20,21 Spät and Józsa2 noted that PGE, was a stimulus in vitro to aldosterone in rats on both high and low sodium diets, whereas PGA, was effective only in rats on a low sodium diet. Further evaluation of prostaglandin effects in patients on low sodium diets are also being pursued.

The ability of the prostaglandin infusions to antagonize the blood pressure and pulse effects of A II point out the possibility that these substances could play a role in blood pressure regulation. Prostaglandins may be released into the circulation from the kidney in response to vasoconstrictors such as A II and norepinephrine. Also, vascular endothelium has been shown to be capable of prostaglandin synthesis22 and prostaglandin synthesis inhibition has been shown to modify the arteriolar response to vasoconstriction.23 In this regard, the slightly greater increase in the blood pressure response to A II after the acute administration of indomethacin requires further evaluation.

Infusions of prostaglandins cause renin release by the dog kidney.24 In hypertensive subjects, Carr25 did not note significant changes in renin activity or urinary aldosterone with PGA, infusions, but Krakoff et al.26 noted an increase in renin activity with PGA, in hypertensives who were receiving furosemide.

Our studies indicate that PGA, (and probably E prostaglandins) can act as a potent stimulus for renin release in normal man. The mechanism of prostaglandin A or E stimulation of renin release is not clear. In the normally hydrated rat, arachidonic acid, a prostaglandin precursor, increases PRA without changing sodium excretion.27 Similar changes in PRA have been demonstrated in the rabbit and this increase can be prevented by indomethacin pretreatment.28 Our studies suggest that the observed rise in PRA is not the result of natriuresis. Fichman et al.8 have shown that PGA, infusion rates similar to those used in our study cause sodium losses of 5–15 mEq/hr. Normal saline was used as the vehicle for our infusions and replaced approximately half of the calculated sodium losses. The remaining sodium deficit (<8 mEq/hr) is an inadequate explanation for the observed increase in renin.29 Additionally, the prostaglandin-induced rise in PRA occurred in the face of volume expansion with saline. Because our protocol involved multiple infusions, the subjects were not catheterized, but no net changes were noted in daily 24-hour urine sodium excretion or body weight. Our data therefore suggest that the prostaglandin-induced release of PRA is independent of sodium excretion.

Although our work does not indicate that prostaglandins play a direct role in aldosterone secretion, these studies do support a possible dynamic relationship between the prostaglandin and renin systems in man.

Acknowledgments

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The effect of prostaglandin A1 on renin and aldosterone in man.
M S Golub, P F Speckart, P K Zia and R Horton

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