Renal prostaglandin production in the Japanese (Kyoto) spontaneously hypertensive rat

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Summary

1. Renal venous and urinary prostaglandin E₂ (PGE₂) and prostaglandin F₂α (PGF₂α) were measured in spontaneously hypertensive (SH) rats and Wistar-Kyoto normotensive rats (WKy) of 4 different ages, ranging from 4 to 54 weeks.

2. Renal venous (plasma) PGE₂ and PGF₂α were similar in WKy and SH rats at all ages, except for greater PGF₂α in 40–54 week old SH rats.

3. Urinary (24 h) PGE₂ and PGF₂α were similar in WKy and SH rats at all ages, except for greater PGE₂ in 7–12 week old SH rats.

4. There was a significant trend for renal venous and urinary PGE₂ and PGF₂α to decrease with advancing age.

5. These experiments did not show evidence that the SH rat kidney, in vivo, has an abnormality of PGE₂ or PGF₂α production or degradation, which alters secretion or excretion of either prostaglandin.

Key words: hypertension, prostaglandins.

Abbreviations: PGI₂ prostacyclin; PGE₂, prostaglandin E₂; PGF₂α, prostaglandin F₂α; SH rats, spontaneously hypertensive rats; WKy, Wistar-Kyoto normotensive rats.

Introduction

I previously reported that renal medullary microsomal prostaglandin cyclo-oxygenase activity was increased in Kyoto spontaneously hypertensive rats (Dunn, 1976). At 2–3 months of age, the renal microsomes from SH rats synthesize, in vitro, 2-fold more PGE₂ and PGF₂α, expressed as pmol of PGE₂ or PGF₂α per 15 min incubation per mg of microsomal protein. There were no differences between SH rats and WKy rats in the total medullary weight or the amount (mg) of microsomal protein per mg of medulla. However, renal medullary tissue levels of immunoassayable PGE were similar in SH rats and WKy controls (Dunn, 1976). The prostaglandin degradative enzyme 15-hydroxy-dehydrogenase was decreased in whole renal homogenates from SH rats (Pace-Asciak, 1976) and in renal cytosolic supernatant from New Zealand rats (Armstrong, Blackwell, Flower, McGiff, Mullane & Vane, 1976). Others have failed to document changes of renal 15-hydroxy prostaglandin dehydrogenase in Kyoto SH rats (Ahnfelt-Ronne & Arrigoni-Martelli, 1977). In the present study, I measured the renal secretory and excretory rates of PGE₂ and PGF₂α in order to test the validity of these in vitro enzymic assays.

Methods

Kyoto SH rats and control WKy animals were bred and housed in the University of Vermont, College of Medicine, SHR facility. Blood pressures were obtained by tail cuff plethysmography. Urine collections (24 h) were made in metabolic cages into urine containers with 1% sodium azide and 5 μg meclofenamate/ml. After a 24 h urine collection, each rat was anesthetized and the inferior vena cava was cannulated. After ligation of the inferior vena cava, superior to the renal veins, 4–5 ml of blood was collected within 30 s into tubes containing EDTA (10 mg) and meclofenamate (15 μg). Plasma (2 ml) and urine (0·5 ml) were
TABLE 1. Renal venous and urine PGE₂ and PGF₂α from SH and WKy rats of various ages

Results are means ± SEM; * differs from WKy, P < 0.05.

<table>
<thead>
<tr>
<th>Age (weeks)</th>
<th>Renal venous (pg/ml)</th>
<th>Urine (ng/mg of creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WKy</td>
<td>SH</td>
</tr>
<tr>
<td></td>
<td>PGE₂</td>
<td>PGF₂α</td>
</tr>
<tr>
<td>4–5 (6–8)</td>
<td>1004 ± 305</td>
<td>528 ± 67</td>
</tr>
<tr>
<td>7–12 (9)</td>
<td>254 ± 52</td>
<td>356 ± 75</td>
</tr>
<tr>
<td>15–23 (8–12)</td>
<td>258 ± 39</td>
<td>264 ± 67</td>
</tr>
<tr>
<td>40–54 (12)</td>
<td>159 ± 24</td>
<td>206 ± 27</td>
</tr>
</tbody>
</table>

extracted, chromatographed and prepared for radioimmunoassay (Dunn, Liard & Dray, 1978). PGE₂ and PGF₂α were radioimmunoassayed, by using techniques and antibodies from Institut Pasteur (Dray, Charbonnel & MacClouf, 1975). Urinary values were divided by urine creatinine excretion to correct for urine losses or variability due to animal size. Statistical significance was examined by Student’s unpaired t-test.

Results

SHR and WKy rats were age-matched at 4–5, 7–12, 15–23 and 40–54 weeks old. The blood pressures in the SH rats were 127 ± 4, 148 ± 4, 158 ± 2 and 192 ± 9 mmHg, in the respective age groups. Blood pressures in the corresponding age groups of WKy rats were 102 ± 6, 117 ± 3, 119 ± 2 and 115 ± 4 mmHg.

Table 1 contains the results for renal venous and urine PGE₂ and PGF₂α. There were no statistically significant differences in reninal venous PGE₂ between SH and WKy rats. Renal venous PGF₂α was greater in SH rats only at 40–54 weeks; however, urine PGF₁α was not different between SH and WKy rats at any age. Urine PGE₂ was statistically increased at 7–12 weeks in SH rats and decreased thereafter. There was a general trend for renal venous PGE₂ and PGF₂α, and urine PGE₂ and PGF₂α to decrease with advancing age of the rats.

Dr L. Levine (Brandeis University) kindly assayed 8 renal venous plasma samples from SH rats and 8 from WKy rats (age matched with 6 rats at 15–17 weeks and 2 rats of 52 weeks) for 13, 14-dihydro-15-keto-PGE₂. This degradative product of PGE₂ gives an additional assessment of renal PGE₂ synthesis. The mean values ± SEM were 222 ± 22 pg/ml in SH rats and 186 ± 29 pg/ml in WKy rats. These differences were not significant.

Discussion

The role of vascular and renal prostaglandins in hypertension has aroused substantial interest, because of the vasodilatory and natriuretic properties of many prostaglandins (Dunn & Hood, 1977). Previous studies of the Kyoto SH rats have yielded conflicting results. Sirois & Gagnon (1974) found decreased bioassayable PGE release from four SH rats renal papillae. Tobian & O’Donnell (1976), found increased PGF₂α after bioassay of SH rat kidneys and others have reported enhanced excretion of PGF₂α in the urine of SH rats (Ahnfelt-Ronne & Arrigoni-Martelli, 1977). Renal medullary content of immunoassayable PGE in snap-frozen tissue, was similar in SH and WKy rats (Dunn, 1976). The latter results are surprising because, in the same study, renal medullary microsomal prostaglandin cyclo-oxygenase activity was enhanced after 2–3 months in SH rats (Dunn, 1976). There are conflicting reports on the renal activity of 15-hydroxy-dehydrogenase, a major degradative enzyme for PGE₂ and PGF₂α. Whereas Pace-Asciak (1976) found decreased activity of the 15-hydroxy-dehydrogenase in whole kidney homogenates of SH rats (17 day to adult), others report no differences in this enzyme in SH and normontensive rats of 3–21 weeks of age (Ahnfelt-Ronne & Arrigoni-Martelli, 1977).

These results in vitro shared the common shortcoming of limited applicability to the steady-state situation in vivo. Table 1 shows that significant abnormalities of renal synthesis and/or degradation of PGE₂ and PGF₂α in vivo in the SH rats are quite unlikely. No consistent increase or decrease of secretion (renal venous) or excretion (urine) of PGE₂ or PGF₂α was detected. There is reasonable evidence that renal excretion of PGE₂ and PGF₂α into the urine closely parallels or
reflects renal synthesis (Frolich, Wilson, Sweetman, Smigel, Nies, Carr, Watson & Oates, 1975; Dunn et al., 1978). If renal synthesis of prostaglandins was increased, and/or degradation was decreased, one would expect demonstrable increases in renal venous and urine levels of PGE and PGF₂α.

The results in Table 1 call into question the importance of the reports of in vitro enzymic alterations for prostaglandins in kidneys of SHR. Several interpretations seem possible.

1. The assays of cyclo-oxygenase and dehydrogenase in vitro do not predict activity in vivo, because the biochemical conditions of assay (co-factors, time, substrate, etc.) do not simulate closely the actual intracellular conditions.

2. Terragno, McGiff & Terragno (1978) have described an endogenous inhibitor of prostaglandin cyclo-oxygenase in the adult pig kidney. If this inhibitor was present in vivo in the SH rat kidney, then washed microsomes would show greater synthetic capacity in vitro (Dunn, 1976). However, an increased amount of cyclo-oxygenase in vivo in the presence of an endogenous inhibitor might produce normal amounts of end-product, namely PGE₂ and PGF₂α.

3. Microscopic analyses of SH rat medullary interstitial cells show decreased granularity, which may indicate decreased amounts of arachidonic acid substrate (Mandal, Frolich, Chrysant, Pfeffer, Yunice & Nordquist, 1974; Anggard, Bohman, Griffin, Larsson & Maunusback, 1972). These results have generally been interpreted to indicate increased substrate utilization for prostaglandin synthesis. An alternative explanation would be that there is restricted substrate availability in the SH rat medullary interstitial cell. Under these circumstances, cyclo-oxygenase activity could increase in order to maintain PGE₂ production at normal levels.

4. It could be argued that prostaglandin cyclo-oxygenase activity is truly increased in vivo and in vitro, but that the major end-product is prostacyclin (PGI₂), which was not measured in the present study. The aortae of SH rats, studied in vitro, produce 3–7 times more PGI₂ than normotensive controls (Pace-Asciak, Carrara & Rangaraj, 1978). The renal cortex of SH rats may also produce increased amounts of PGI₂. However, it is unlikely that this would affect our interpretation of the present data, since our earlier studies of cyclo-oxygenase activity used medullary microsomes and PGI₂ may be primarily cortical in origin.

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References


