Involvement of endogenous prostaglandins in salt-induced hypertension

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Abstract. Insufficient production of prostaglandins, which are possible antihypertensive agents, may be a pathogenetic factor in hypertensive patients on salt loading. We compared the levels of plasma PGE\(_2\), plasma renin activity (PRA) and urinary 6-keto-PGF\(_{1\alpha}\) (6-O-PGF\(_{1\alpha}\)), a major stable metabolite of PGI\(_2\), on day 5 of salt deprivation and also on day 5 of subsequent salt loading in 17 patients with essential hypertension.

Salt loading decreased plasma PGE\(_2\), and slightly increased urinary 6-O-PGF\(_{1\alpha}\). On salt loading, a positive correlation was found between the levels of plasma PGE\(_2\) and urinary sodium excretion. On salt deprivation, PRA was significantly correlated with plasma PGE\(_2\). The per cent change in mean blood pressure on changing from salt restriction to salt loading was inversely correlated with the per cent change in PGE\(_2\), and positively correlated with the per cent change in 6-O-PGF\(_{1\alpha}\) excretion. These findings suggest that on salt restriction, PGE\(_2\) is involved in the renin-angiotension system and that on salt loading, PGE\(_2\) is produced to compensate for the excessive sodium. The finding that PGE\(_2\) production was attenuated progressively as the mean blood pressure increased on salt loading in patients with essential hypertension suggests that insufficient compensatory PGE\(_2\) production is a pathogenetic factor in salt-induced hypertensive patients. In contrast, PGI\(_2\) may be produced adaptively to regulate blood pressure during changes in salt balance.

Kawasaki et al. (1978) classified patients with essential hypertension into those that were sensitive and not sensitive to salt, according to the response of their blood pressure to salt loading. On salt loading, salt-sensitive patients gained more weight and retained more sodium than those that were not salt sensitive. The mechanism of the elevation of blood pressure on excess salt intake is unknown, but it may involve the sympathetic nervous system, since Fujita et al. (1980) reported that a persistent autonomic ‘drive’ in salt-sensitive patients may play a role in their relative high sodium retention and increase in blood pressure on sodium loading. Abnormalities of prostaglandin metabolism may also contribute to salt-induced hypertension. Renal prostaglandins have been thought to increase renal sodium loss (Stokes 1979), though findings on the effect of salt balance on PGE\(_2\) have been variable in humans (Pace-Asciak et al. 1978; Nielsen et al. 1979; Fujita et al. 1980; Campbell et al. 1982) and animals (Lifschitz et al. 1978; Tobian et al. 1982), because of differences in the assay methods and experimental protocols (acute or chronic salt balance) used. Prostacyclin (PGI\(_2\)), which is generated in the arterial wall, may serve to dilate the vessel wall. Moreover, the rise in tension of the vessel wall with increase in blood pressure causes an increase in PGI\(_2\) production (Pace-Asciak et al. 1978; Limas et al. 1981). There are only a few reports (Pace-Asciak et al. 1978; Limas et al. 1981) of the relation of 6-O-PGF\(_{1\alpha}\) to salt balance, and it is uncertain whether PGE\(_2\) contributes to natriuresis during changes in salt balance.

To explore the pathogenesis of salt-induced hypertension and the mechanism of the effects of PGE\(_2\) and PGI\(_2\) in regulating blood pressure during salt loading, we measured PGE\(_2\) and 6-O-PGF\(_{1\alpha}\) in hypertensive patients on day 5 after change to salt deprivation or salt loading, since at this time sodium excretion and intake are considered to be in equilibrium (Kawasaki et al. 1978; Nielsen et al. 1979).
Materials and Methods

Subjects
In the present study, 12 female and 13 male patients with essential hypertension, aged 35–74 years, were studied. Patients with secondary hypertension and hypertensives with complications were not included in the study. In all subjects, renal function was in the normal range. All medications were discontinued at least 1 month before the study. Subjects received an ad libitum salt diet, then a low salt diet (30 ± 7 mEq/day, mean ± se) for 5 days and then a high salt diet (275 ± 20 mEq/day) for 5 days. Urinary prostaglandins and sodium were measured in 24-h urine samples collected at 4°C. Blood samples were collected in the morning before breakfast on day 6 of the period on high or low salt intake from the patients who had been recumbent for 1 h previously. For plasma PGE2 determination, 10 ml of blood was placed in an ice-cooled tube containing 10 mg of EDTA·Na2 and 10 mg of acetylsalicylic acid, and immediately centrifuged at 4°C. Plasma or urine samples were kept at −20°C until assay. PRA was measured by radioimmunoassay of the angio-

Table 1.

<table>
<thead>
<tr>
<th>Dietary sodium</th>
<th>Low sodium</th>
<th>High sodium</th>
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</thead>
<tbody>
<tr>
<td>Urinary sodium (mEq/day)</td>
<td>30 ± 7</td>
<td>275 ± 20***</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>95 ± 4</td>
<td>109 ± 5**</td>
</tr>
<tr>
<td>Urine volume (ml)</td>
<td>1100 ± 112</td>
<td>1850 ± 150**</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>3.9 ± 0.8</td>
<td>1.1 ± 0.4**</td>
</tr>
<tr>
<td>Plasma PGE2 (pg/ml)</td>
<td>64 ± 8</td>
<td>42 ± 7**</td>
</tr>
<tr>
<td>Urinary 6-O-PGF1α (ng/day)</td>
<td>90 ± 16</td>
<td>124 ± 27*</td>
</tr>
</tbody>
</table>

*P < 0.1; **P < 0.01; ***P < 0.001 for difference between low and high sodium intakes.

Relationship between Plasma PGE2 and Urinary Na Excretion on Salt Balance

![Graph showing the relationship between Plasma PGE2 and Urinary Na Excretion on Salt Balance](image)

Plasma PGE2 levels relative to levels of urinary sodium excretion on salt depletion or loading. The level of urinary sodium excretion is correlated with that of plasma PGE2 on salt loading, but not on salt depletion.
tensin 1 production rate. Blood pressure was measured just before blood sampling, and the average of three determinations was recorded.

**Radioimmunoassay of prostaglandins**

Plasma and urinary PGE₂ was determined by the same method as 6-O-PGF₁α (Gotoh et al. 1983). Briefly, 1000 dpm of [³H]PGE₂ or [³H]6-O-PGF₁α (specific activity 165 or 120 Ci/mmol, New England Nuclear, Boston, MA) was added to samples for assessing recovery and the mixture was adjusted to pH 3.5 with citric acid. Prostaglandins were then extracted with ethylacetate and purified by column chromatography on a silica acid column that had been washed with 5 ml of a mixture of benzene:ethylacetate:methanol (60:4:20 vol/vol). Purified prostaglandins were measured by radioimmunoassay with specific antibodies. Authentic prostaglandins and antibodies were kindly supplied by Ono Pharmaceutical Co. (Osaka, Japan). The cross-reactivities of anti-6-O-PGF₁α antibody with known prostaglandins were as follows: PGE₂, 1.5%; TXB, 0.1%; 13,14-dihydro-6,15-diketo-PGF₁α, 0.1%; PGF₂, 0.1%. The intra- and inter-assay coefficients of variation were respectively 8.3 and 10.2% for 6-O-PGF₁α, and 8.2 and 11.3% for PGE₂. All data are presented as means ± SEM. Statistical analyses were performed by Student's paired t-test.

![Graph](image)

**Fig. 2.**
Relation between plasma renin activity (PRA) and plasma PGE₂ on salt deprivation.

**Fig. 3.**
Relation between the ratios of changes in plasma PGE₂ and in mean blood pressure (MBP). The ratio of change is represented by [value on salt loading – value on salt depletion]/value on salt depletion.

**Results**

When patients were given a low salt diet followed by a high salt diet, their plasma PGE₂ and PRA decreased significantly (P < 0.001 and P < 0.01, respectively), while their urinary 6-O-PGF₁α increased slightly, but not significantly, and their mean blood pressure increased significantly (P < 0.01) (Table 1).

Fig. 1 shows that the plasma level of PGE₂ after salt loading, but not after salt deprivation, was positively correlated with urinary sodium excretion. In the salt loaded state, there was no significant correlation between plasma PGE₂ and the urine volume. After salt depletion, PRA showed a significant correlation with PGE₂ (Fig. 2), but not with 6-O-PGF₁α. Fig. 3 shows the inverse correlation found between the relative change in PGE₂ and the mean blood pressure on changing from a low salt to a high salt diet. Fig. 4 shows the reciprocal phenomenon of a positive correlation between the relative change in the level of urinary 6-O-PGF₁α and the blood pressure on salt loading.
Relation between the ratios of changes in urinary 6-O-PGF1α and in mean blood pressure (MBP). The ratio of change is represented by [value on salt loading − value on salt depletion]/value on salt depletion.

Discussion

The mechanism of blood pressure increase caused by salt loading in patients with essential hypertension has not been clarified. Dahl ‘sensitive’ rats have been considered to be a model of salt-sensitive hypertensive patients. These ‘sensitive’ rats have a reduced capacity for natriuresis at given levels of arterial inflow pressure. The urinary level of PGE2 is lower in ‘sensitive’ rats than in ‘resistant’ rats on salt loading (Sustarsic et al. 1981). PGE2 inhibits the transport of sodium through the tubular wall in both the ascending limb of the loop of Henle and in the collecting tubule (Stokes 1979). Thus, a low level of PGE2 may result in reduced sodium excretion in ‘sensitive’ rats and may lead to hypertension on salt loading.

Kawasaki et al. (1978) classified patients with essential hypertension into salt-sensitive and salt-resistant types, the former retaining more sodium than the latter. Campese et al. (1982) demonstrated that salt-sensitive patients showed inappropriately high plasma noradrenaline levels in relation to their urinary excretion of sodium during high sodium intake and suggested that impaired suppression of plasma noradrenaline, namely hyperreactivity of the sympathetic nervous system, may be responsible for salt-sensitive hypertension.

However, the contribution of the sympathetic nervous system to salt-sensitive hypertension remains to be elucidated. Campbell et al. (1982) and Fujita et al. (1980) demonstrated that on salt deprivation, both patients that were not sensitive to salt and normotensive subjects show higher levels of urinary PGE2 excretion than salt-sensitive or hypertensive patients. Thus in salt-sensitive and hypertensive patients, PGE2 production may be decreased.

In the present study we found that salt-sensitive patients showed decreased PGE2 production on salt loading, whereas patients who did not show a substantial increase in blood pressure on salt loading did not show a substantial decrease in PGE2. Moreover, some patients showed an increase in PGE2 with a decrease in blood pressure even on salt loading. Papanicolaou et al. (1976) suggested that PGE2 has a saluretic action because they observed a close relation between urinary sodium and PGE2 excretion, especially with rates of sodium excretion above 200 mEq/day. Kawasaki et al. (1978) and Nielsen et al. (1979) showed that in humans, sodium excretion is equal to sodium intake on day 5 of a fixed salt intake. Thus, our findings that PGE2 was associated with urinary sodium excretion, not with urine volume, support the idea that PGE2 is produced to compensate for increased sodium intake by causing excretion of excessive sodium and that this hormone has an antihypertensive effect that attenuates the increase in blood pressure on salt loading. Furthermore, we conclude that sensitivity to salt-induced hypertension may be related to PGE2 production and that decrease in the plasma PGE2 concentration in salt-induced hypertensive patients may be a pathogenetic factor in hypertension on salt loading.

Prostaglandins, PGI2 (Scholkens 1978) and PGE2 (Franco et al. 1977) induce renin release. Frölich et al. (1979) demonstrated that inhibition of prostaglandin synthesis results in reduction of PRA, which is independent of sympathetic tone. The close relation between PRA and PGE2 observed in the present study is consistent with the idea that PGE2 production is associated with the renin-angiotensin system during salt deprivation. However, since we did not find a significant relationship between PRA and 6-O-PGF1α, PGI2 may not contribute to renin release on salt deprivation.

The production of PGI2 generated in the arterial wall increases with increase in the blood pressure (Limas et al. 1981). PGI2 may also induce sodium
excretion (Ohde et al. 1982), and there is a report that the urinary level of 6-O-PGF1α may reflect the circulating level of PG12 or 6-O-PGF1α (Rosenkranz et al. 1981). But in the present study, we obtained no evidence for a natriuretic effect of PG12, because we found no significant correlation between the levels of sodium excretion and 6-O-PGF1α excretion on salt repletion. Limas et al. (1981) proposed that enhancement of PG12 synthesis in Dahl ‘sensitive’ rats may be secondary to hypertension on salt loading. Patients with essential hypertension were reported to show a decreased level of urinary 6-O-PGF1α excretion (Grose et al. 1980), but in a previous study (Gotoh et al. 1983), we observed a tendency for an increase in plasma 6-O-PGF1α in hypertensive patients. Our finding that urinary 6-O-PGF1α excretion increased with increase in blood pressure during administration of a high sodium diet suggests that PG12 is produced adaptively to regulate blood pressure during salt loading. Thus, decreased PGE2 production may contribute to the pathogenesis of hypertension in salt-induced hypertensive patients and increase in PG12 production may be an adaptive response to increased blood pressure on salt loading.

References


Received on February 21st, 1984.