Prostaglandin Synthesis by Glomeruli Isolated from Rats with Glycerol-Induced Acute Renal Failure

JEAN-DANIEL SRAER, LUC MOULONGUET-DOLERIS, FRANCOISE DELARUE, JOSÉE SRAER, AND RAYMOND ARDAILOU

SUMMARY In vitro PG synthesis by glomeruli isolated from rats with glycerol-induced acute renal failure (ARF) was measured by radiometric high performance liquid chromatography after incubation with [14C]arachidonic acid and radioimmunoassay (RIA). The four PGs, 6-keto-PGF₁α, TXB₂, PGF₂α, and PGE₂ were each synthesized by glomeruli from both control and treated rats but the synthesis rates were greater after glycerol. This increase was not apparent 1 hour after injection but, at 24 hours, all PGs were produced in greater amounts by glomeruli of treated rats. Thus, we studied PGE₂, PGF₂α, and TXB₂ synthesis by glomeruli at various time intervals after induction of ARF using direct RIA. PGF₂α and TXB₂ synthesis were greater only at 24 hours and only in the presence of arachidonic acid, whereas PGE₂ synthesis was greater at 24 hours, irrespective of arachidonic acid, but at 48 hours only with arachidonic acid. The stimulatory effect of arachidonic acid was always greater in glycerol-treated than in control rats for these three PGs in the later period, whereas a significant decrease for PGE₂ was observed at 1 hour. The late increase in PG synthesis may be due to stimulation of the renin-angiotensin system since it was abolished in rats pretreated for 48 hours with captopril. A late increase in PG synthesis by the papilla of the treated rats also was observed. We conclude that any increase in the glomerular production of vasoconstrictor PGs could contribute to the maintenance of acute renal failure, whereas the early fall in the stimulatory effect of arachidonic acid on PGE₂ synthesis could play a role in its initiation.


GLYCEROL, when injected intramuscularly or subcutaneously in large doses to dehydrated rats, produces acute renal failure (ARF) similar to that observed in patients with crush syndrome (Oken et al., 1966; Ayer et al., 1971; Flamenbaum et al., 1973; Churchill et al., 1977), but the mechanism of the failure remains largely unknown. Whereas renal plasma flow and glomerular filtration rate decrease (Chedru et al., 1972) due to an increased pre-glomerular resistance (Ayer et al., 1971; Chedru et al., 1972), a change in the function of the glomerular cells themselves has not been suggested, although it is now recognized that the glomerular capillary ultrafiltration coefficient may be reduced in various pathological models (Baylis et al., 1977; Bohrer et al., 1977) and with various agents, particularly angiotensin II (Blantz et al., 1976). This effect of angiotensin II is enhanced by substances that inhibit PG synthesis (Baylis and Brenner, 1978), a potentially important finding in relation to our demonstration that isolated glomeruli synthesize various PGs and mainly PGE₂ (Sraer et al., 1979b). Taken together with the findings that indomethacin enhances glycerol-induced ARF in rabbits (Papanicolaou et al., 1975) and that salt loading protects glycerol-injected animals (Torres et al., 1975; Chedru et al., 1972), roles for both PGs and renin-angiotensin seem possible in ARF. The present study was designed to follow PG synthesis by isolated glomeruli during the development, the sustained phase, and the recovery from glycerol-induced ARF in the rat in order to appreciate better whether changes in synthesis play a role in the initiation and the maintenance of this syndrome.

Methods

Preparation of Animals

Male Sprague-Dawley rats weighing 180-200 g were kept without water for 24 hours before the experiment. They were anesthetized lightly with ether. Acute renal failure was induced by the injection into both hindlimbs of 10 ml/kg body weight of 50% glycerol in 0.28 m glucose (30.5 mmol glycerol/kg). Control rats received the same amount of solvent. The animals were allowed free access to tap water after the injection. At different times after the induction of acute renal failure (0.5, 1, 2, 4, 24, 48, 72, and 192 hours), two treated and two control rats were anesthetized with pentobarbital sodium (5 mg/100 g, ip). A cannula was inserted into the lower aorta, and isotonic cold heparinized saline was perfused after the aorta had...
been clamped above the renal arteries and a renal vein or vena cava opened for drainage. Blanched kidneys were removed and immersed in ice-cold 20 mM Tris-HCl buffer, pH 7.4, containing 125 mM NaCl, 10 mM KCl, 10 mM sodium acetate, and 5 mM glucose. All subsequent steps were carried out in the same buffer at 0–4°C. This experiment was repeated 4–12 times according to the stage of ARF investigated.

A limited number of rats were treated differently. They were not dehydrated before glycerol administration but for 48 hours were offered either water or water containing 2.5 g/liter captopril (Squibb), an orally active inhibitor of angiotensin I-converting enzyme. Each of these groups was then divided into two subgroups treated either with glycerol in glucose solution or with glucose solution alone. The rats were killed after a further 24 hours, during which time captopril was maintained in the drinking solution.

Preparation of Glomeruli and Papilla

Glomeruli were isolated as previously described with minor modifications (Sraer et al., 1979b). Kidney cortical tissue from two rats was minced to a paste-like consistency and gently pressed through a 106-μm stainless steel sieve. The sieved tissue was suspended in 10 ml buffer, poured onto a 50-μm stainless sieve, and washed with buffer. The tissue recovered on the upper face was then resuspended in 10 ml buffer, passed through a 25-gauge needle, and centrifuged at 120 g for 90 seconds. This operation was repeated three times. The final pellet consisted of decapsulated glomeruli with less than 2% tubular contamination. The glomeruli of treated and control rats were prepared in parallel. Glomeruli isolated in this way can be considered as viable for at least 1 hour for two reasons: They exclude trypan blue stain; their cells grow rapidly after seeding in a plastic flask in the presence of a culture medium (Sraer et al., 1979a).

Papillary homogenates were prepared from the same rats as follows: The cone-shaped white papilla protruding in the renal pelvis (inner medulla) was separated from the red outer medulla, minced and homogenized mildly by 3–5 strokes in a tissue grinder. The resulting suspension was filtered and homogenized papillary tissue was kept in 2 ml cold buffer until use.

Incubations

A few minutes before incubation, glomeruli and papillary homogenates were centrifuged (1500 g for 10 minutes) and resuspended in the same buffer but with addition of 1 mM CaCl₂. Glomeruli and papillary homogenates from both control and treated rats were incubated in this buffer in the absence or in the presence of arachidonic acid, 5 μg/ml final concentration. This concentration produced maximal stimulation in both papillary homogenates and glomeruli. Arachidonic acid (sodium salt) was obtained from Sigma, kept under nitrogen atmosphere at −20°C, and extemporaneously dissolved in ethanol-water (7:10, vol/vol). Incubations were carried out in 200-μl aliquots at 37°C in room air with continuous agitation. Incubation was stopped usually after 60 minutes by centrifugation at 3000 g for 2 minutes at 10°C. In some experiments, three incubation times (15, 30, and 60 minutes) were studied. Supernatants of each tube were collected and frozen until PG radioimmunoassays were performed. Protein concentration (300–800 μg/ml) was determined according to the method of Lowry et al. (1951).

PGs of the incubation medium were measured by radioimmunoassay either directly or after separation by high performance liquid chromatography (HPLC). When HPLC was used, isolated glomeruli (approximately 2.6 mg protein) were incubated in the presence of 8.9 μg [14C]arachidonic acid (1.6 μCi) under a volume of 1.3 ml. The other conditions of incubation were similar to those stated above. Incubation was stopped after 60 minutes by centrifugation. The supernatant was collected and immediately used for extraction and chromatography analysis.

Prostaglandin Assays

High Performance Liquid Chromatography

PGs resulting from the conversion of [14C]arachidonic acid were extracted and purified by silicic acid chromatography according to the method of Dray et al. (1975), with the following modification: the totality of cyclo-oxygenase end-products were eluted simultaneously by 10 ml of benzene: ethylacetate: methanol (60:40:20, vol/vol). Prior to extraction, triturated PGs (PGE₂, PGF₂α, TXB₂, and 6-keto-PGF₁α) purchased from the Radiochemical Center or New England Nuclear were added as internal standards to the supernatant of the glomerular suspension. The elution product was evaporated at 45°C under a nitrogen stream. The dry residue was dissolved in 120 μl of HPLC eluent (acetonitrile:benzene:acetic acid:water, 210:2:1:790, vol/vol). Five microliters were kept for 14C and 3H counting, and 100 μl were submitted to HPLC. We used the model 5000 Varian liquid chromatograph equipped with a micropack CH 10 column (4 mm id x 30 cm). The flow rate of the eluent was 1.6 ml per min and per tube. The content of each tube was divided into two aliquots. One was immediately used for 14C and 3H counting. The other was lyophilized and kept for PG radioimmunoassay.

PG Radioimmunoassay

RIA was carried out according to the method of Dray et al. (1975) for PGE₂ and PGF₂α, that of Sors Dray et al. (1975) for PGE₂ and PGF₂α, that of Sors
et al. (1978) for TXB₂ and that of Dray et al. (1978) for 6-keto-PGF₁₀. The corresponding antiserums were obtained from the Institut Pasteur. Each of them is specific and cross-reacts only negligibly with the other PGs. RIA was performed either directly, using the untreated incubation medium, or after HPLC purification. In most experiments, direct RIA was used. A blank value obtained with the medium incubated in the absence of glomeruli was subtracted.

Statistical Analysis

Replicate data were subjected to two-factor (time of sacrifice-treatment by glycerol) analysis of variance. Separate analyses were performed for data obtained under basal conditions, in the presence of arachidonic acid and also for the differences between these two. The replications (4 to 12) corresponded to identical experiments performed on different days. In order to evaluate the effect of the treatment by glycerol at each time after the injection, we performed t-tests using as variance of each group the residual variance calculated from the two-factor analysis of variance. We have similarly evaluated the differences between two selected times when we felt it necessary.

Results

HPLC Profiles of [¹⁴C]PGs Produced by Glomeruli Isolated from Control and Glycerol-Treated Rats

Separation of the metabolites of [¹⁴C]arachidonic acid was performed using the incubation mediums of glomeruli isolated from control and glycerol-treated rats sacrificed at 1 and 24 hours. The results are shown in Figure 1. The data obtained from control rats sacrificed at one hour have been omitted since they were strictly identical to those obtained with control rats killed at 24 hours. The same profile was observed in each case. Four PGs, PGE₂, PGF₂α, TXB₂, and 6-keto-PGF₁₀, were clearly identified since, for each of them, the [¹⁴C] peak coincided both with the peak of the corresponding [³H] standard and with that of PG concentration measured by specific radioimmunoassay. Coincidence was perfect in the latter case, whereas there was a short delay between the elution times of [¹⁴C] and [³H] PGs. Other peaks localized between 6-keto-PGF₁₀ and TXB₂ or eluted initially before 6-keto-PGF₁₀ were also present but could not be identified. A clear difference appeared between the heights of the peaks obtained under the three different conditions. The [¹⁴C] peaks of PGE₂, PGF₂α, TXB₂, and, to a lesser degree, of 6-keto-PGF₁₀, were markedly greater with glomeruli obtained from glycerol-treated rats killed at 24 hours than with the two other preparations (Fig. 1). There was, however, no clear difference between the heights of the unidentified peaks. These results were confirmed by the

![Figure 1](http://circres.ahajournals.org/)

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Control rate</th>
<th>Glycerol-treated rats (1 hr)</th>
<th>Glycerol-treated rats (24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Keto PGF₁₀</td>
<td>0.54 ± 0.08</td>
<td>0.58 ± 0.03</td>
<td>2.08 ± 0.07†</td>
</tr>
<tr>
<td>TXB₂</td>
<td>6.0 ± 1.94</td>
<td>5.0 ± 1.06</td>
<td>12.2 ± 2.3*</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>3.14 ± 0.71</td>
<td>2.37 ± 0.30</td>
<td>6.4 ± 0.9*</td>
</tr>
<tr>
<td>PGE₂</td>
<td>4.52 ± 0.28</td>
<td>2.95 ± 0.30</td>
<td>16.3 ± 0.55†</td>
</tr>
</tbody>
</table>

PGs were estimated by radioimmunoassay after HPLC purification. Results are means ± SEM from six (control rats) or four (treated rats) individual values. Rank sum test was used to compare the means (glycerol-treated rats vs. control rats).

* P < 0.05; †P < 0.01.
PGE₂ synthesis by glomeruli (direct RIA) isolated from control and glycerol-treated rats that were killed at different times (0-4 hours below and 24-192 hours above) after administration of the solvent or of the drug. On the left are shown the results obtained under basal conditions and on the right those obtained in the presence of arachidonic acid (5 μg/ml).

The height of each rectangle represents the mean, and the vertical bar the SEM of the individual results (4-12 according to the time of sacrifice). The results obtained with and without arachidonic acid were analyzed separately according to a two-factor (glycerol-treated vs. control at eight times of sacrifice) analysis of variance with a variable number (4-12) of repetitions.

*P < 0.05; **P < 0.01; ***P < 0.001.

Note the differences in scale between the right and the left parts.

Quantitative data obtained by RIA after HPLC separation (Table 1), showing that the production rate of PGs by glomeruli from glycerol-treated rats killed at 24 hours was much greater (2- to 4-fold) than that by glomeruli from the corresponding control rats. No modification of PG synthesis by the glomeruli could be observed 1 hour after glycerol administration (Table 1). These initial results prompted us to analyze more precisely the changes with time of PG synthesis by glomeruli isolated from control and treated rats.

PGE₂, PGF₂α, and TXB₂ Synthesis by Glomeruli from Control and Glycerol-Treated Rats Killed at Different Times after Administration of the Drug

In vitro PGE₂ production was studied by direct RIA both under basal conditions and in the presence of 5 μg/ml arachidonic acid (Fig. 2). Under basal conditions, there was no difference between control and treated rats at the early times (0.5-4 hours) after administration of glycerol, whereas PGE₂ synthesis by the glomeruli from treated rats was increased at 24 hours (P < 0.05). This difference disappeared at later times. Similarly, when incubation was performed with arachidonic acid, no difference between the preparations from both groups was observed early but PGE₂ synthesis by the glomeruli from treated rats was greater at 24 (P < 0.001) and 48 (P < 0.01) hours. The stimulatory effect of arachidonic acid estimated as the difference between PG production obtained under basal conditions and in the presence of this precursor was also tested. Stimulation was smaller at 1 hour (P < 0.05) and greater at 24 (P < 0.001) and 48 (P < 0.001) and 72 (P < 0.05) hours in glycerol-treated rats than in control rats (Table 2). There was also an influence of time on PGE₂ production by the...

Table 2: Stimulatory Effect of Arachidonic Acid on PG Production by Glomeruli Isolated from Control (C) and Glycerol-Treated (G) Rats (ng/mg per hr).

<table>
<thead>
<tr>
<th>Time of sacrifice (hr)</th>
<th>PGE₂ C</th>
<th>G</th>
<th>PGF₂α C</th>
<th>G</th>
<th>TXB₂ C</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>3.38 ± 0.34</td>
<td>3.68 ± 0.95</td>
<td>1.36 ± 0.36</td>
<td>1.02 ± 0.33</td>
<td>0.266 ± 0.22</td>
<td>0.027 ± 0.14</td>
</tr>
<tr>
<td>1</td>
<td>3.49 ± 0.59</td>
<td>2.40 ± 0.37*</td>
<td>1.10 ± 0.44</td>
<td>0.651 ± 0.20</td>
<td>0.43 ± 0.13</td>
<td>0.37 ± 0.21</td>
</tr>
<tr>
<td>2</td>
<td>2.37 ± 0.38</td>
<td>1.81 ± 0.32</td>
<td>2.33 ± 0.46</td>
<td>3.48 ± 0.22</td>
<td>2.84 ± 0.091</td>
<td>0.010 ± 0.003</td>
</tr>
<tr>
<td>4</td>
<td>3.23 ± 0.58</td>
<td>1.22 ± 1.23†</td>
<td>1.44 ± 0.39</td>
<td>1.26 ± 0.48</td>
<td>0.085 ± 0.087</td>
<td>0.85 ± 0.33</td>
</tr>
<tr>
<td>24</td>
<td>2.57 ± 0.63</td>
<td>12.02 ± 1.23†</td>
<td>1.84 ± 0.36</td>
<td>1.75 ± 0.42</td>
<td>0.758 ± 0.34</td>
<td>2.51 ± 1.2</td>
</tr>
<tr>
<td>48</td>
<td>3.48 ± 0.39</td>
<td>6.74 ± 1.37†</td>
<td>1.84 ± 0.36</td>
<td>1.75 ± 0.42</td>
<td>0.464 ± 0.11</td>
<td>0.97 ± 0.28</td>
</tr>
<tr>
<td>72</td>
<td>3.71 ± 0.81</td>
<td>5.42 ± 0.94*</td>
<td>1.84 ± 0.36</td>
<td>1.75 ± 0.42</td>
<td>0.464 ± 0.11</td>
<td>0.97 ± 0.28</td>
</tr>
<tr>
<td>192</td>
<td>4.71 ± 0.7</td>
<td>4.24 ± 0.60</td>
<td>1.30 ± 0.16</td>
<td>1.88 ± 0.42</td>
<td>0.758 ± 0.34</td>
<td>2.51 ± 1.2</td>
</tr>
</tbody>
</table>

Results represent the means ± SEM of individual differences between PG productions obtained in parallel with and without arachidonic acid. Two-factor (time of sacrifice, treatment by glycerol) analysis of variance with replication was used to analyze the data obtained for each PG; a test between the two groups was subsequently performed at each time using as variance of each group the residual variance calculated from the two-factor analysis of variance.

* P < 0.05; † P < 0.001
glomeruli from both groups of rats; production fell at 2 hours whatever the origin of the glomerular preparation studied and increased again at 4 hours. Differences between production at 2 hours and production at either 1 or 4 hours were significant \( P < 0.01 \) under basal conditions as well as in the presence of arachidonic acid.

PGF\(_{2a}\) and TXB\(_2\) syntheses were studied for a limited number of periods after sacrifice (0.5 and 4 hours were omitted). PGF\(_{2a}\) synthesis by the glomeruli from both groups was similar under basal conditions, whatever the times of sacrifice (Fig. 3). In the presence of arachidonic acid, PGF\(_{2a}\) synthesis by the glomeruli from treated rats was greater at 24 hours \( P < 0.001 \). A similar pattern was observed for TXB\(_2\) synthesis (Fig. 4). There was an increase in TXB\(_2\) synthesis by the glomeruli from treated rats only at 24 hours and in the presence of arachidonic acid \( P < 0.001 \). For both PGs, the stimulatory effect of arachidonic acid was greater at 24 hours in glycerol-treated rats \( P < 0.001 \). It is noteworthy that, contrary to what was observed for PGE\(_2\) and PGF\(_{2a}\), there was no stimulation of TXB\(_2\) synthesis by arachidonic acid when glomeruli from control rats were studied. Stimulation was observed only with glomeruli from glycerol-treated rats.

These experiments confirmed and extended the data obtained after HPLC purification. The main new observation was the early decrease of the stimulatory effect of arachidonic acid on PGE\(_2\) production at 1 hour.

**Effect of Pretreatment by Captopril on PGE\(_2\) Synthesis by Glomeruli Isolated from Control and Glycerol-Treated Rats Killed at 24 Hours**

In the absence of pretreatment by captopril, the results obtained confirmed those already observed. PGE\(_2\) synthesis by glomeruli isolated from glycerol-

\[ \text{PGF}_{2a} \text{ synthesis by glomeruli (direct RIA) isolated from control and glycerol-treated rats that were killed at different times after administration of the solvent or of the drug. On the left are shown the results obtained under basal conditions and on the right those obtained in the presence of arachidonic acid (5 \( \mu \text{g/ml} \)). The height of each rectangle represents the mean and the vertical bar twice the SEM of the individual results (4-12 according to the time of sacrifice). The results obtained with and without arachidonic acid were analyzed separately according to a two-factor (glycerol-treated vs. control at six times of sacrifice) analysis of variance with a variable number (4-12) of repetitions. ***} P < 0.001. \]

\[ \text{TXB}_{2} \text{ synthesis by glomeruli (direct RIA) isolated from control and glycerol-treated rats that were killed at different times after administration of the solvent or of the drug. On the left are shown the results obtained under basal conditions and on the right those obtained in the presence of arachidonic acid (5 \( \mu \text{g/ml} \)). The height of each rectangle represents the mean and the vertical bar twice the SEM of the individual results (4-12 according to the time of sacrifice). The results obtained with and without arachidonic acid were analyzed separately according to a two-factor (glycerol-treated vs. control at six times of sacrifice) analysis of variance with a variable number (4-12) of repetitions. ***} P < 0.001. \]
Effects of Treatment by Captopril on PGE₂ Production (ng/mg per hr) by Glomeruli Isolated from Glycerol-Treated Rats Killed at 24 Hours

<table>
<thead>
<tr>
<th>Time</th>
<th>Control rats</th>
<th>Glycerol-treated rats</th>
<th>Control rats</th>
<th>Glycerol-treated rats</th>
<th>Glycerol control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal conditions</td>
<td>15 min</td>
<td>1057 ±311</td>
<td>1557 ±362</td>
<td>1344 ±137</td>
<td>1296 ±440</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>1314 ±377</td>
<td>1618 ±438</td>
<td>1653 ±536</td>
<td>1632 ±488</td>
</tr>
<tr>
<td></td>
<td>60 min</td>
<td>1541 ±532</td>
<td>1853 ±583</td>
<td>2135 ±557</td>
<td>1977 ±537</td>
</tr>
<tr>
<td>With arachidonic acid</td>
<td>15 min</td>
<td>4267 ±214</td>
<td>5869 ±819</td>
<td>5659 ±517</td>
<td>5171 ±888</td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td>5343 ±1037</td>
<td>6085 ±996</td>
<td>5869 ±850</td>
<td>5840 ±986</td>
</tr>
<tr>
<td></td>
<td>60 min</td>
<td>5779 ±1042</td>
<td>7509 ±1083</td>
<td>7509 ±1083</td>
<td>7007 ±1083</td>
</tr>
</tbody>
</table>

Results are means ± sem from three individual values. Three-factor (time of incubation, treatment by captopril, treatment by glycerol) analysis of variance with replication was used to analyze separately the data obtained under basal conditions and in the presence of 6 μg/ml arachidonic acid. There was a highly significant interaction (P < 0.01) between the factors "captopril" and "glycerol," thus showing that treatment by captopril modifies the effect of glycerol on PGE₂ synthesis.

PGE₂ Synthesis by Papillary Homogenates from Control and Glycerol-Treated Rats at Different Times after Administration of the Drug

In order to appreciate whether the modifications in PGE₂ synthesis induced by glycerol administration were specific to glomeruli or more general in the kidney, we also studied PGE₂ synthesis by papillary homogenates, since papilla is the main renal site for PGE₂ synthesis. A limited number of time intervals were studied (0.5 and 48 hours were omitted). There was a late increase (72 hours) in PGE₂ production both under basal conditions and in the presence of arachidonic acid (P < 0.05) by the papilla prepared from glycerol-treated rats (Fig. 5). No difference was observed when the stimulatory effect of arachidonic acid was tested.

Discussion

The decrease in renal blood flow and glomerular filtration rate reported in glycerol-induced ARF prompted investigation of the possible role played by the prostaglandins. These products have been implicated since PGE₂ protected (Papanicolaou et al., 1975; Werb et al., 1978) and indomethacin worsened (Torres et al., 1975; Papanicolaou et al., 1975).

Figure 5 PGE₂ synthesis by papillary homogenates (direct RIA) prepared from control and glycerol-treated rats that were killed at different times after administration of the solvent or of the drug. On the lower part are shown the results obtained under basal conditions and on the upper part those obtained in the presence of arachidonic acid (6 μg/ml). The height of each rectangle represents the mean and the vertical bar the SEM of the individual results (4-12 according to the time of sacrifice). The results obtained with and without arachidonic acid were analyzed separately according to a two-factor (glycerol-treated vs. control at six times of sacrifice) analysis of variance with a variable number (4-12) of repetitions. **P < 0.001.
GLOMERULAR PROSTAGLANDINS AND ACUTE RENAL FAILURE/Straer et al. 781

The consequences of the late increase of PG production by the glomeruli on the glomerular function remain unclear. Acute renal failure is associated at 24 hours with a marked decrease in renal blood flow and glomerular filtration rate (Oken et al., 1966; Ayer et al., 1971; Reinecke et al., 1980). At this time, the rats have not yet begun to recover. Since the synthesis of all PGs was increased, irre-
spective of their effect on vasoactivity, it is difficult to predict the consequences. Indeed TXA₂, precursor of TXB₂, and PGF₂α are considered as producing vasoconstriction, whereas the effect of PGE₂ in the rat is still open to discussion. In some studies, PGE₂ has been reported to have a vasoconstrictor effect in the rat (Malik and MacGiff, 1974), whereas it is considered elsewhere as a vasodilator agent (Dunham, 1976; Rosenthal and Pace-Asciak, 1980). Furthermore, Baylis et al. (1976) have shown that PGs of the E series could produce a decrease in the glomerular filtration coefficient. It is possible that the simultaneous activation, at this time of the disease, of the renal renin-angiotensin system (Baranowski et al., 1978) and of vasoconstricting PGs participates in the maintenance phase of acute renal failure. Alternatively, the effects of the vasodilatory PGs could be predominant. This would be a response to compensate for a vasoconstrictor effect by keeping the glomerular capillaries patent. This latter hypothesis is supported by the observation of Papanicolaou et al. (1975), who reported that indomethacin pretreatment enhanced the glycerol nephrotoxicity.

A decrease in the stimulatory effect of arachidonic acid on PGE₂ production was observed at 1 hour in glycerol-treated rats and raises the question as to whether this plays a role in the mechanism of this model of ARF. The decrease of synthesis was observed only for PGE₂. This PG represents the main PG produced by rat isolated glomeruli (Sraer et al., 1979b) and also rat epithelial (Sraer et al., 1979a; Petrulis et al., 1980) and mesangial (Sraer et al., 1979a) cultured cells. If, as proposed in several studies (Dunham, 1976; Rosenthal and Pace-Asciak, 1980), PGE₂ is a vasodilatory agent in the rat, it would be possible that this early defect in PGE₂ production at a time when the renin-angiotensin system is not yet activated, should produce vasoconstriction of the glomerular capillaries and a fall in GFR. This early modification is not a direct toxic effect of glycerol on glomeruli, since glycerol added in vitro did not modify PGE₂ synthesis (data not shown), but it could reflect the glomerular vasoconstrictor response to myohemoglobinemia and reduction in plasma volume which follow glycerol injection.

Acknowledgments

We are grateful to A. Morin and N. Knobloch for secretarial assistance, to Dr. C. Gaudebout for his help in the statistical analysis, to Dr. F. Dray and Dr. W. Siess for teaching us the technique of HPLC, and to Pr. S. Skinner for revision of the manuscript.

References


Prostaglandin synthesis by glomeruli isolated from rats with glycerol-induced acute renal failure.

J D Sraer, L Moulonguet-Doleris, F Delarue, J Sraer and R Ardaillou

*Circ Res.* 1981;49:775-783
doi: 10.1161/01.RES.49.3.775

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/49/3/775

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/