Urinary Prostaglandin and Sodium Metabolism in Patients with Essential Hypertension

MINORU YASUJIMA, KEISHI ABE, NOBUO IROKAWA, SATORU CHIBA, MAKITO SATO, MASAHIDE SEINO, YUTAKA SAKURAI, KEITARO SAITO, TORU ITO, KANCHO RITSU and KAORU YOSHINAGA

The Second Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980

YASUJIMA, M., ABE, K., IROKAWA, N., CHIBA, S., SATO, M., SEINO, M., SAKURAI, Y., SAITO, K., ITO, T., RITSU, K. and YOSHINAGA, K. Urinary Prostaglandin and Sodium Metabolism in Patients with Essential Hypertension. Tohoku J. exp. Med., 1978, 124 (3), 277-283 — Urinary prostaglandin E (PGE) excretion as an indicator of renal PGE, urinary aldosterone excretion, plasma renin activity, urinary sodium excretion, and urinary potassium excretion were measured after sodium depletion in 15 patients with essential hypertension to investigate the interaction between renal PGE and sodium metabolism. Following sodium depletion, urinary PGE excretion decreased, whereas urinary aldosterone excretion and plasma renin activity increased. Significant positive correlations were found between urinary PGE excretion and urinary sodium excretion (r=0.41, p<0.01) or urinary sodium excretion-urinary potassium excretion ratio (r=0.43, p<0.005). These results support the hypothesis that the renal PGE may play an important role in the regulation of sodium metabolism and this action of PGE is independent of the renin-angiotensin-aldosterone system. urinary PGE excretion; renal PGE; urinary sodium excretion; renin-angiotensin-aldosterone system; essential hypertension

The renal prostaglandin (PG), identified as PGE2, has been known to play an important role in the renal depressor mechanism with its vasodilatic, natriuretic, diuretic and antiadrenergic actions.

The presence of primary PG in human urine has not been shown until Frolich's original (Frolich et al. 1975). They found the presence of PG in human urine and discussed that the urinary PG is derived from the kidneys, and that the amount of PG in urine is a reflection of the extent to which renal PG is synthesized.

We have been interested in the pathophysiological roles of renal PG in the regulation of blood pressure through its natriuretic effect and antagonizing action to renin-angiotensin-aldosterone system in hypertensive diseases.

The present study was undertaken to examine the influence of sodium depletion, a potent stimulus to release renin and aldosterone, on urinary PGE in essential hypertensive patients.

Received for publication, August 29, 1977.
PATIENTS AND METHODS

The study was performed in 15 patients with essential hypertension. They were 11 men and 4 women ranging in age from 15 to 50 years with an average of 29. All patients were studied in Tohoku University Hospital. The clinical diagnosis as essential hypertension has been made by physical and laboratory examinations, renal angiography, and determinations of various hormones. They had blood pressures of 90 mmHg in diastolic or higher on repeated observations and no complications in cardiovascular and renal organs. These patients were either untreated or had discontinued their therapy for at least 2 weeks before the study. They were allowed to take unrestricted diet containing approximately 200 mEq of sodium per day for at least one week before the study. To examine the effects of sodium depletion on urinary PGE excretion and urinary aldosterone excretion, each patient received a diet containing approximately 100 mEq of sodium per day for 3 days. Thereafter, approximately 50 mEq of sodium per day was given for 3 days. 24-hour-urine was collected on the last day of each period. On the next morning of the two periods of sodium intake of 200 mEq per day and 50 mEq per day, blood samples were drawn from the cubital vein after one hour recumbency for the measurement of plasma renin activity and at the same time blood pressure was measured.

Urinary PGE was measured radioimmunologically. After the chemical conversion of PGE to PGB performed according to the method described by Zusman (1972), the samples were acidified and were extracted with ethyl acetate. Thereafter, PGB was separated by silicic acid column chromatography according to Jaffe's method (Jaffe et al. 1973), and it was measured with antisera to PGB available in commercial kits (CA 501, Clinical Assays). Urinary aldosterone was assayed radioimmunologically with the commercial kits after the procedure of extraction described by Langen et al. (1974), and plasma renin activity was determined as described previously (Abe et al. 1972). Urinary excretions of sodium and potassium were calculated by the usual method. Electrolyte concentration was measured by an autoanalyzer.

RESULTS

The results are summarized in Table 1. Following sodium depletion, a lowering of mean blood pressure of 10% or more was observed in 7 out of 15 cases. In the remaining 8 patients the mean blood pressure was unchanged or increased. Taken as a whole, the changes in mean blood pressure were not statistically significant. Whereas, urine volume decreased from 1432±122 ml/day (mean±S.E.) to 1075±83 ml/day with a statistical significance (p<0.05).

The changes in urinary sodium excretion, urinary PGE excretion, urinary aldosterone excretion and plasma renin activity in all subjects under various

<table>
<thead>
<tr>
<th>Sodium intake</th>
<th>MBP (mmHg)</th>
<th>UV (ml/day)</th>
<th>UNaV (mEq/day)</th>
<th>UNaV/UkV</th>
<th>UPGEV (ng/day)</th>
<th>UALDOV (ng/day)</th>
<th>PRA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mEq/day</td>
<td>116.8±5.2</td>
<td>1432±122</td>
<td>167.5±14.2</td>
<td>5.8±0.4</td>
<td>529.1±36.1</td>
<td>2.1±0.4</td>
<td>24.0±5.8</td>
</tr>
<tr>
<td>100 mEq/day</td>
<td>120.9±9.6</td>
<td>1295±96</td>
<td>92.7±9.13</td>
<td>3.2±0.24</td>
<td>451.1±40.4</td>
<td>3.4±0.6</td>
<td></td>
</tr>
<tr>
<td>50 mEq/day</td>
<td>107.2±4.0</td>
<td>1070±83*</td>
<td>25.9±5.73</td>
<td>1.2±0.19</td>
<td>305.1±33.15</td>
<td>5.8±1.3*</td>
<td>58.0±8.6</td>
</tr>
</tbody>
</table>

* p<0.05; † p<0.02; ‡ p<0.01; § p<0.001.
sodium intakes are illustrated in Fig. 1. Urinary PGE excretion was 529.1±36.1 ng/day on a diet containing 200 mEq/day of sodium. Under mild restricted diet containing 100 mEq/day of sodium, it decreased to 451.1±40.4 ng/day but with no statistical significance. Under the strict diet containing 50 mEq/day of sodium, it decreased to 305.1±33.1 ng/day (p<0.01). Urinary aldosterone excretion was 2.1±0.4 μg/day during sodium intake of 200 mEq/day. Under sodium intake of 100 mEq/day, it increased to 3.4±0.6 μg/day without statistical significance, and increased to 5.8±1.2 μg/day on sodium intake of 50 mEq/day (p<0.02). Plasma renin activity was increased from 24.0±5.8 ng/ml to 58.0±8.0 ng/ml by the strict restriction of sodium intake (p<0.01).

Fig. 2 shows the relationship between urinary sodium excretion and urinary PGE excretion in all subjects under various sodium intakes. Slightly positive correlation was found between them (r=0.41, p<0.01).

Similarly, there was also a weakly positive correlation between urinary sodium excretion-urinary potassium excretion ratio and urinary PGE excretion (r=0.43, p<0.005) (Fig. 3).
Fig. 2. The relationship between the urinary sodium excretion and the urinary PGE excretion in all subjects under various sodium intakes ($r=0.41$, $p<0.01$).

Fig. 3. The relationship between the urinary sodium excretion-urinary potassium excretion ratio and the urinary PGE excretion in all subjects under various sodium intakes ($r=0.43$, $p<0.005$).

On the other hand, no correlation was observed between urinary aldosterone excretion and urinary PGE excretion.

Fig. 4 demonstrates the relationship between the levels of plasma renin activity and the excretion of urinary PGE in all subjects under sodium intake of 200 mEq/day. There was no significant negative correlation between them.

**DISCUSSION**

The increases in urinary aldosterone excretion and plasma renin activity in most patients with essential hypertension following sodium depletion have been repeatedly confirmed (Ledingham et al. 1967; Laragh et al. 1972). In the present experiment, similar results were obtained.
Recent reports regarding the synthesis of renal PG and sodium metabolism have been conflicting. In 1974, Tobian et al. found a decrease in renal tissue PGE\(_2\) after sodium loading in rats. From this result, he proposed a hypothesis that intrarenal PGE may be an antinatriuretic substance. On the contrary, Terashima et al. (1976) reported that renal arterial infusion of hypertonic NaCl was capable of stimulating PGE release in the canine kidney. Papanicolau et al. (1976) also reported that significant positive correlation was found between urinary sodium excretion and urinary PGE excretion. These results seem to support the view that the intrarenal PGE may be a natriuretic substance. The causes of these conflicting data might be due to some differences in each experimental condition and a lack of common indicator of renal PG. Some papers described that it was very difficult to evaluate levels of renal tissue PG because of postmortem synthesis of PGs in spite of technical improvement in preventing it, and of the fact that PGs are not stored within cells (Ånggård et al. 1972; Dunn 1976).

Recently, urinary excretion of PGE has been considered to be a proper indicator of the synthesis or release of renal PG, because urinary PGE has been shown to be of renal origin (Frolich et al. 1975).

The result of our present study which indicated that urinary PGE excretion decreased after sodium depletion supports the Papanicolau’s report, and seems to be reasonable because it is known that PGE has natriuretic action. The positive correlation between urinary sodium excretion-urinary potassium excretion ratio and urinary PGE excretion suggests that renal PG acts in an opposite direction to mineralocorticoids on the renal handling of electrolytes. Nasjletti and Colina-Chourio (1976) showed that mineralocorticoids increased the urinary excretion of PGE-like substances in rat, and proposed the possibility that activation of the renal kallikrein-kinin system by aldosterone promoted renal release of PGE. Our previous data (Seino et al. 1975) indicated that renal kallikrein-kinin system was under the influence of mineralocorticoid levels. We observed an enhancement of
urinary kallikrein after sodium depletion in essential hypertension, and an increase in primary aldosteronism and renovascular hypertension. It has been known that angiotensin II also stimulates the synthesis and release of renal PG. The present findings show, however, that the changes in urinary PGE excretion following sodium depletion do not correlate with enhancements of urinary aldosterone excretion and plasma renin activity.

The present study suggests that renal PGE might play an important role in the regulation of sodium metabolism, and that renal PGE might act on sodium metabolism independently of the renin-angiotensin-aldosterone system and kallikrein-kinin system after sodium depletion. If there is a deficiency in renal PGE synthesis, it may cause a retention of sodium in the body, raising the blood pressure of that individual. Such a mechanism might be considered as a cause of elevated blood pressure in some cases of so-called “essential hypertension”.

Acknowledgment

We gratefully acknowledge the skillful technical assistance of Miss Michiko Abe. This work was supported by the grant (No. 257244) from the Ministry of Education, Science and Culture of Japan.

References


14) Zusman, R.M. (1972) Quantitative conversion of PGA or PGE to PGB. Prostaglandins, 1, 167–168.