Modulation of sympathetic vascular tone by prostaglandins in corticosterone-induced hypertension in rats


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Summary

1. In corticosterone-induced hypertension in rats the activity of the peripheral sympathetic nervous system and its modulation by prostaglandins was studied.

2. Plasma concentrations of noradrenaline were reduced if compared with those in normotensive control rats.

3. The sensitivity of the isolated perfused hindlimb preparation to noradrenaline was enhanced before blood pressure rose and increased further with the development of hypertension.

4. Arachidonic acid, prostacyclin (prostaglandin I₂), but not 6-keto-prostaglandin F₁₀, reversed the supersensitivity to noradrenaline.

5. These results suggest that corticosterone induces a supersensitivity to noradrenaline by inhibiting the biosynthesis of prostaglandins. Changes in the sensitivity of the vascular smooth muscle may play a role in the development of glucocorticoid hypertension.

Key words: corticosterone hypertension, isolated hindlimb perfusion, plasma noradrenaline, prostaglandins, supersensitivity to noradrenaline.

Abbreviations: PG, prostaglandin; PGI₂, prostacyclin.

Introduction

In glucocorticoid hypertension of rats an increase in vascular smooth muscle sensitivity to noradrenaline has been reported which precedes the rise in blood pressure (Schömig, Lüth, Dietz & Gross, 1976). The present study was undertaken to investigate the role of the peripheral sympathetic nervous system in corticosterone-induced hypertension by measuring plasma concentrations of noradrenaline and the reactivity of the resistance vessels to noradrenaline. Since glucocorticoids inhibit the release of the prostaglandin (PG) precursor arachidonic acid from phospholipids (Hong & Levine, 1976; Blackwell, Flower, Nijkamp & Vane, 1978), it was also intended to study the role PG compounds may play in the modulation of sympathetically induced vasoconstriction in glucocorticoid hypertension.

Material and methods

Male Wistar rats (200–250 g) received corticosterone (Fluka, 2 × 20 mg day⁻¹ kg⁻¹) for 2, 7 and 21 days. Systolic blood pressure was measured by tail plethysmography under light ether anesthesia. Plasma concentrations of noradrenaline and adrenaline were measured by a radioenzymatic method (Da Prada & Zürcher, 1976). Blood was collected in conscious rats via a catheter in the femoral artery.

An isolated perfused hindlimb preparation was used to assess changes in reactivity of the vascular smooth muscle to noradrenaline. Weight- and age-matched pairs of rats were perfused at constant flow by the method of Folkow, Hallbäck, Lundgren & Weiss, 1970. The preparation was perfused with an oxygenated Tyrode’s solution containing 2% colloid (Ficoll). Cumulative dose–response curves to noradrenaline were obtained by perfusion with concentrations from 10⁻⁸ to 10⁻⁴ mol/l.

In rats which had received corticosterone for 2 days and in sham-treated controls a dose–response
curve to noradrenaline was first established. After maximum dilatation had been restored, arachidonic acid (10^{-5} \text{ mol/l}), or PGI\(_2\) (10^{-9} \text{ mol/l}) or 6-keto-PGF\(_{1\alpha}\) (10^{-9} \text{ mol/l}) was infused for 5 min. Immediately after the infusion was stopped, a second dose–response curve to noradrenaline was determined.

PGI\(_2\), as sodium salt, and 6-keto-PGF\(_{1\alpha}\) were generously provided by Upjohn Company (Bensheim, West Germany) and dissolved in Tyrode’s solution of pH 8.5 and 7.4 respectively. Arachidonic acid was purchased from Sigma (Munich, West Germany) and prepared as the sodium salt daily by dissolving the acid in absolute ethanol and then diluting with sodium carbonate solution (100 mmol/l) under nitrogen.

Results are given as means ± SEM. Significance of differences between the two experimental groups studied was assessed by Student’s \(t\)-test.

### Results

Within 10 days administration of corticosterone there was an increase in blood pressure (159 ± 2 mmHg vs 117 ± 2 mmHg), which afterwards levelled off at 160 mmHg (Table 1).

Plasma concentrations of noradrenaline measured at various intervals after the beginning of treatment with corticosterone were significantly lower than those obtained in sham-treated normotensive control rats. Plasma concentrations of adrenaline did not differ between the experimental groups (Table 1).

In the isolated perfused hindlimb preparation the dose–response curve to noradrenaline was shifted to the left before the rise in blood pressure. During the development of hypertension the shift to the left became more pronounced.

Arachidonic acid and PGI\(_2\) given for 5 min immediately before a second perfusion period with increasing concentrations of noradrenaline reversed the corticosterone-induced shift of the dose–response curve. The metabolite of PGI\(_2\), 6-keto-PGF\(_{1\alpha}\), did not have such an effect (Table 1).

### Discussion

These studies demonstrate that corticosterone reduces the plasma concentrations of noradrenaline, but increases the sensitivity of the vascular smooth muscle to noradrenaline. This supersensitivity to noradrenaline can be reversed by the administration of arachidonic acid and PGI\(_2\), but not by 6-keto-PGF\(_{1\alpha}\), the metabolite of PGI\(_2\). Reduction of plasma concentrations of noradrenaline might be regarded as compensatory

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**Table 1. Blood pressure, plasma concentrations of noradrenaline and adrenaline, and the response of the isolated perfused hindlimb preparation to noradrenaline in corticosterone-induced hypertension of rats**

<table>
<thead>
<tr>
<th>Time of treatment with corticosterone (days)</th>
<th>Blood pressure</th>
<th>Plasma concentration (pg/ml)</th>
<th>Response of the isolated perfused hindlimb preparation to noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood pressure</td>
<td>Noradrenaline</td>
<td>Adrenaline</td>
</tr>
<tr>
<td></td>
<td>(n) (mmHg)</td>
<td>(\text{pg/ml})</td>
<td>(\text{pg/ml})</td>
</tr>
<tr>
<td>2</td>
<td>B (20) 123 ± 3</td>
<td>(12) 125 ± 17**</td>
<td>83 ± 14</td>
</tr>
<tr>
<td></td>
<td>Control (20)</td>
<td>116 ± 2</td>
<td>121 ± 22</td>
</tr>
<tr>
<td>7</td>
<td>B (20) 146 ± 3**</td>
<td>(10) 135 ± 11**</td>
<td>85 ± 10</td>
</tr>
<tr>
<td></td>
<td>Control (20)</td>
<td>115 ± 2</td>
<td>198 ± 18</td>
</tr>
<tr>
<td>21</td>
<td>B (20) 161 ± 2**</td>
<td>(8) 134 ± 24*</td>
<td>82 ± 15</td>
</tr>
<tr>
<td></td>
<td>Control (20)</td>
<td>119 ± 2</td>
<td>206 ± 19</td>
</tr>
</tbody>
</table>

B, Corticosterone; \(n\), number of animals per group. Values are means ± SEM. Significance of difference from control values: *\(P < 0.05\); **\(P < 0.01\).

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<td>(\text{pg/ml})</td>
<td>(\text{pg/ml})</td>
</tr>
<tr>
<td>2</td>
<td>B (9) 2.5 ± 0.1**</td>
<td>3.8 ± 0.3</td>
<td>Saline</td>
</tr>
<tr>
<td></td>
<td>Control (9)</td>
<td>3.5 ± 0.2</td>
<td>Arachidonic acid</td>
</tr>
<tr>
<td>2</td>
<td>B (8) 2.9 ± 0.1**</td>
<td>3.5 ± 0.2</td>
<td>10^{-5} \text{ mol/l}</td>
</tr>
<tr>
<td></td>
<td>Control (8)</td>
<td>4.2 ± 0.3</td>
<td>PGI(_2) (10^{-9} \text{ mol/l})</td>
</tr>
<tr>
<td></td>
<td>B (9) 2.0 ± 0.1**</td>
<td>3.1 ± 0.2</td>
<td>6-Keto-PGF(_{1\alpha}) (10^{-9} \text{ mol/l})</td>
</tr>
</tbody>
</table>

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mechanism for the increased sensitivity of the vascular smooth muscle to noradrenaline. Recently a negative correlation between the plasma concentration of noradrenaline and the reactivity to exogenous noradrenaline has been reported in man (Philipp, Distler & Cordes, 1978). This relationship is altered in patients with essential hypertension, and it has been suggested that sympathetic nervous activity and the response to noradrenaline are important determinants for the level of arterial blood pressure.

In our study plasma concentrations of noradrenaline are reduced by 40% during the whole observation period. Whereas the sensitivity of the resistance vessels to noradrenaline increases up to 150% during the development of hypertension. The marked increase in vascular sensitivity together with the rise in blood pressure suggest that these changes in sensitivity may play a role in the development of corticosterone-induced hypertension.

In the established phase of hypertension, the increase in maximum contraction to noradrenaline indicates that structural changes in the wall of the resistance vessels contribute to the maintenance of high blood pressure (Folkow et al., 1970).

Studies on the mechanism of the supersensitivity of the hindlimb vessels after treatment with corticosterone revealed that neither changes in neuronal uptake nor extraneuronal metabolism of noradrenaline can be responsible for these changes (Schömig et al., 1976).

Corticosterone is the main glucocorticoid in the rat and glucocorticoids in high doses inhibit the release of arachidonic acid from phospholipids (Hong & Levine, 1976, Blackwell et al., 1978). Reversal of the supersensitivity to noradrenaline by arachidonic acid and PGI₂, the principal metabolite of arachidonic acid synthesized in vascular tissue (Armstrong, Dusting, Moncada & Vane, 1978), suggests that corticosterone induces supersensitivity to noradrenaline by inhibiting the biosynthesis of PG.

Decreases of PGI₂ after treatment with corticosterone represents a deficiency of a potent vasodepressor agent. The resulting increased vasoconstrictor tone cannot be sufficiently compensated by a reduction in sympathetic activity and in the activity of the renin-angiotensin system (Haack, Möhring, Möhring, Petri & Hackenthal, 1977).

Inhibition of the PG biosynthesis by the cyclo-oxygenase inhibitor indomethacin (Flower, 1974) also causes a supersensitivity of the isolated perfused hindlimb preparation to noradrenaline (unpublished observation). However, the shift of the dose–response curve to the left was not as marked as seen with corticosterone.

In conclusion our results demonstrate that inhibition of PG biosynthesis by cortisosterone causes a supersensitivity of resistance vessels to noradrenaline, which may be the trigger mechanism for the development of hypertension.

Acknowledgments

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References


