Urinary prostaglandins and kallikrein in essential hypertension

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Summary

1. Urinary prostaglandins (PG), kallikrein and plasma renin activity (PRA) were measured in 35 patients with essential hypertension and 22 normotensive controls before and 15 min after frusemide (40 mg intravenously).

2. PGE₂ and kallikrein excretion rates were lower in hypertensive subjects, and failed to rise to the same extent after frusemide. PGF₂α excretion was not significantly different in the two groups of patients either before or after frusemide. PRA rose less in the hypertensive subjects after frusemide.

3. These findings support the view that there is an abnormality of renal vasodilator systems (PGE₂ and kallikrein) in essential hypertension.

Key words: frusemide, hypertension, kallikrein, prostaglandins, renin.

Abbreviations: PG, prostaglandin; PRA, plasma renin activity.

Introduction

Impairments of vascular vasodilatory negative feedback systems, such as the prostaglandin (PG) and the kallikrein–kinin systems, operating to offset vasoconstrictive influences, are now generally believed to be a major abnormality in hypertensive disease, including essential hypertension (McGiff & Vane, 1975). Such vascular defects, when present in the kidney, would play a predominant role in the natural history of essential hypertension, since they could increase systemic blood pressure by a variety of mechanisms.

In patients with essential hypertension the increase of renal vascular resistance, with its consequences for sodium excretion, is associated with a reduced renin secretion (Schalekamp, Schalekamp-Kuyken & Birkenhager, 1970). Previous studies from this and other laboratories have indicated that renal prostaglandins are critically involved in the mechanisms which regulate renin release and other renal vascular functions, such as renal blood flow, the adrenergic neuro-effector response or the tubulo–vascular feedback loop (Weber, Holzgreve, Stephan & Herbst, 1975; Hedquist, 1976; Terragno, Terragno & McGiff, 1977; Schnermann, Schubert, Hermle, Herbst, Stowe, Yarimizu & Weber, 1979). Furthermore, a close inter-relationship has been reported between the renal PG- and kallikrein–kinin systems in the kidney (McGiff, Itskowitz, Terragno & Wong, 1976). In the present study we measured plasma renin activity (PRA) and the excretion of PG and kallikrein from the kidney before and after frusemide in patients with essential hypertension and in normotensive controls, in order to evaluate the possibility that an impairment of the latter systems could contribute to the well-known abnormalities of the kidney in essential hypertension, i.e. reduction of renin and renal blood flow.

Patients and methods

In 35 untreated patients essential hypertension (14 males, 21 females; mean age 42 ± 10 years) and in 22 normotensive controls (10 males, 12 females; mean age 39 ± 14 years) measurements were performed according to the following protocol. After an overnight fast the urinary bladder was emptied and a 24 h urine collection period terminated. This urine served for the evaluation of sodium balance.
In the urine sample produced by spontaneous voiding after a subsequent 2 h period of supine rest, basal rates of renal PGE₂, PGF₂α and kallikrein excretion were measured. PG were analysed by radioimmunoassay, as described previously (Scherer, Schnermann, Sofroniev & Weber, 1978). Kallikrein activity was determined photometrically with a chromogenic, synthetic tripeptide-p-nitranilide substrate (Kabi S 2266). After the 2 h resting period, 40 mg of frusemide were injected intravenously, and 15 min later the subjects (who remained in the supine position) again emptied their bladders. In these urine samples, also, PG and kallikrein were determined. At the time of the frusemide injection, as well as 15 min later, peripheral venous blood was obtained for the determination of PRA (Weber, Scherer & Larsson, 1977).

Results

The mean blood pressure was 163/105 mmHg in the hypertensive patients and 116/80 mmHg in the control subjects. Urinary 24 h sodium excretion (hypertensive, 136 ± sd 51 mmol; normotensive controls: 149 ± 48 mmol) and stimulated sodium excretion after frusemide were not different in hypertensive and normotensive subjects. In the patients, basal PGE₁ and kallikrein excretion rates were significantly (P < 0.02 and P < 0.01 respectively) lower than in the control subjects, although the difference for PGE₁ and kallikrein (in males only) did not remain significant when evaluated for males and females separately. PGF₂α was not different in the two groups. In the urine sample, collected during the initial 15 min period after frusemide, PGE₁ and PGF₂α as well as kallikrein excretion increased significantly in all groups (P < 0.001). However, the increases of PGE₁ and of kallikrein were all significantly lower in the hypertensive patients, in males as well as in females (Table 1). The response of PGF₂α, PGE₁, kallikrein or PRA. In the resting period, but not after frusemide, a weak positive correlation was found between urine flow rate and PGE₂ excretion (r = 0.38; P < 0.05).

Discussion

The reduced increase of PGE₁ and of kallikrein excretion as found in this study in patients with essential hypertension points to a reduced capacity of the kidney in hypertension to produce vasodilatory compounds upon challenge with frusemide. Previous studies have indicated that the rapid increases of PRA and renal blood flow, normally observed after this or similar loop diuretics, are most probably due to increased vascular PG formation; the changes are completely blocked by inhibition of PG synthesis (Olsen & Ahnfelt-Ronne, 1976; Weber et al., 1977; Scherer & Weber, 1979). The renal PG- and kallikrein-kinin systems are, however, highly compartmentalized. It is difficult, therefore, to extrapolate from determinations in urine (or renal venous plasma) to the origin and action of the measured compounds within the kidney. Intrarenal infusions

| Table 1. Changes of urinary prostaglandins (PG) and kallikrein excretion, and stimulation of plasma renin activity (PRA), by 40 mg of frusemide intravenously in patients with essential hypertension and in normotensive controls

<table>
<thead>
<tr>
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<th>Basal conditions; II, 15 min after frusemide. Mean results ± SEM are shown. Significance of differences, compared with controls: * P &lt; 0.05; ** P &lt; 0.02; *** P &lt; 0.01; **** P &lt; 0.001.</th>
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<tbody>
<tr>
<td></td>
<td>PGE₁ (pg/min)</td>
<td>PGE₂α (pg/min)</td>
<td>PRA (m units/min)</td>
<td>PRA (% stimulation)</td>
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<td>Males and females together</td>
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<tr>
<td>Hypertensive (n = 35)</td>
<td>174 ± 16**</td>
<td>502 ± 51****</td>
<td>416 ± 55</td>
<td>1023 ± 155</td>
<td>47 ± 3***</td>
</tr>
<tr>
<td>Controls (n = 22)</td>
<td>324 ± 58</td>
<td>1293 ± 184</td>
<td>497 ± 84</td>
<td>1667 ± 209</td>
<td>75 ± 6</td>
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<td>Males</td>
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<tr>
<td>Hypertensive (n = 14)</td>
<td>196 ± 27</td>
<td>467 ± 56***</td>
<td>515 ± 128</td>
<td>1025 ± 241</td>
<td>55 ± 15</td>
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<tr>
<td>Controls (n = 10)</td>
<td>335 ± 107</td>
<td>1431 ± 290</td>
<td>508 ± 121</td>
<td>2199 ± 529</td>
<td>70 ± 13</td>
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<td>Females</td>
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<td>Hypertensive (n = 21)</td>
<td>160 ± 20</td>
<td>525 ± 79*</td>
<td>350 ± 48</td>
<td>1020 ± 201</td>
<td>41 ± 10**</td>
</tr>
<tr>
<td>Controls (n = 12)</td>
<td>315 ± 62</td>
<td>1178 ± 254</td>
<td>466 ± 112</td>
<td>1113 ± 126</td>
<td>78 ± 12</td>
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of angiotensin II or bradykinin, manoeuvres generally assumed to activate vascular receptors and to interfere with vascular PG formation, have been shown to increase renal venous PG and urinary output of PG in parallel (Dunn, Liard & Dray, 1978). Moreover, the initial increases of urinary PG and kallikrein after frusemide or bumetanide seem to reflect the production and action of PG and bradykinin at renal vascular sites (Olsen & Ahnfelt-Ronne, 1976; Scherer & Weber, 1979).

Because of these findings, and since strong evidence has accumulated that it is the PG production in renal cortical structures (Weber, Larsson, Ånggard, Hamberg, Corey, Nicolaou & Samuelsson, 1976; Data, Crump, Hollifield, Frölich & Nies, 1978) which mediates renin secretion, we conclude that the reduced increase of PRA, observed in hypertensive patients after frusemide is due to an impairment of PG synthesis at the site of the renin-producing cells in the afferent arteriole. In addition, since in hypertensive patients a low or an unresponsive PRA correlates with an increase of renal vascular resistance (Schalekamp et al., 1970), our findings suggest that the reduced increases of PGE₂ and kallikrein excretion after frusemide reflect a functionally important renal abnormality of these vasodilating systems possibly resulting in the observed decreases of renal blood flow and PRA in essential hypertension. Such an impaired capacity of the kidney to activate the PG- and kallikrein–kinin systems, whether due to genetic or to environmental factors, might also lead to a reduced buffering of vasoconstrictive compounds such as noradrenalin and angiotensin II with the consequence of an increased pressor response to these stimuli.

Acknowledgment

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References


