THE EFFECT OF CHRONIC SODIUM LOADING AND SODIUM RESTRICTION ON PLASMA AND RENAL CONCENTRATIONS OF PROSTAGLANDIN A IN NORMAL WISTAR AND SPONTANEOUSLY HYPERTENSIVE AOKI RATS

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SUMMARY

1. In normal and hypertensive rats prostaglandin A (PGA) in plasma and kidney increased on low sodium intake and decreased on high sodium intake.
2. Plasma and renal concentrations of PGA were higher in spontaneously hypertensive rats than in normal Wistar rats in each dietary group.

Key words: prostaglandins, sodium loading, sodium restriction, hypertension, spontaneously hypertensive rats, kidney.

Lee (1972) has suggested that prostaglandins A and E (PGA and PGE) may play a role in the control of sodium homeostasis and the regulation of blood pressure. Infusions of PGA or PGE into the renal artery have been shown to result in an increase in sodium, potassium and chloride excretion, glomerular filtration rate, total renal blood flow, and cortical blood flow. Further, intravenous administration of PGA to normal and hypertensive humans resulted in lowered blood pressure (Lee, 1972).

The purpose of this study was to examine the effect of chronic sodium loading and sodium restriction on plasma and renal tissue levels of PGA in the normal Wistar and spontaneously hypertensive Aoki rat, and to determine the effect of hypertension on these prostaglandin levels, by using a recently developed radioimmunoassay.

MATERIALS AND METHODS

Normotensive Wistar and spontaneously hypertensive Aoki rats (Aoki, 1963), weighing 330-

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380 g, were placed on high, low and normal sodium diets. The three diets used were as follows. 1. Normal sodium intake, rat chow containing 102 mEq of sodium/kg; distilled water was used for drinking. 2. Low sodium intake, rat chow with no sodium content; water was used for drinking. 3. High sodium intake, rat chow containing 102 mEq of sodium/kg; 0.9% sodium chloride was used for drinking.

After 2 weeks on one of the above diets, the animals were killed by decapitation, and blood was collected by using EDTA (sodium salt) as the anticoagulant, centrifuged (1200 g at 4°C), and the plasma stored at -20°C. The kidneys were removed, cleaned of fat and weighed; each kidney was homogenized in 10 ml of saline. 3H-labelled PGA₁ (New England Nuclear Corp., specific radioactivity 50-60 μCi/mmol) was added to allow for calculation of total PGA recovery after homogenization and assay.

For PGA analysis the sample was extracted twice with 5 vol. of distilled ethyl acetate, and applied to a 0.5 g silicic acid column for separation of the A, E and F group prostaglandins. This technique does not separate PGA₂ from PGA₁ and our results will therefore be expressed as PGA. By using antiserum prepared by immunization of rabbits with a bovine serum albumin-prostaglandin E₂ conjugate, PGA concentrations were determined by radioimmunoassay (Zusman, Caldwell, Speroff & Behrman, 1972).

The blood pressures were determined by the tail-cuff plethysmographic method in unanaesthetized rats (Williams, Harrison & Grollman, 1939).

RESULTS

The results of plasma and renal PGA determinations are shown in Table 1. Student’s t test was used for statistical analysis.

High salt suppressed and low salt increased plasma and renal PGA concentrations significantly in both normal and spontaneously hypertensive rats.

In the normotensive Wistar rats, plasma PGA levels on the low and high sodium diets differed significantly from the levels found in rats on the normal sodium intake (P<0.001). Renal tissue PGA levels were also significantly altered on low and high sodium diets in comparison with normal sodium intake (P<0.005 and 0.001 respectively).

In the spontaneously hypertensive Aoki rats plasma PGA levels on the low and high sodium

<table>
<thead>
<tr>
<th>Dietary sodium content*</th>
<th>Plasma PGA (ng/ml) (mean ± SEM)</th>
<th>Renal PGA (ng/g) (mean ± SEM)</th>
<th>Plasma PGA (ng/ml) (mean ± SEM)</th>
<th>Renal PGA (ng/g) (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1.69±0.07 (n=6)</td>
<td>100.6±8.5 (n=6)</td>
<td>3.92±0.58 (n=6)</td>
<td>181.7±26.5 (n=6)</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00±0.05 (n=6)</td>
<td>61.4±6.4 (n=6)</td>
<td>1.88±0.32 (n=6)</td>
<td>88.2±9.1 (n=6)</td>
</tr>
<tr>
<td>High</td>
<td>0.51±0.04 (n=6)</td>
<td>23.0±2.6 (n=6)</td>
<td>0.91±0.03 (n=4)</td>
<td>43.8±4.7 (n=6)</td>
</tr>
</tbody>
</table>

* Low: no sodium in diet, Normal: 102 mEq of sodium/kg of diet, distilled water to drink, High: 102 mEq of sodium/kg of diet, 0.9% sodium chloride to drink (mean intake 40 ml/day, range 20-70 ml).
Prostaglandin A in normal and hypertensive rats

Diets differed significantly from the levels found in these hypertensive rats on the normal sodium diet ($P<0.02$ and $0.04$ respectively). Renal tissue PGA levels were also significantly altered on low and high sodium diets in comparison with normal sodium intake ($P<0.01$ and $0.002$ respectively).

Moreover plasma PGA levels were significantly higher in the spontaneously hypertensive rats in comparison with the normotensive rats on each diet, $P$ values were less than $0.005$, $0.02$ and $0.001$ on the low, normal, and high sodium diets respectively. Similarly renal PGA levels were higher in the spontaneously hypertensive rats, $P$ less than $0.02$, $0.04$ and $0.004$ on the low, normal and high sodium diets respectively.

Blood pressure did not significantly change in any of the rats on the three sodium intake diets.

**DISCUSSION**

Our results show that salt intake markedly affects plasma and renal concentrations of PGA. In both normotensive Wistar and spontaneously hypertensive Aoki rats sodium restriction resulted in increased PGA levels in plasma and renal tissue. We also found that sodium loading resulted in decreased PGA levels in both plasma and renal tissue. Further, we found that the spontaneously hypertensive rats had significantly elevated PGA levels in comparison with normotensive Wistar rats on each of the dietary sodium intakes.

The role of the kidney in the pathogenesis of hypertension secondary to renal artery stenosis is well established (Mulrow & Goffinet, 1969). Evidence has been obtained, however, which shows that the kidney also serves an antihypertensive function (Goldblatt, 1947). The ability of normal renal tissue to blunt the hypertensive effect of contralateral renal artery stenosis is well documented. Further, renoprival hypertension is prevented by perfusion of a normal kidney whose urinary excretion is blocked by ureteral anastomosis to the inferior vena cava (Muirhead & Stirman, 1958). Thus a physiological role for the kidney in control of blood pressure is established.

Intraperitoneal or intravenous injections of saline homogenates of either whole kidney or renal medulla have been found to protect against renoprival hypertension (Muirhead, Stirman & Jones, 1960). Examination of these cells after intraperitoneal injection of renal homogenates revealed the survival and viability of interstitial stromal cells. Electron microscopic study of these renal interstitial cells (Nissen, 1968a) revealed the presence of intracellular lipid-containing granules. These granules were thought to be storage sites for intracellularly synthesized saturated and unsaturated lipids. Further study revealed that salt loading resulted in a marked increase in the number of granules per cell (Nissen, 1968b). Studies by Tobian, Ishii & Duke (1969) revealed that the number of such lipid granules in salt-loaded hypertensive rats are markedly reduced in comparison with normotensive controls. Recently by using renal interstitial cells grown in tissue culture it has been shown that these cells contain prostaglandins $A_2$, $E_2$ and $F_2a$ (Muirhead, Germain, Leach, Brooks, Pitcock, Stephenson, Brosius, Hinman & Daniels, 1972). In a study with human renal tissue Muehrcke, Mandel & Volini (1970) have shown a significant decrease in the number of granules in hypertensive patients in comparison with normal humans. These observations suggest that PGA may play a role in the physiological state during hypertension.

Our results indicate that salt intake influences both plasma and intrarenal PGA levels in the
rat. In both normotensive and hypertensive rats PGA increased on the low sodium intake diet and decreased with high sodium intake. We have shown similar changes in prostaglandin A concentrations in normal humans with chronic sodium restriction and sodium loading (Zusman, Spector, Caldwell, Speroff & Mulrow, 1973). The increase in PGA in response to low sodium intake may be mediated by the anticipated increase in circulating angiotensin under these conditions as it has been shown that infusions of angiotensin have resulted in the release of prostaglandins from the kidney (McGiff, Crowshaw, Terragno & Lonigro, 1970).

It is significant to note that the plasma and renal concentrations of PGA in the spontaneously hypertensive rats were higher than in the Wistar rats in each dietary group. This report is the first observation of altered prostaglandin levels in hypertensive animals. The spontaneously hypertensive rat does not appear to have elevated renin levels; however, an increased sensitivity to normal amounts of circulating angiotensin may be the stimulus to increased PGA synthesis and release. It is possible that PGA, a vasodilator, is released as a compensatory response. It is also possible that intrarenal stimuli, perhaps vascular spasm or local ischaemia, stimulate increased PGA production.

The changes in plasma and renal PGA concentrations in response to changes in sodium intake as demonstrated in this study suggest that prostaglandins may play a role in sodium homeostasis. In humans infusions of PGA have been shown to increase aldosterone secretion (Fichman, Littenberg, Woo & Horton, 1972). Further, the increase in PGA levels found in the hypertensive animals suggests that PGA may be important in the control of blood pressure. The mechanism responsible for increased PGA synthesis and release in hypertensive states is still unknown and is under investigation.

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REFERENCES


Prostaglandin A in normal and hypertensive rats


