SHORT COMMUNICATION

Insulin-induced renin release: blockade by indomethacin in the rat

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Summary

1. Since prostaglandins appear to mediate adrenergically stimulated renin release, the effect of indomethacin was examined on insulin-induced renin and catecholamine release in conscious rats. Insulin (10 units/kg subcutaneously) increased plasma renin activity from 2.8 ± 0.5 to 9.0 ± 1.1 pmol h⁻¹ ml⁻¹ (P < 0.001) while also increasing plasma adrenaline, noradrenaline and the urinary excretion of prostaglandin E₂ and F₂α. Plasma potassium and glucose were reduced by 16 and 54% respectively.

2. Indomethacin (14 μmol/kg subcutaneously) reduced the urinary excretion of prostaglandin E₂ and F₂α by 67 and 54% respectively, without altering the other parameters.

3. Indomethacin inhibited insulin-induced renin release by 67% (P < 0.01) and blocked the insulin-induced increases in urinary prostaglandin E₂ and F₂α. The insulin-induced changes in plasma catecholamines, potassium and glucose were unaltered by indomethacin.

4. These findings suggest that renal prostaglandins mediate this form of adrenergically stimulated renin release by acting at a site distal to the β-adrenoreceptor.

Key words: adrenaline, glucose, indomethacin, insulin, noradrenaline, potassium, prostaglandin E₂, prostaglandin F₂α, renin.

Introduction

Insulin-induced hypoglycaemia has been found to stimulate the release of renin (Otsuka, Assaykeen, Goldfien & Ganong, 1970; Assaykeen, Clayton, Goldfien & Ganong, 1970; Hedeland, Dymling & Hokfelt, 1972; Lowder, Frazer & Liddle, 1975). This renin release is apparently mediated by a β-adrenergic mechanism since (1) it is accompanied by an increase in plasma catecholamine concentrations, (2) it is blocked by adrenalectomy, and (3) it is blocked by the β-adrenoreceptor antagonist propranolol and the α-adrenoreceptor agonist clonidine. We have found that renal prostaglandins mediate adrenergically stimulated renin release based on the observations that the prostaglandin-synthesis inhibitors, indomethacin and meclofenamate, block this form of renin release (Campbell, Graham & Jackson, 1979a). To examine this mechanism further, we have examined the effect of prostaglandin-synthesis inhibition on the adrenergically mediated renin release stimulated by insulin in the conscious rat.

Methods

Male Sprague–Dawley rats (250–300 g/body weight) (Simonsen Laboratories, Gilroy, California, U.S.A.) were used in these studies. Rats were maintained on Wayne rat chow and tap water to drink.

Indwelling arterial catheters were placed in the descending abdominal aorta by the method of Weeks (1970). After allowing 3–4 days for the rats to recover from the surgery, the rats were placed in cages in a quiet room and their arterial catheters
TABLE 1. Effect of indomethacin on insulin-induced renin release in the conscious rat

Each value is the mean ± SEM for eight rats. Significance of differences: *P < 0.05, **P < 0.01, ***P < 0.001 (compared with saline); †P < 0.05, ††P < 0.01, †††P < 0.001 (compared with insulin).

<table>
<thead>
<tr>
<th></th>
<th>Olive oil</th>
<th>Indomethacin</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Indomethacin</td>
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<tr>
<td>Plasma renin activity</td>
<td>2.8 ± 0.5</td>
<td>9.0 ± 1.1***</td>
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<td>(pmol of angiotensin I h⁻¹ ml⁻¹)</td>
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<tr>
<td>Plasma noradrenaline</td>
<td>1.18 ± 0.15</td>
<td>2.25 ± 0.48*</td>
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<td>(pmol/ml)</td>
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<tr>
<td>Plasma adrenaline</td>
<td>0.31 ± 0.07</td>
<td>4.31 ± 1.31***</td>
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<tr>
<td>(pmol/ml)</td>
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<tr>
<td>Mean arterial pressure</td>
<td>106 ± 5</td>
<td>103 ± 5</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>368 ± 9</td>
<td>376 ± 9</td>
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<tr>
<td>Plasma potassium</td>
<td>4.01 ± 0.25</td>
<td>3.38 ± 0.13*</td>
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<tr>
<td>(mmol/l)</td>
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<tr>
<td>Plasma glucose</td>
<td>5.0 ± 0.3</td>
<td>2.3 ± 0.3***</td>
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<tr>
<td>(mmol/l)</td>
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<tr>
<td>Urinary prostaglandin E₁ (pmol/8 h)</td>
<td>124.4 ± 20.7</td>
<td>219.6 ± 19.6**</td>
</tr>
<tr>
<td>Urinary prostaglandin F₂₁ (pmol/8 h)</td>
<td>125.3 ± 7.6</td>
<td>213.1 ± 33.0*</td>
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</table>

Plasma renin activity was measured by the antibody-trapping method of Poulsen & Jorgensen (1974), plasma catecholamines by the radio-enzymatic method of Peuler & Johnson (1977), and urinary prostaglandins by a modification (Campbell et al., 1979a, b) of the method of Dray, Charbonnel & Maclouf (1975). Plasma potassium was measured by flame photometry (Beckman Instruments) and glucose by a Beckman glucose analyser.

Statistical analyses to determine whether the four treatments differed from each other were performed with an analysis of variance. Then Student's t-test was used to determine the statistical significance between the treatments and values are reported in the text and Table 1.

Results

Insulin increased plasma renin activity from 2.8 ± 0.5 to 9.0 ± 1.1 pmol h⁻¹ ml⁻¹ (P < 0.001) as well as increasing plasma noradrenaline and adrenaline (Table 1). The increase in plasma adrenaline was greater than the increase in noradrenaline and was more variable. Plasma potassium and glucose were decreased by 16 and 54% respectively. The urinary excretions of prostaglandin E₁ and F₂₁ were increased significantly by insulin. Blood pressure and heart rate were unaltered.
Indomethacin alone decreased the urinary excretion of prostaglandin \( E_2 \) and \( F_{2 \alpha} \) by 67 and 54% respectively (Table 1). The other parameters measured were unchanged.

In contrast, indomethacin inhibited the insulin-induced increase in plasma renin activity by 68% \((P < 0.01)\) and completely blocked the insulin-induced increases in urinary prostaglandin \( E_2 \) and \( F_{2 \alpha} \). Indomethacin failed to reduce the elevated plasma noradrenaline concentrations and tended to further elevate the plasma adrenaline concentrations. However, this latter effect was variable and failed to attain statistical significance. Indomethacin also failed to elevate the reduced plasma potassium and glucose concentrations produced by insulin. Although blood pressure was unchanged, heart rate was found to decrease slightly (12%, \(P < 0.01)\).

**Discussion**

Studies have indicated that renal prostaglandins function as important mediators of renin release from the kidney. This conclusion has been based on direct evidence obtained from the administration of the prostaglandin precursor, arachidonic acid, or the various prostaglandins themselves. In these studies, arachidonic acid increased the release of renin both in vivo and in vitro, an effect blocked by the prostaglandin-synthesis inhibitor indomethacin (Larsson, Weber & Anggard, 1974; Weber, Larsson, Anggard, Hamberg, Corey, Nicolaou & Samuelsson, 1976; Whorton, Misono, Hollifield, Frolich, Inagami & Oates, 1977). Thus arachidonic acid must be converted into one of its prostaglandin metabolites to exert this action. Similarly, prostaglandin \( E_2 \), prostaglandin \( D_2 \) and prostaglandin \( I_2 \) stimulated renin release in vivo (Bolger, Eissner, Ramwell & Slotkoff, 1978; Gerber, Branch, Nies, Gerkens, Shand, Hollifield & Oates, 1978). However, only the prostaglandin endoperoxides and prostaglandin \( I_2 \) stimulated renin release in vitro (Weber et al., 1976; Whorton et al., 1977). Since the prostaglandin endoperoxides are converted into prostaglandin \( I_2 \) in the renal cortex (Whorton, Smigel, Oates & Frolich, 1978), prostaglandin \( I_2 \) appears to be the arachidonic acid metabolite that is involved in the control of renin release.

Additional evidence indicating that endogenous renal prostaglandins participate in the control of renin release has been obtained with the prostaglandin-synthesis inhibitors. In these studies, indomethacin inhibited baroreceptor-mediated renin release (Data, Gerber, Crump, Frolich, Hollifield & Nies, 1978) and sympathetically mediated renin release (Campbell et al., 1979a) but not macula densa-mediated renin release (Norbiato, Bevilacqua, Raggi, Micossi, Moroni & Fasoli, 1978; Campbell et al., 1979b). These studies suggest that renal prostaglandins function as chemical mediators of baroreceptor-mediated and sympathetically mediated renin release.

In the present study, insulin-induced hypoglycaemia stimulated the release of catecholamines, renal prostaglandins and renin. The prostaglandin-synthesis inhibitor, indomethacin, inhibited this insulin-induced release of renal prostaglandins and renin without reducing the elevated plasma catecholamine concentrations. In fact, the plasma adrenaline concentrations tended to increase more with insulin in indomethacin-pretreated rats than in normal rats. These findings indicate that indomethacin inhibits the release of renin in the presence of elevated concentrations of circulating catecholamines indicating that the prostaglandin-synthesis inhibitor is acting at a site distal to the juxtaglomerular beta-adrenoreceptor. This contention is supported by our previous findings that indomethacin and meclofenamate inhibited adrenergically mediated release of renin that was stimulated by hydralazine, the beta agonists, isoprenaline and compound H133/22, and dibutyryl cyclic AMP (Campbell et al., 1979a). These two studies indicate that renal prostaglandins mediate adrenergically stimulated renin release in the rat.

A similar inhibition of insulin-induced renin release has been reported with the beta-adrenoreceptor antagonist propranolol (Assaykeen et al., 1970; Lowder et al., 1975). As with indomethacin, propranolol blocked insulin-induced renin release without altering the hypoglycaemia, hypokalaemia or catecholamine release caused by insulin (Assaykeen et al., 1970). In contrast, Hedeland et al. (1972) found that clonidine inhibited the increase in catecholamine release and renin release induced by insulin without altering insulin hypoglycaemia. These studies indicate that the adrenergically mediated renin release stimulated by insulin may be inhibited distal to the beta-adrenoreceptor by indomethacin, at the beta-adrenoreceptor by propranolol, and before the beta-adrenoreceptor at the level of catecholamine release by clonidine.

Alternatively, potassium depletion and hypokalaemia stimulated the release of renin (Abbrecht & Vander, 1970; Galvez, Bay, Roberts & Ferris, 1977), and this effect was blocked by inhibition of
prostaglandin synthesis in the dog (Galvez et al., 1977). Since insulin reduced the plasma potassium concentrations in this study, the possibility must be considered that hypokalaemia as well as the elevated circulating plasma catecholamines mediated the renin release. However, this possibility appears unlikely since Otsuka et al. (1970) found that maintaining the plasma potassium within the normal range failed to alter insulin-induced renin release. This finding, combined with the observations that blocking of β-adrenoceptors with propranolol or blocking the increase in circulating catecholamine with adrenalectomy or clonidine inhibit insulin-induced renin release, emphasizes that the sympathetic nervous system rather than hypokalaemia mediates the renin release produced by insulin (Assaykeen et al., 1970; Hedeland et al., 1972; Lowder et al., 1975).

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References


