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SHORT COMMUNICATION

The effect of indomethacin and prostaglandin (PGE₂) on renal failure due to glycerol in saline-loaded rats

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Summary

1. Acute renal failure was induced in conscious rats by subcutaneous injection of glycerol.
2. Expansion of the extracellular space by infusion of 150 mmol/l sodium chloride (saline) partly protected the animals against acute renal failure.
3. This protective effect of saline infusion disappeared when the animals were treated with indomethacin. This effect could be reversed by the addition of prostaglandin (PGE₂) to the saline infusion.
4. We suggest that prostaglandins may be involved in mediating the protection afforded by saline infusion against acute renal failure due to glycerol.

Key words: extracellular space expansion, glycerol-induced renal failure, prostaglandins release.

Introduction

In acute renal failure in the rat it has been shown that the decrease in renal plasma flow and glomerular filtration rate may result from an increase in pre-glomerular resistance (Oken, Arce & Wilson, 1966; Ayer, Grandchamp, Wyler & Truniger, 1971).

The mechanism responsible for the increase in pre-glomerular resistance is not fully understood but among the factors that have been implicated in the afferent arteriolar contraction are the renin–angiotensin system, renal nerves, circulating catecholamines and other vasoactive mediators (Brown, Brown, Gavras, Jackson, Lever, McGregor, MacAdam & Robertson, 1972; Kokot & Kuska, 1969; Oken et al., 1966; Ayer et al., 1971; Powell-Jackson, Brown, Lever, McGregor, MacAdam, Titterington, Robertson & Watte, 1972).

It is established that infusion of 150 mmol/l sodium chloride (saline) protects against acute renal failure caused by glycerol (Wilson, Thiel, Arce & Oken, 1967, 1969) since saline infusion has been shown to induce the release of prostaglandins (Papanicolaou, 1972; Shimizu, Yamamoto & Yoshitoshi, 1973), which are known to increase renal blood flow (Johnston, Herzog & Lauler, 1967; Vander, 1968; Shimizu, Kurosawa, Maeda & Yoshitoshi, 1969; Hornych, Safar, Papanicolaou, Meyer & Milliez, 1973) and to inhibit the renal effects of pressor systems (McGiff, Terragno, Crowshaw & Lonigro, 1970), we decided to investigate whether the protective effect of saline infusion against acute renal failure could be attributed to release of prostaglandins.

Material and methods

Male Wistar rats weighing 300–350 g (mean 330 g) were used. The animals were divided into seven groups and treated as indicated in Table 1. Acute renal failure was induced in conscious animals by injecting (10 ml/kg) a 50% (v/v) glycerol solution in physiological saline into subcutaneous tissues of the
Subcutaneous doses: saline, 10 ml/kg; glycerol, 10 ml/kg of 50% (v/v) glycerol in saline. Infusions: saline, 83 µl min⁻¹ kg⁻¹; indomethacin, 67 µmol (8 mg) 24 h⁻¹ kg⁻¹; PGE₂, 0.57 nmol (0.2 µg) min⁻¹ kg⁻¹. No statistically significant differences were found in mean plasma creatinine concentrations and urinary outputs between groups 2 and 4 (P<0.10 and 0.35 respectively) and between groups 3 and 5 (P<0.35 and 0.25 respectively).

<table>
<thead>
<tr>
<th>Group no.</th>
<th>Subcutaneous injection</th>
<th>Infusion or gavage</th>
<th>Conc. of plasma creatinine (µmol/l)</th>
<th>Volume of urine (ml 24 h⁻¹ kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 12</td>
<td>+ -</td>
<td>-</td>
<td>38±9 ± 1.8</td>
<td>17±7 ± 1.5</td>
</tr>
<tr>
<td>2 12</td>
<td>- +</td>
<td>-</td>
<td>125.5±15.0</td>
<td>35±1 ± 7.0</td>
</tr>
<tr>
<td>3 17</td>
<td>- +</td>
<td>+</td>
<td>83.1±10.6</td>
<td>72±2 ± 7.2</td>
</tr>
<tr>
<td>4 16</td>
<td>- +</td>
<td>+</td>
<td>160.9±17.7</td>
<td>31.4± 5.5</td>
</tr>
<tr>
<td>5 14</td>
<td>- +</td>
<td>+</td>
<td>98.1±25.6</td>
<td>65.4± 4.6</td>
</tr>
<tr>
<td>6 12</td>
<td>- -</td>
<td>+</td>
<td>51.3± 2.7</td>
<td>44±1 ± 8.8</td>
</tr>
<tr>
<td>7 15</td>
<td>- -</td>
<td>+</td>
<td>42±4± 1.8</td>
<td>110±9 ±13.6</td>
</tr>
</tbody>
</table>

(1) Administered by gastric gavage.

The subhypotensive dose of PGE₂ used in group 5 was determined as follows. Rats were anaesthetized and a polyethylene catheter was inserted into a carotid artery, and brought to the back of the neck. After recovering from the anaesthetic, the animals were immobilized in metabolic cages, the catheter was connected to a Palmer mercury manometer and blood pressure recordings were made on a Palmer recording drum. Various concentrations of PGE₂ solutions were infused intramuscularly by a Braun continuous-infusion pump at a rate of 83 µl min⁻¹ kg⁻¹. The subhypotensive dose was found to be lower in the rats with renal insufficiency. Fichman (1970) found the same phenomenon when PGA₁ was infused into anephric patients. Doses in excess of the subhypotensive dose resulted in decrease in blood pressure and subsequent death of the animal.

Results

Glycerol injected subcutaneously in normal rats induced acute renal failure. Although urinary output increased significantly, this increase was accompanied by a significant increase of plasma creatinine concentration (group 2). Saline infusion partly protected the animals against the effect of glycerol (group 3). Thus plasma creatinine concentration was significantly lower and urinary output significantly higher

Abbreviation: PGE₂, prostaglandin E₂.
in group 3 than in group 2. This protective effect of saline infusion disappeared when the animals were treated with indomethacin, plasma creatinine being significantly higher and urinary output significantly lower in this group of animals (group 4) than in group 3. Furthermore, no significant differences were found in mean plasma creatinine and urinary output respectively, between the groups 4 and 2. The addition of PGE2 to the saline infusion partly restored the protective effect of saline in indomethacin-treated animals (group 5). Thus plasma creatinine was statistically lower and urinary output statistically higher in group 5 than in group 4. Furthermore, no statistically significant difference was found in plasma creatinine and urinary output between groups 3 and 5.

**Discussion**

The mechanism by which glycerol, administrated either intramuscularly or by the subcutaneous route, causes the functional and anatomical changes of acute renal failure has been studied extensively. Glycerol is not toxic per se (Finck, 1959; Mason, Alexander & Teschan, 1963). Finck (1959, 1965) attributed renal insufficiency to a number of vascular mechanisms. Oken *et al.* (1966) attributed acute renal failure to an aberration in glomerular afferent- effenter arteriolar tone. Ayer *et al.* (1972) showed that renal plasma flow and glomerular filtration rate decreased during glycerol-induced acute renal failure and concluded that renal failure in this experimental model is due to a primary decrease in glomerular filtration rate resulting from an increased pre-glomerular resistance. Brown *et al.* (1972) and Powell-Jackson *et al.* (1972) suggested that the renin–angiotensin system may be responsible for this and is probably involved in the pathogenesis of ischaemic acute renal failure.

The above suggestion is in agreement with the protection afforded by saline infusion against acute renal failure (Wilson *et al.*, 1967, 1969). Thus it has been shown that saline loading and denervation of the kidney reduce its renin content (Gross & Vander, 1960; Gavras, Brown, Lever & Robertson, 1970) and protect against acute renal failure (McDonald, Thiel, Wilson, Dibona & Oken, 1969; Thiel, McDonald & Oken, 1970; Haves, Boonshaft, Maher, O'Connell & Schreiner, 1970).

In this investigation, we have shown that the partial protective effect of saline infusion against glycerol-induced acute renal failure disappeared after treatment with indomethacin, which inhibits prostaglandin synthesis (Vane, 1971). We have further shown that the addition of PGE2, which reduces peripheral resistance and increases renal plasma flow and glomerular filtration rate as well as sodium and water excretion (Johnston *et al.*, 1967; Vander, 1968; Shimizu *et al.*, 1969; Hornych *et al.*, 1973), to the saline infusion restored protection by saline even after the administration of indomethacin (group 5).

Because prostaglandins are released by saline infusion (Papanicolaou, 1972; Shimizu *et al.*, 1973) we have concluded that in this model of experimental acute renal failure the partial protection afforded by saline infusion may result from the renal stimulatory effect on prostaglandin synthesis and the inhibition of renin synthesis and release (Gross & Vander, 1968; Gavras *et al.*, 1970).

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