Possible Mechanism of Prostaglandin-Induced Renal Vasoconstriction in the Rat

NESTOR SCHOR, M.D., PH.D., AND BARRY M. BRENNER, M.D.

SUMMARY We studied the role of the renin-angiotensin system in the vasoconstrictor effect induced by prostaglandins (PG) on the renal microcirculation in 25 euveolemic Munich-Wistar rats. Infusions of subvasodepressor doses of PGE, and PGII led to lower mean values for single nephron (SN) glomerular filtration rate (GFR), total kidney GFR, glomerular plasma flow rate, QA, and ultrafiltration coefficient (Kf) than were found in animals given vehicle alone (control group). On the other hand, the mean values for glomerular transcapillary hydraulic pressure difference, \( \Delta P \), and total renal arteriolar resistance, RTA, tended to be higher in the experimental groups. The effects of PGII on the renal microcirculation were more pronounced than for PGE. These increases in \( \Delta P \) and RTA and decreases in QA and Kf are typical of changes induced by angiotensin II (AII). To further explore this AII-like phenomenon, an infusion of saralasin, a competitive AII antagonist, was used. Indeed, when saralasin was infused together with either PGE or PGII, the previously noted effects on \( \Delta P \), QA, RTA, and Kf were largely abolished. Thus, saralasin transformed the renal action of PGE and PGII from vasoconstrictor (low QA, high RTA) to vasodilator (high QA and low RTA). Therefore, the effects of nonvasodepressor doses of PGE and PGII on the renal microcirculation appear to depend on an intermediate action of AII. (Hypertension 3 (suppl II): II-81-II-85, 1981)

KEY WORDS  • PGE, • PGII • renal microcirculation • glomerular hemodynamics • angiotensin II • saralasin

I T has been suggested that in the rat, in contrast to other species, prostaglandin (PG) E2 causes an increase in intrarenal resistance.1,2 Hockel and Cowley3 observed in dogs that chronic subdepressor PGE2 infusions induces an increase in both mean arterial pressure (AP) and plasma renin activity. Since PGs are produced in the renal cortex, both in glomeruli and arterioles, and since they can stimulate renin release, it is possible that angiotensin II (AII) formation induced by PGs can alter the renal microcirculation.

We undertook the present study to evaluate the role of the activation of the renin-angiotensin system during subvasodepressor infusions of PGE and PGII (prostacyclin) by using an AII antagonist (saralasin) in euveolemic Munich-Wistar rats.

Methods

General

Micropuncture studies were performed in 25 adult male Munich-Wistar rats weighing between 215 to 320 g. Each rat was allowed free access to water and a standard rat pellet diet until the morning of study. Immediately after anesthesia was induced with inactin (100 mg/kg, i.p.), the left femoral artery was catheterized and approximately 70 μl of arterial blood was collected for baseline hematocrit determination. This arterial catheter was used for subsequent periodic blood sampling and estimation of mean arterial pressure (AP). AP was monitored with an electronic transducer (model P23Db, Statham Instruments Division, Gould Inc., Hato Rey, Puerto Rico) connected to a direct-writing recorder (Model 7712, Hewlett Packard, Waltham, Massachusetts). Polyethylene catheters were also inserted into right and left jugular veins for infusion of inulin, prostaglandin synthetase inhibitors (indomethacin or meclofenamate), saralasin, and isonicotic rat serum. Intravenous infusion of 7.5% inulin solution in 0.9% NaCl was then started at a rate of 1.2 ml/hr. To suppress the possibility of endogenous prostaglandin release in response to the vasoactive effects of exogenous PG infusion, indomethacin or meclofenamate was added to the inulin
solution to deliver 2.0 mg/kg/hr throughout the experiments in all groups. Vehicle solution (isotonic saline or tris buffer solution, pH 8.5, 300 mOsm/liter) was infused into seven rats (control group), whereas for the other groups, PGE₂ (PGE₂ group, n = 10, 125 ng/kg/min) or PGI₂ (PGI₂ group, n = 8, 62 ng/kg/min) were infused via a 27-gauge needle placed into the abdominal aorta just above the origin of the left renal artery.* Following tracheostomy, rats were prepared in routine fashion for micropuncture study, as described previously. Throughout the period of surgical preparation and experimental study, all rats received a continuous infusion of isoncotic rat serum to maintain circulating plasma volume at conscious (or euvoletic) levels. Since plasma volume of rats prepared for micropuncture is reduced by approximately 20% relatively to the conscious animal, the following protocol for maintaining the euvoletic state was employed. Soon after collection of the baseline arterial blood sample, isoncotic rat serum was infused for 45 minutes at the rate of 7-10 ml/kg/hr, followed by reduction in infusion rate to 1.5 ml/kg/hr for the remainder of each experiment in order to maintain the hematocrit value at the baseline level measured immediately after induction of anesthesia. In a previous study, this protocol was found to be successful in maintaining plasma volume at the level that existed before anesthesia.

Pre-Saralasin Period

In all experiments, initial micropuncture measurements were performed as follows. Exactly timed (1-3 min) samples of fluid were collected from surface proximal tubule convolutions of at least three nephrons from the left kidney for determination of flow rate and inulin concentration and calculation of single nephron glomerular filtration rate (SNFGR). Coincident with these tubule fluid collections, two or three samples of femoral arterial blood were obtained in each period for determination of systemic arterial hematocrit (Hct), and total protein and inulin concentrations in plasma. In addition, two or three samples of urine from the experimental (left) kidney were collected for determination of flow rate, inulin concentration, and calculation of whole kidney glomerular filtration rate (GFR). For these urine collections, an indwelling ureteral polyethylene catheter (PE-10) was inserted into the left ureter.

Time-averaged pressures were measured in surface glomerular capillaries (Pgc), proximal tubules (Pt), and third order peritubular capillaries (Pc) with a continuous recording, servo-null micropipette transducer, employing pipettes with outer tip diameters of 2-4 μm and containing 2.0 M NaCl. Hydraulic output from the servo system was coupled electronically to a second channel of the Hewlett-Packard recorder by means of a pressure transducer. To estimate the colloid osmotic pressure of plasma entering and leaving glomerular capillaries, protein concentrations (C) in femoral arterial (C₀) and surface efferent arteriolar (C放心) blood plasmas were measured as described previously. Colloid osmotic pressure (Π) was calculated according to the equation of Deen et al.* Values for Π放心, and thus Π₀, for femoral arterial plasma are taken as representative of values of C and Π for the afferent end of the glomerular capillary network. These estimates of pre- and postglomerular plasma protein concentration permit calculation of single nephron filtration fraction (SNFF) and initial glomerular capillary plasma flow rate (Q₀), using equations given elsewhere.*

Saralasin Period

Upon completion of the initial measurements, all rats in each group were given a continuous intravenous infusion of saralasin acetate (Eaton Laboratories, Division of Morton Norwich Products, Inc., Norwich, New York) at the rate of 5.0 μg/kg/min (1.2 ml/hr). After a 30-minute equilibration period, all of the measurements and collections described above were repeated.

Analysis

The volume of fluid collected from individual proximal tubules was estimated from the length of the fluid column in a constant-bore capillary tube of known internal diameter. The concentration of inulin in tubule fluid was measured, usually in duplicate, by the microfluorescence method of Vurek and Pegram. Inulin concentrations in plasma and urine were determined by the macrantone method of Führ et al. Protein concentrations in efferent arteriolar and femoral arterial blood plasmas were determined, usually in duplicate, using the fluorometric method of Vietz et al.

Statistical analysis was performed by the paired and unpaired t test, where appropriate. Statistical significance is defined as at least p < 0.05.

Results

PGE₂ vs Control Group

Despite no significant change in ΔP relative to the control group, PGE₂ led to a significant mean increase in Pgc, 53 ± 1 (se) vs 49 ± 1 mm Hg (p < 0.001). Since values for Pt were, on average, the same for both groups (table 1), PGE₂ led to a significantly higher mean value for ΔP, 41 ± 1 vs 37 ± 1 mm Hg (p < 0.001). The declines in GFR (1.04 ± 0.07 vs 1.13 ± 0.08 ml/min), SNFF (35.2 ± 2.6 vs 39.5 ± 1.9 nl/min), and Q放心 (96 ± 7 vs 119 ± 6 nl/min) observed...
TABLE 1. Summary of Whole and Single Nephron Function in Rats Given Prostaglandins (PGE2 and PGI2) Before and During Saralasin (SAR) Infusion

<table>
<thead>
<tr>
<th>Rat group</th>
<th>AP (mm Hg)</th>
<th>POC (mm Hg)</th>
<th>PT</th>
<th>ΔP</th>
<th>GFR (ml/min)</th>
<th>SNGFR (nl/min)</th>
<th>QA</th>
<th>SNFF</th>
<th>RA</th>
<th>Re</th>
<th>RTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-SAR period</td>
<td>111</td>
<td>49</td>
<td>12</td>
<td>37</td>
<td>1.13</td>
<td>39.5</td>
<td>119</td>
<td>0.32</td>
<td>2.1</td>
<td>1.8</td>
<td>3.9</td>
</tr>
<tr>
<td>SAR period</td>
<td>± 4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.08</td>
<td>1.9</td>
<td>6</td>
<td>0.02</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>PGE2 (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-SAR period</td>
<td>108</td>
<td>53</td>
<td>12</td>
<td>41</td>
<td>1.04</td>
<td>35.2</td>
<td>96</td>
<td>0.37</td>
<td>2.2</td>
<td>2.5</td>
<td>4.7</td>
</tr>
<tr>
<td>SAR period</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.07</td>
<td>2.6</td>
<td>7</td>
<td>0.02</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>PGI2 (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-SAR period</td>
<td>110</td>
<td>54</td>
<td>12</td>
<td>42</td>
<td>0.92</td>
<td>30.3</td>
<td>82</td>
<td>0.38</td>
<td>2.5</td>
<td>2.9</td>
<td>5.4</td>
</tr>
<tr>
<td>SAR period</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.07</td>
<td>1.5</td>
<td>5</td>
<td>0.01</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Values are expressed as means ± 1 SE. AP = mean arterial pressure, POCC = average pressure in surface glomerular capillaries; PT = proximal tubules; GFR = glomerular filtration rate; SNGFR = single nephron glomerular filtration rate; QA = initial glomerular capillary plasma flow rate; SNFF = single nephron filtration fraction; RTA = total renal arteriolar resistance.

Calculated from paired data; pre-saralasin vs saralasin period, p < 0.05.
Calculated from unpaired data; pre-saralasin vs saralasin period in control group, p < 0.05.
Calculated from unpaired data; saralasin period for each PG vs saralasin period in control group, p < 0.05.

in the PGE2 group, when compared with the control group, were not statistically significant. Mean values for SNFF were numerically higher in the PGE2 group, 0.37 ± 0.02 vs 0.32 ± 0.02 (p > 0.10) for the control group. Whereas mean values for RA were similar in these two groups (table 1), mean values for RE (2.5 ± 0.1 vs 1.8 ± 0.1 × 10^6 dyn.s.cm^-6, p < 0.005), and thus R_\text{TÀ} (4.7 ± 0.2 vs 3.9 ± 0.1 × 10^6 dyn.s.cm^-4, p < 0.05) were significantly higher in the PGE2 group.

As shown in table 2, mean values for C_A and C_E and thus, II_A and II_E, were similar in the PGE2 and control groups. For both groups, average values for II_E/ΔP were significantly less than unity, indicating that these animals were at filtration pressure disequilibrium.

TABLE 2. Summary of Effects of PGE2 and PGI2 on Determinants of SNGFR Before and During Saralasin (SAR) Infusion

<table>
<thead>
<tr>
<th>Rat group</th>
<th>C_A (g/dl)</th>
<th>C_E</th>
<th>II_A (mm Hg)</th>
<th>II_E (mm Hg)</th>
<th>II_E/ΔP</th>
<th>K_E (nl/(l.min))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-SAR period</td>
<td>5.8</td>
<td>8.6</td>
<td>19.1</td>
<td>35.5</td>
<td>0.93</td>
<td>0.081</td>
</tr>
<tr>
<td>SAR period</td>
<td>± 0.3</td>
<td>0.2</td>
<td>0.7</td>
<td>1.5</td>
<td>0.03</td>
<td>0.010</td>
</tr>
<tr>
<td>PGE2 (n = 10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-SAR period</td>
<td>5.4</td>
<td>8.4</td>
<td>17.5</td>
<td>34.3</td>
<td>0.82</td>
<td>0.032</td>
</tr>
<tr>
<td>SAR period</td>
<td>0.2</td>
<td>0.2</td>
<td>0.4</td>
<td>1.0</td>
<td>0.03</td>
<td>0.003</td>
</tr>
<tr>
<td>PGI2 (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-SAR period</td>
<td>5.2</td>
<td>7.5</td>
<td>16.5</td>
<td>28.5</td>
<td>0.87</td>
<td>0.073</td>
</tr>
<tr>
<td>SAR period</td>
<td>0.2</td>
<td>0.2</td>
<td>0.6</td>
<td>0.5</td>
<td>0.03</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are expressed as means ± 1 SE. See table 1 for abbreviations.
Calculated from paired data; pre-saralasin vs saralasin period, p < 0.05.
Calculated from unpaired data; pre-saralasin period for each PG vs pre-saralasin period in control group, p < 0.05.
Calculated from unpaired data; saralasin period for each PG vs saralasin period in control group, p < 0.05.
Therefore, it was possible to calculate unique values for $K_f$ in each group. The mean $K_f$ value was significantly lower in the PGE$_2$ group than in the control group, 0.032 ± 0.003 vs 0.081 ± 0.010 nl/(s. mm Hg) ($p < 0.001$) respectively.

As shown in table 1, infusion of saralasin essentially reversed the effects of PGE$_2$ on the renal microcirculation. Whereas values for GFR rose an average of 16% ($p < 0.05$), SNGFR, ~10% ($p > 0.10$), and $Q_A$, ~45% ($p < 0.05$), mean values for $P_GC$, $\Delta P$, $R_E$, and $R_T$ declined significantly. Due to a greater average increase in $Q_A$ than in SNGFR, saralasin led to a significant decline in SNFF in PGE$_2$-treated rats, on the average from 0.37 ± 0.02 to 0.31 ± 0.02 ($p < 0.05$). As shown in table 2, values for $C_A$ and $\Pi_A$ were largely unaffected by saralasin but $C_E$ (7.5 ± 0.2 vs 8.4 ± 0.2 g/dl, $p < 0.05$) and $\Pi_E$ (28.5 ± 0.5 vs 34.3 ± 1.0 mm Hg, $p < 0.05$) declined significantly in this second study period. Mean values for $\Pi_E/\Delta P$ were unaffected by saralasin infusion in either group, indicating persistence of filtration pressure disequilibrium. Nevertheless, in response to saralasin the average value for $K_f$ in the PGE$_2$ group increased markedly, to a value indistinguishable from that in the control group (table 2).

**Discussion**

The purpose of the present study was to examine the effects of PGE$_2$ and PGI$_1$ on the renal microcirculation. During infusion of a nonvasodepressor dose of PGE$_2$, $\Delta P$ rose significantly, due largely to an increase in $P_GC$ (table 1). A mild decline in SNGFR and $Q_A$ were observed. The latter due to an increase in $R_E$ and $R_T$. PGE$_2$ infusion led to an impressive reduction in $K_f$.

These increases in $\Delta P$, $R_E$, $R_T$, and decreases in $Q_A$ and $K_f$ are changes usually seen when exogenous AII is infused$^{11,19}$ or when endogenous AII levels are augmented, as during chronic low salt diet.$^{14}$ This tendency to renal vasoconstriction is similar to that described previously.$^{13,14}$ During combined infusion of PGE$_2$ and saralasin, GFR and SNGFR rose proportionately. Saralasin effectively antagonized the increases in $R_E$ and $R_T$ induced by PGE$_2$ alone and also reversed the declines in $K_f$ and $Q_A$. Saralasin, therefore, transformed the renal action of PGE$_2$ from vasoconstrictor to vasodilator. Thus, in the Munich-Wistar rat, the action of systemic subvasodepressor PGE$_2$ infusion on the renal circulation appears to involve an intermediate action of AII.

In the control group, however, no significant effects of either prostaglandin inhibition alone or in combination with saralasin were found, suggesting that endogenous prostaglandin or AII plays little role in regulating glomerular hemodynamics under euvoletic conditions. An identical conclusion for the kidney as a whole has also been reported.$^{14,19}$

The effects of PGI$_1$ on glomerular hemodynamics were qualitatively similar to those of PGE$_2$ in that $\Delta P$, $R_E$, and $R_T$ increased whereas SNGFR, $Q_A$, and $K_f$ fell significantly (tables 1 and 2). In contrast to our observation, Baer et al.$^{18}$ have reported that infusion of PGI$_1$ at nonvasodepressor doses was without effect on total GFR. In the present study, however, the simultaneous infusion of prostaglandin inhibitor and
PGI₂ could cause an enhancement in the vasoactive effect of the latter, as reported by others,\(^{17, 18}\) and thus lead to a ~20% fall in GFR and SNGFR, as observed. Our findings of a decrease in QA with PGI₁ are similar to those reported by Baer and McGiff\(^{19}\) and Gerber and Nies,\(^{20}\) who observed significant decreases in renal blood flow during PGI₁ infusion in the rat. With respect to the total renal vascular resistance (RVR), however, PGE₂ infusion led to an increase in RVR\(^{1, 4}\) although for PGI₁, Baer and McGiff\(^{19}\) reported that the mean value for RVR did not differ from the control or was only slightly reduced.\(^{19}\) During combined saralasin and PGI₁ infusion, however, the striking vasoconstrictor effects of PGI₁ on the renal cortical microcirculation were largely abolished. Indeed, in the presence of saralasin, the action of PGI₁ was transformed from that of a potent vasoconstrictor (low QA and high R\(TA\)) to an equally potent vasodilator (high QA and low R\(TA\)).

Therefore, our data suggest that systemic subepidural infusion of PGE₂ and PGI₁ leads to augmented renin release and intrarenal AII formation. The increases in the intrarenal AII levels blunt the renal vasodilatory effects of PGs, leading to a pattern of renal vasoconstriction in rats. This also could explain the systemic hypertension observed in dogs by Hockel and Cowley\(^{4}\) during a chronic systemic subepidural infusion of PGE₂.

Finally, the most pronounced effect on the renal microcirculation observed with PGI₁ could be due to a higher potency in stimulating glomerular adenyly cyclase.\(^{18}\) Since cAMP has been invoked as a second messenger in regulating vascular smooth muscle tone as well as renin release from the juxtaglomerular apparatus,\(^{18}\) enhanced stimulation of glomerular cAMP production by PGI₁ might therefore contribute to the more pronounced effects of PGI₁ than PGE₂ observed in our present study.

**Acknowledgments**

The authors are grateful to Julia Troy, Nancy Illes, and Michele Pavia for expert technical assistance, and Janete Claudia Machado for expert secretarial assistance. We thank Dr. J. E. Pike of the Upjohn Company for the generous donation of prostaglandins I\(_2\) and E\(_2\).

**References**


Possible mechanism of prostaglandin-induced renal vasoconstriction in the rat.
N Schor and B M Brenner

Hypertension. 1981;3:II-81
doi: 10.1161/01.HYP.3.6_Pt_2.II-81

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/3/6_Pt_2/II-81