Hemodynamic Effects of Platelet Activating Factor in the Dog Kidney in Vivo

HARALD SCHERF, ALAN S. NIES, ULLRICH SCHWERTSCHLAG, MICHAEL HUGHES, AND JOHN G. GERBER

SUMMARY The effect of platelet activating factor (PAF) on renal hemodynamics and function was examined in anesthetized dogs. The infusion of PAF into the renal artery at 5, 10, and 20 ng·min⁻¹·kg⁻¹ body weight resulted in dose-dependent reductions in renal blood flow, glomerular filtration rate, urine volume, and urinary sodium excretion, whereas the infusion of vehicle alone in the contralateral kidney did not result in significant changes in these parameters. The maximum decrease expressed as the percent change from baseline was 22.2 ± 1.7% for renal blood flow, 50.8 ± 11% for glomerular filtration rate, 67.3 ± 4.2% for urine volume, and 69.0 ± 8.5% for urinary sodium excretion, respectively. These renal effects were not accompanied by significant alterations in systemic arterial blood pressure and heart rate. Pretreatment with indomethacin to block prostaglandin synthesis enhanced the effect of PAF on kidney function. Our data demonstrate that, unlike the rat kidney, intrarenal PAF infusion into the intact dog results in vasoconstriction and severe reduction in glomerular filtration rate. (Hypertension 8: 737-741, 1986)

KEY WORDS • platelet activating factor • renal hemodynamics • renal function • glomerular filtration rate • urine volume • platelet count

PLATELET activating factor (PAF, PAF-acether) is a low molecular weight, biologically active phospholipid released from stimulated basophils, macrophages, and platelets and proposed as one of the mediators of inflammation and allergic reactions. Its molecular structure is 1-O-alkyl-2-O-acetyl-sn-glycero-3-phosphorylcholine. In addition to its ability to affect inflammation, PAF has been found to have various cardiovascular effects. Interest in the cardiovascular effects of PAF has escalated in part because of the suggestion that antihypertensive polar renomedullary lipid, a renomedullary phospholipid with antihypertensive activity, has a structure identical to PAF. When infused intravenously, PAF lowers blood pressure in normotensive rats and dogs and in spontaneously hypertensive rats. Kamitani et al. found that PAF dilated arterioles directly when infused into the rat hindlimb. In addition, it has been reported to reduce the cardiovascular response to a variety of vasoconstrictor substances. A negative inotropic effect of PAF has been demonstrated in both intact heart and isolated heart preparation. Although a vasoconstrictor in the lung, PAF has been reported to be a vasodilator in both the autoperfused rat kidney and the isolated perfused rat kidney.

Recent data indicate that kidneys stimulated with calcium ionophore release PAF, suggesting that kidneys have the capacity to synthesize PAF. Further evidence for the renal synthesis of PAF was suggested by the findings that the measurable concentration of PAF in normal rat blood was undetectable in nephrectomized rats. Masugi et al. found that removal of the clip in the one-kidney, one-clip hypertensive rat model resulted in a fall in blood pressure that could be blocked by a specific antagonist of PAF, suggesting that PAF may have a role as an endogenous modulator of blood pressure. Although Vemulapalli et al. have demonstrated that intravenously administered PAF results in reduction in renal blood flow (RBF) and glomerular filtration rate (GFR) in the dog, systemic hypotension was present in this study and could have been responsible for the renal effects either directly or through reflex mechanisms. We therefore examined
the effect of intrarenally infused PAF on renal hemodynamics and function in the anesthetized dog to avoid systemic hemodynamic changes and used the contralateral, noninfused kidney as the control. In addition, we examined the effect of PAF in cyclooxygenase-inhibited dogs to be sure that released thromboxane A2 was not mediating the response in the kidney as it has been described in the coronary circulation.

Materials and Methods
A total of 12 mongrel dogs of either sex weighing between 18 and 30 kg were used for these studies. The dogs were anesthetized with sodium pentobarbital, 25 mg/kg i.v., and supplemented with 30 to 60 mg of pentobarbital as necessary to maintain a stable plane of anesthesia. The dogs were artificially respired with a Harvard respirator (Millis, MA, USA) at 12 breaths/min. The right femoral artery and vein were cannulated for blood pressure monitoring (Hewlett-Packard system F7543, Waltham, MA, USA) and for collection of blood and drug administration, respectively. Both arterial and venous cannulae for platelet counts while the renal arteries were punctured with a 25-gauge needle for the infusion of PAF, and electromagnetic flow probes were placed around the arteries for continuous blood flow monitoring. Both ureters were cannulated for urine flow monitoring. Approximately 500 ml of normal saline was infused intravenously throughout the experiments to replace fluid losses and ensure an adequate urine flow.

After the surgical procedure had been completed, a priming dose of inulin, 50 mg/kg i.v., was infused over 30 minutes and immediately followed by a continuous infusion at a rate of 20 mg/min throughout the experiments. One hour was allowed for equilibration before sample collection. Urine was collected every 15 minutes, and blood samples were taken at the end of each urine collection period. In six dogs, PAF was infused into the experimental kidney at a rate of 5, 10, and 20 ng·min⁻¹·kg⁻¹ of body weight for 15 minutes at each dose. Vehicle alone was infused into the control kidney. The experiments were continued for another 15-minute recovery period after the highest PAF dose.

Identical experiments were performed in six additional dogs, except that indomethacin was given as an i.v. bolus dose of 8 mg/kg body weight 30 minutes before the PAF administration. The efficacy of indomethacin to inhibit prostaglandin synthesis was determined by its ability to block the renal vasodilation produced by the intrarenal arterial infusion of arachidonic acid (10 μg/kg/min) at the end of the experiment.

The PAF (L-α-phosphatidylcholine, Sigma Chemicals, St. Louis, MO, USA) was stored at −20°C in chloroform. For the infusion, PAF was dissolved in normal saline containing 0.25% bovine serum albumin. Urine and plasma samples were analyzed for inulin by an autoanalyzer (Technicon, Tarrytown, NY, USA) and for sodium and potassium concentrations by flame photometry.

Mean comparisons for the data were made using a randomized complete block design two-way analysis of variance and Dunnett's multiple range test. Differences were considered significant when the p value was less than or equal to 0.05.

**Table 1. Renal Functional Data in Dogs After Intrarenal Infusion of Platelet Activating Factor**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>5 ng PAF</th>
<th>10 ng PAF</th>
<th>20 ng PAF</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBF (ml/min)</td>
<td>Infused</td>
<td>233 ± 29</td>
<td>211 ± 27*</td>
<td>186 ± 24†</td>
<td>177 ± 26†</td>
</tr>
<tr>
<td></td>
<td>Noninfused</td>
<td>215 ± 25</td>
<td>213 ± 25</td>
<td>205 ± 26</td>
<td>194 ± 27</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>Infused</td>
<td>53.2 ± 4.8</td>
<td>44.2 ± 3.1</td>
<td>36.8 ± 6.4*</td>
<td>26.6 ± 6.3†</td>
</tr>
<tr>
<td></td>
<td>Noninfused</td>
<td>38.2 ± 6.6</td>
<td>36.7 ± 6.7</td>
<td>33.7 ± 6.4</td>
<td>36.3 ± 8</td>
</tr>
<tr>
<td>RVR (mm Hg·min⁻¹·ml⁻¹)</td>
<td>Infused</td>
<td>0.74 ± 0.11</td>
<td>0.83 ± 0.12</td>
<td>0.90 ± 0.1*</td>
<td>0.96 ± 0.13†</td>
</tr>
<tr>
<td></td>
<td>Noninfused</td>
<td>0.80 ± 0.15</td>
<td>0.84 ± 0.16</td>
<td>0.84 ± 0.14</td>
<td>0.88 ± 0.5</td>
</tr>
<tr>
<td>UV (ml/15 min)</td>
<td>Infused</td>
<td>9.6 ± 2.0</td>
<td>6.8 ± 1.8*</td>
<td>4.7 ± 1.1†</td>
<td>3.1 ± 0.7†</td>
</tr>
<tr>
<td></td>
<td>Noninfused</td>
<td>6.0 ± 1.4</td>
<td>5.7 ± 1.7</td>
<td>5.1 ± 1.2</td>
<td>4.6 ± 0.9</td>
</tr>
<tr>
<td>UNaV (μEq/min)</td>
<td>Infused</td>
<td>113.1 ± 18.0</td>
<td>77.8 ± 19.5*</td>
<td>60.3 ± 14.0†</td>
<td>38.6 ± 10.1†</td>
</tr>
<tr>
<td></td>
<td>Noninfused</td>
<td>81.4 ± 15.8</td>
<td>69.6 ± 19.1</td>
<td>64.7 ± 19.5</td>
<td>62.3 ± 12.0</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>Infused</td>
<td>0.021 ± 0.005</td>
<td>0.017 ± 0.005</td>
<td>0.012 ± 0.002*</td>
<td>0.009 ± 0.001*</td>
</tr>
<tr>
<td></td>
<td>Noninfused</td>
<td>0.023 ± 0.013</td>
<td>0.025 ± 0.019</td>
<td>0.019 ± 0.007</td>
<td>0.014 ± 0.004</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>Infused</td>
<td>155.8 ± 6.4</td>
<td>157.1 ± 7.8</td>
<td>156.3 ± 7.0</td>
<td>152.8 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>158.2 ± 7.2</td>
<td>158.2 ± 7.2</td>
<td>164.1 ± 4.0</td>
<td>166.8 ± 3.8</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

PAF = platelet activating factor; RBF = renal blood flow; GFR = glomerular filtration rate; RVR = renal vascular resistance; UV = urine volume; UNaV = urinary sodium excretion; FENa = fractional excretion of sodium; HR = heart rate; MAP = mean arterial pressure.

*p < 0.05; †p < 0.01 (analysis of variance and multiple range test). compared with control values.
Results

Intrarenal administration of PAF caused dose-dependent decreases in RBF and GFR and concomitant, dose-dependent increases in renal vascular resistance (RVR) that were significant at the 10 and 20 ng·min⁻¹·kg⁻¹ dose (Figure 1). There were no significant changes from baseline in RBF, GFR, or RVR of the noninfused kidney. During the recovery period, RBF and GFR returned toward baseline values within 10 to 15 minutes.

Administration of PAF also resulted in a dose-dependent decrease in urine volume (UV), urinary sodium excretion (UN,V), and fractional sodium excretion (Table 1). The PAF-induced alterations were significant at all three drug doses for UV and UN,V and at the 10 and 20 ng/min/kg dose for fractional sodium excretion. In the noninfused kidney, the changes in UV, UN,V, and fractional sodium excretion were not significantly different from baseline.

Although heart rate tended to increase, PAF induced no significant changes in systemic arterial blood pressure or heart rate (see Table 1). In addition, PAF did not significantly change hematocrit values (data not shown).

Pretreatment of the dogs with indomethacin tended to increase the PAF-induced changes in RBF, GFR, and RVR (Figure 2). The PAF-induced decrease in RBF and GFR and increase in RVR were dose-dependent and significant at all doses except for the GFR, which was significantly altered only at the 10 and 20 ng·min⁻¹·kg⁻¹ dose. The contralateral, noninfused kidney demonstrated no changes in RBF, GFR, or RVR throughout the experimental periods.

In addition to the hemodynamic effects, indomethacin tended to enhance renal excretory response to PAF (see Table 1). The effect of indomethacin on PAF-induced changes in renal function was significant for

![Figure 1. Effect of intrarenal infusions of platelet activating factor (PAF) on renal blood flow (RBF), glomerular filtration rate (GFR), and renal vascular resistance (RVR). Results are expressed as percentage of control values, and each point represents mean ± SEM of six experiments. Single (p<0.05) and double (p<0.01) asterisks indicate a significant change from baseline values. NS = not significant (when compared with baseline).](image-url)

<table>
<thead>
<tr>
<th>TABLE 1. (continued)</th>
<th>Group 2 (PAF + Indomethacin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5 ng PAF</td>
</tr>
<tr>
<td>264 ±24</td>
<td>206±17*</td>
</tr>
<tr>
<td>255±25</td>
<td>255±26</td>
</tr>
<tr>
<td>51.4±6.7</td>
<td>43.5±10.0</td>
</tr>
<tr>
<td>60.5±7.4</td>
<td>61.3±13.3</td>
</tr>
<tr>
<td>0.63±0.09</td>
<td>0.96±0.26*</td>
</tr>
<tr>
<td>0.64±0.09</td>
<td>0.64±0.09</td>
</tr>
<tr>
<td>6.2±1.7</td>
<td>4.6±1.5</td>
</tr>
<tr>
<td>5.7±1.6</td>
<td>6.1±1.4</td>
</tr>
<tr>
<td>93.3±17.8</td>
<td>70.6±16.2</td>
</tr>
<tr>
<td>97.3±20.6</td>
<td>99.0±13.6</td>
</tr>
<tr>
<td>0.018±0.005</td>
<td>0.015±0.002</td>
</tr>
<tr>
<td>0.012±0.002</td>
<td>0.011±0.001</td>
</tr>
<tr>
<td>152.5±7.2</td>
<td>153.3±7.1</td>
</tr>
<tr>
<td>182.5±8.5</td>
<td>182.5±6.0</td>
</tr>
</tbody>
</table>
Baseline 5 10 20 Recovery

PAF ng min⁻¹·kg⁻¹

RBF and RVR at the 20 ng/min/kg dose of PAF. As in the other group, PAF had no effect on systemic arterial blood pressure and heart rate at any of the given doses.

Discussion

Alkyl ether analogues of PAF, which have been studied by Muirhead and co-workers,¹⁻²⁵ have been proposed to be potent endogenous antihypertensive agents because PAF elicits striking cardiovascular effects, including hypotension, selective vasodilation, cardiac depression, and vasodilation of some vascular beds with vasoconstriction of others. Our data from this study indicate that PAF is a vasoconstrictor in the dog kidney in vivo. Infusion of PAF at increasing doses into one kidney caused dose-dependent decreases in RBF, GFR, UV, and $U_{Na, V}$ without altering systemic arterial blood pressure and heart rate. Our data are in contrast to reports by Yokota and Dunham,¹⁹ and Schwertschlag et al.²⁰ that PAF caused renal vasodilation in rats. Whether or not these differences are secondary to species differences or to the methodological setup requires further investigation, but several reports support the possibility of species differences. While PAF caused an increase in total peripheral resistance in the dog,⁷,¹⁴ Sanchez-Crespo et al.²⁶ reported that PAF markedly decreased systemic resistance in the rat. A recent study by Vemulapalli et al.³ found marked decreases in RBF, GFR, UV, and the fractional excretion of sodium and potassium after intravenous infusion of PAF in the dog. However, the changes in renal function in this study may have been secondary to the systemic hypotension induced by intravenous PAF as well as to the direct effect of PAF on the kidney. The observation that PAF is a potent hypotensive agent is supported by the literature, but the mechanism by which this occurs is unclear. That PAF attenuated the pressor responses to epinephrine and norepinephrine suggests that PAF may be an $\alpha$-adrenergic receptor blocking substance.²⁶ However, Kami-tani et al.⁸ showed that PAF attenuated the pressor response to diverse pressor stimuli, suggesting that PAF-induced vasodilation inhibits vasoconstriction nonspecifically. This vasodilation appeared to be mediated by its own receptor, since PAF-induced vasodilation was unaltered by $\beta$-adrenergic, histaminergic, and cholinergic blockers.⁹

Although a systemic vasodilator, PAF has been reported to be a vasoconstrictor in the lung¹⁷,¹⁸ and the coronary circulation.²⁴ Voelkel et al.¹⁸ have shown that the pulmonary vasoconstrictor response to PAF was not inhibited by indomethacin but was inhibited by diethylcarbamazine, an inhibitor of leukotriene synthesis. Although the kidney is able to synthesize leukotrienes,²¹ we have not examined the possibility that leukotrienes mediate the effect of PAF on the kidney. However, it is unlikely that leukotrienes would mediate renal vasoconstriction because Feigen²⁷ has shown that leukotrienes vasodilate the canine renal circulation. In the coronary circulation, PAF has been described to cause a thromboxane-dependent vasoconstriction.²⁴ However, our finding that pretreatment of the dogs with indomethacin enhanced the effects of PAF on kidney function excludes thromboxane $A_2$ as the mediator of renal vasoconstriction. In fact, the enhanced responsiveness of the kidney to PAF after indomethacin pretreatment suggests the release of vasodilator prostaglandins in response to a vasoconstrictor stimulus. Since PAF is a potent aggregator of platelets, we could not exclude the possibility that the observed effect was secondary to platelet plugging. Against this hypothesis are the observations that the return of renal function after cessation of PAF infusion was very rapid and that indomethacin did not block the effect of PAF even though PAF is known to release platelet thromboxane $A_2$.

One interesting observation from our data is that PAF reduced GFR more than it reduced RBF. One mechanism for this reduction in filtration fraction would be a reduction in glomerular filtration pressure if PAF caused a greater afferent arteriolar constriction than efferent arteriolar constriction. However, we hypothesize that PAF preferentially decreases the GFR by reducing the surface area for filtration. This hypo-
Platelet Activating Factor and Renal Function

PLATELET ACTIVATING FACTOR AND RENAL FUNCTION


References


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Hypertension. 1986;8:737-741
doi: 10.1161/01.HYP.8.9.737
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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