Platelet Activating Factor Vasoconstriction of Dog Kidney
Inhibition by Alprazolam

PHILIP G. BAER AND LAUREN M. CAGEN

SUMMARY Systemic administration of platelet activating factor (PAF; acetyl glyceryl ether phosphocholine) reduces renal blood flow, but the mechanism responsible for that effect has not been defined. To address that problem, we determined the effects on renal blood flow of PAF administered directly into the renal artery in pentobarbital (30 mg/kg)-anesthetized dogs. Bolus injections of PAF (0.2–0.8 μg) caused transient renal vasoconstriction, reducing renal blood flow by 20 to 60% without altering systemic blood pressure; lyso-PAF (1 μg) had no effect. The effects of PAF on renal blood flow were not altered by α-adrenergic blockade (phentolamine, 3 mg/kg) or by angiotensin II receptor blockade ([Sar¹,Ala⁸]angiotensin II, 6 μg/kg/min), but they were increased in magnitude and duration by meclofenamate (5 mg/kg), a cyclooxygenase inhibitor. Methysergide (3 mg/kg), a serotonin antagonist, slightly reduced PAF effects, but a specific blocker of vascular serotonin receptors did not. Renal venous plasma platelet density was not altered by infusion of PAF into the renal artery at a dose (1–2 μg/min) that caused a sustained 20% renal blood flow decrease. Alprazolam, a benzodiazepine that competitively inhibited PAF-induced aggregation in canine platelet-rich plasma, also inhibited the renal vasoconstrictor action of PAF (0.8 mg/min, into the renal artery) but did not alter renal vasoconstrictor effects of norepinephrine or angiotensin II. (Hypertension 9: 253–260, 1987)

KEY WORDS • acetyl glyceryl ether phosphocholine • antihypertensive polar renomedullary lipid • platelet activating factor acether • renal blood flow

Platelet activating factor (PAF), a glycerophospholipid with the chemical structure 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine,¹,² is often referred to as acetyl glyceryl ether phosphoryl choline, or PAF-acether. PAF is identical in structure to the antihypertensive polar renomedullary lipid described by Muirhead and colleagues.³

In addition to its platelet activating effect and its role as a mediator in inflammatory and allergic reactions, PAF is a potent blood pressure–lowering substance with complex cardiovascular effects. In the dog, intravenously infused PAF causes a fall in blood pressure and cardiac output, an increase in total peripheral resistance, and a reduction of femoral arterial blood flow,⁴,⁵ whereas PAF administered directly into the femoral artery dilates the femoral vasculature and increases femoral blood flow.⁶

Renal tissues have the capacity to synthesize PAF,⁶ and there is evidence that under basal conditions the kidney releases PAF into the circulation and is the primary source of PAF found in blood.⁷ There is also evidence that, at least in some conditions, the kidney can release PAF into the systemic circulation in amounts sufficient to affect cardiovascular function.⁸

If the kidney does, in fact, synthesize and release PAF into the vascular compartment in amounts sufficient to affect systemic hemodynamics, this raises the possibility that PAF levels within the kidney might be sufficient to affect renal hemodynamics and excretory function. Renal blood flow effects of PAF have previously been examined only during systemic administration. Vemulapalli et al.,⁴ infused PAF intravenously over a 1-hour period and observed progressive reduction of renal blood flow concomitant with reduction of blood pressure. They speculated that the reduction of
renal blood flow was secondary to the reduction of blood pressure, but they could not rule out the possibility of a direct action of PAF on the renal vasculature. Because PAF produced intrarenally and released into the vascular compartment potentially could affect renal function, the present study was designed to determine the effects of increased renal arterial blood PAF concentration on renal hemodynamics and to examine possible mechanisms responsible for those effects.

### Materials and Methods

#### Experimental Preparation

Experiments were conducted using male and female mongrel dogs (random source) weighing 15 to 20 kg, anesthetized with sodium pentobarbital, 30 mg/kg i.v., and ventilated with room air through a tracheal cannula. A femoral artery and vein were cannulated for arterial blood pressure measurement, arterial blood sampling, and administration of additional anesthetic and other drugs as specified. Isotonic saline was infused i.v. at 5 ml/min throughout the study to replace fluid losses. The left kidney was exposed through a flank incision, and the left renal artery and vein were gently dissected free of adventitial tissue. A calibrated blood flow transducer was placed on the renal artery, and a needle-tipped cannula attached to a syringe infusion pump was inserted into the renal artery for direct intrarenal drug administration. Throughout the experiment, 0.9% NaCl was infused at 0.5 ml/min through the renal artery cannula to prevent clotting. In some dogs a PE-190 cannula was inserted directly into the renal vein through a small puncture and advanced to the level of the renal pelvis for sampling of renal venous blood.

### PAF Effects on Renal Blood Flow

PAF (Sigma Chemical, St. Louis, MO, USA) was given into the renal artery as bolus injections, 0.2 to 0.8 μg, or as a continuous infusion, 1 to 2 μg/min. Preliminary studies revealed no tachyphylaxis in responses to PAF, in that consistent renal blood flow effects were observed when concentration on renal hemodynamics and to examine possible mechanisms responsible for those effects.

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### Effects of Various Blocking Agents on PAF-Induced Changes

To investigate whether effects of PAF on renal blood flow were secondary to activation of other systems, we determined the effects of the following on renal blood flow responses to PAF: an α-adrenergic antagonist, phentolamine (3 mg/kg i.v.; CIBA Pharmaceuticals, Summit, NJ, USA); an angiotensin II receptor blocker, [Sar¹,Ala³]angiotensin II (6 μg/kg/min i.v.; Sigma); a cyclooxygenase inhibitor, sodium meclofenamate (5 mg/kg i.v.; Warner-Lambert Pharmaceuticals, Morris Plains, NJ, USA); a serotonin antagonist, methysergide maleate (3 mg/kg i.v.; Sandoz, East Hanover, NJ, USA); a selective antagonist of the serotoninergic 5-hydroxytryptamine receptors,⁹ LY 53857 (1.5–3 mg/kg i.v.; Lilly Research Laboratories, Indianapolis, IN, USA); and alprazolam (U-31889), a benzodiazepine previously shown to inhibit platelet activating effects of PAF on human platelets (0.8 mg/min into the renal artery; Upjohn, Kalamazoo, MI, USA).¹⁰ To test for adequacy of dosage of the various blocking agents, effects of intrarenal arterial injection of the following on renal blood flow were determined before and during administration of the appropriate agent: norepinephrine (1–4 μg; Sigma), angiotensin II (0.1–0.3 μg; Sigma), and serotonin (5-hydroxytryptamine HCl, 10–500 μg; Sigma). Agonist dosages were shown during preliminary studies to produce renal blood flow effects comparable to those of 0.2 to 0.8 μg of PAF. The dose of meclofenamate used was shown in preliminary studies to block the effects of the prostaglandin precursor arachidonic acid on renal blood flow. Effects of alprazolam on renal blood flow responses to angiotensin II and norepinephrine were also determined.

### Preparation of Solutions

The PAF stock solution, 1 mg/ml in methanol, was stored at −30°C; just before administration, the PAF stock was diluted to a final concentration of 2 μg/ml in 0.9% NaCl containing 0.01 M Tris and 0.25% bovine serum albumin, pH 7.4. Alprazolam for infusion into the renal artery was prepared as a 5 mM solution by dissolving in 1 ml of ethanol and diluting with 9 ml of isotonic saline containing 0.5 ml of 1 M HCl. Norepinephrine was prepared as a 10 μg/ml solution in isotonic saline containing ascorbic acid, 1 mg/ml. Solutions of angiotensin II (1 μg/ml), serotonin (500 μg/ml), methysergide (1 mg/ml), LY 53857 (1 mg/ml), [Sar¹,Ala³]angiotensin II (0.1 mg/ml), and meclofenamate (10 mg/kg) were prepared in isotonic saline. None of the drug vehicles used had any consistent effect on blood pressure or renal blood flow.

### Intrarenal PAF Effect on Platelet Density

To determine whether PAF caused intrarenal platelet aggregation, arterial and renal venous blood samples were drawn simultaneously before, during, and after continuous infusion of PAF, 1 to 2 μg/min for 15 minutes, into the renal artery, and platelet density of whole blood was determined using a Coulter counter (Model ZM; Coulter Electronics, Hialeah, FL, USA).

### Effect of Alprazolam on PAF-Induced Canine Platelet Aggregation

Blood was drawn from pentobarbital-anesthetized dogs and mixed with 3.8% sodium citrate (9:1, vol/vol). Platelet-rich plasma was prepared by centrifugation...
Results

Control renal blood flow in these studies averaged 211 ± 15 ml/min (range, 125–270 ml/min). Control mean arterial blood pressure averaged 129 ± 10 mm Hg. Effects of various blocking agents used on renal blood flow, renal vascular resistance, and blood pressure are shown in Table 1. Alprazolam and methysergide both reduced renal vascular resistance by reducing blood pressure without altering renal blood flow, while renal vascular resistance increased after meclofenamate because of a combination of increased blood pressure and decreased renal blood flow. Phentolamine reduced blood pressure and renal blood flow but did not affect renal vascular resistance. Neither LY 53857 nor [Sar^1, Ala^8]angiotensin II had any effect on blood pressure or renal blood flow.

Bolus injections of PAF, 0.2 to 0.8 μg, into the renal artery transiently increased renal vascular resistance, reducing renal blood flow in a dose-dependent fashion by 20 to 60% without significantly altering systemic blood pressure. The onset of the renal blood flow reduction was apparent within 1 to 3 seconds after PAF injection, and a nadir value was achieved within 5 to 10 seconds; the onset of recovery was apparent within seconds after the nadir had been reached. Renal blood flow returned toward control levels in a roughly exponential fashion and did not overshoot control. The time required for complete recovery ranged from 2 to 8 minutes and varied with the dose of PAF administered.

Injection of a 2-μg bolus of PAF into the renal artery resulted in complete, transient cessation of renal blood flow and a 20 to 50 mm Hg fall in blood pressure. As shown in Figure 1, alprazolam significantly attenuated the renal vasoconstrictor effect of PAF, reducing the response to the highest dose of PAF by 50% and that to the lowest dose by almost 100%. In contrast, alprazolam did not alter the renal vasoconstrictor effects of either norepinephrine or angiotensin II.

The effects of other blocking agents tested on the renal vasoconstrictor response to bolus PAF injection are shown in Figures 2 to 5. Like PAF, bolus injections of norepinephrine or angiotensin II into the renal artery caused transient renal vasoconstriction, reducing renal blood flow in a dose-related fashion. Administration of phentolamine (see Figure 2) or [Sar^1, Ala^8]angiotensin II (see Figure 3), in doses that completely inhibited renal vasoconstrictor responses to norepinephrine or angiotensin II, respectively, did not alter renal vasoconstrictor responses to equieffective doses of PAF.

Treatment with meclofenamate, shown in Figure 4, increased by approximately 30% the renal vasocon-

Table 1. Effects of Various Drug Treatments on Resting Blood Pressure, Renal Blood Flow, and Renal Vascular Resistance

<table>
<thead>
<tr>
<th>Treatment groups*</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Renal blood flow (ml/min)</th>
<th>Renal vascular resistance (mm Hg/ml-min^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 5)</td>
<td>164 ± 6</td>
<td>214 ± 14</td>
<td>0.77 ± 0.03</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>131 ± 6†</td>
<td>218 ± 30</td>
<td>0.63 ± 0.07†</td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>148 ± 10</td>
<td>211 ± 15</td>
<td>0.73 ± 0.10†</td>
</tr>
<tr>
<td>Phenolamine</td>
<td>112 ± 12†</td>
<td>158 ± 28†</td>
<td>0.82 ± 0.17†</td>
</tr>
<tr>
<td>Control (n = 7)</td>
<td>129 ± 11</td>
<td>171 ± 14</td>
<td>0.81 ± 0.10†</td>
</tr>
<tr>
<td>Meclofenamate</td>
<td>149 ± 11†</td>
<td>143 ± 8†</td>
<td>1.12 ± 0.11†</td>
</tr>
<tr>
<td>Control (n = 6)</td>
<td>147 ± 10</td>
<td>209 ± 18</td>
<td>0.71 ± 0.05†</td>
</tr>
<tr>
<td>[Sar^1, Ala^8]angiotensin II</td>
<td>147 ± 12</td>
<td>208 ± 22</td>
<td>0.73 ± 0.09†</td>
</tr>
<tr>
<td>Control (n = 9)</td>
<td>132 ± 6</td>
<td>198 ± 9</td>
<td>0.67 ± 0.03†</td>
</tr>
<tr>
<td>Methysergide</td>
<td>100 ± 7†</td>
<td>210 ± 23</td>
<td>0.52 ± 0.07†</td>
</tr>
<tr>
<td>Control (n = 3)</td>
<td>143 ± 13</td>
<td>183 ± 22</td>
<td>0.79 ± 0.08†</td>
</tr>
<tr>
<td>LY 53857</td>
<td>135 ± 23</td>
<td>175 ± 9</td>
<td>0.78 ± 0.17†</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

*Control indicates pretreatment period. Each treatment group acted as its own control.
†p < 0.05, compared with value in control period.
strictor effect of all doses of PAF tested. In addition, the time required for renal blood flow to return to control after PAF bolus injections was doubled.

Individual dogs varied greatly in sensitivity to bolus injections of serotonin into the renal artery. Responses typically included a brief (approximately 30 seconds) initial renal vasoconstriction followed by a more prolonged (2-5 minutes) renal vasodilation that usually was accompanied by reduction of systemic blood pressure. After treatment with either methysergide or LY 53857, the renal vasodilator effects of serotonin were completely blocked, while the transient initial renal vasoconstrictor effect was completely blocked in some dogs but unaffected in others. As shown in Figure 5, methysergide also reduced the renal vasoconstrictor effect of PAF by 15 to 30%, but the selective serotoninergic 5-hydroxytryptamine, blockerLY 53857 did not alter the effects of PAF.

Two considerations suggested that we should examine the possibility that the renal vasoconstrictor action of PAF could be the result of intrarenal platelet activation, which could reduce renal blood flow both as a result of capillary plugging by platelet aggregates and through the release of vasoconstrictor agents from platelets during aggregation. First, the intrarenal arterial infusion rate of alprazolam that produced inhibition of PAF-induced renal vasoconstriction, as depicted in Figure 1, was 3.5 µmol/min. Given an average renal blood flow of approximately 200 ml/min and an average hematocrit of approximately 30%, this should have produced an average renal arterial plasma concentration of alprazolam of approximately 25 nM, a concentration reported by others to inhibit the platelet activating effects of PAF. In addition, as shown in Figure 5, the renal vasoconstrictor effect of PAF was partially inhibited by the serotonin antagonist methysergide, and serotonin is one of the vasoactive materials released from platelets during PAF-induced aggregation. Two additional studies were conducted to assess whether intrarenal platelet aggregation could contribute to the renal vasoconstrictor effects of PAF. In the first, shown in Figure 6, in vitro studies of platelet-rich dog plasma revealed a dose-dependent aggregation of platelets by PAF that was antagonized by alprazolam. In the presence of 25 µM and 100 µM alprazolam the ED₅₀ for PAF was increased from 20 nM to 62 nM and 382 nM, respec-
ALPRAZOLAM BLOCKS PAF RENAL VASOCONSTRICTOR EFFECT

FIGURE 4. Change in renal blood flow and renal blood flow recovery time caused by intrarenal arterial bolus injections of PAF under control conditions (closed circles and bars) and after administration of meclofenamate (open circles and bars). An asterisk indicates a significant difference (p < 0.05) between control and meclofenamate treatment period response.

FIGURE 5. Effects of intrarenal arterial bolus injections of PAF on renal blood flow under control conditions (closed symbols) and after treatment (open symbols) with methysergide (left panel) or LY 53857 (right panel). An asterisk indicates a significant difference (p< 0.05) between control and treatment period response.

In the second study, PAF was infused continuously over a 15-minute period into the dog renal artery at 1 to 2 μg/min, and renal venous blood was collected to assess intrarenal effects on platelet density. As shown in Table 2, PAF infusion caused a sustained 15 to 20% decrease in renal blood flow but did not significantly alter either arterial or renal venous blood platelet counts. The arterial-renal venous platelet count difference was not significantly different from zero before, during, or after PAF infusion into the renal artery.

An additional observation regarding renal effects of serotonin is also relevant. In contrast to the effect of continuous PAF infusion into the renal artery, which produced sustained renal vasoconstriction as already described, continuous serotonin infusion caused only a transient renal vasoconstriction (data not shown). Thus, the sustained, if not the transient, renal vasoconstrictor effect of PAF does not appear to be mediated by serotonin.

Discussion

This study demonstrates that PAF is a potent, direct-acting renal vasoconstrictor in the dog. When injected into the renal artery in doses (approximately 0.4–1.6 nmol) that had no effect on blood pressure, PAF caused renal blood flow decreases comparable to those caused by angiotensin II (approximately 0.1–0.3 nmol) or by norepinephrine (approximately 3–12 nmol). Thus, on a molar basis, PAF is approximately 10-fold more potent a renal vasoconstrictor than is norepinephrine and one fourth as potent as angiotensin II.

That PAF is a direct-acting renal vasoconstrictor is consistent with a report that intravenous PAF infusion increased renal vascular resistance in the dog. However, from that study it was not possible to conclude whether the renal vasoconstriction was a direct effect of PAF or was secondary to increased levels of some other renal vasoconstrictor agent, since the renal blood flow reduction was concomitant with blood pressure reduction, and systemic PAF administration causes compensatory pressor systems activation. The results
of the present study indicate that PAF can reduce renal blood flow independently of its blood pressure-lowering effects and that the renal vasoconstrictor effect of PAF administered directly into the renal artery is not secondary to release of angiotensin II or norepinephrine.

The possibility that PAF effects on renal blood flow are secondary to platelet release of serotonin could not be ruled out from this study, because we were unable to block consistently the renal vasoconstrictor effect of serotonin. However, several of our observations argue against mediation by serotonin of PAF effects on renal hemodynamics. First, bolus injections of serotonin invariably produced a biphasic effect consisting of a brief initial renal vasoconstriction followed by a prolonged renal vasodilatation; in contrast, bolus injections of PAF produced only a monophasic renal vasoconstrictor response. Second, during sustained renal vasoconstriction resulting from continuous intrarenal arterial PAF infusion, there was no alteration in platelet density in renal venous blood. Although this finding does not preclude an effect of PAF on intrarenal platelet aggregation and subsequent microvesSEL plugging were not responsible for the fall in renal blood flow. Third, we noted that continuous infusion of serotonin into the renal artery did not produce a sustained renal vasoconstriction, indicating that serotonin release could not be responsible for the sustained renal vasoconstriction produced by continuous PAF infusion.

It is becoming increasingly clear that vascular responses to PAF vary between species and according to the route of administration and the tissue studied. In the conscious rat, systemic PAF administration reduced blood pressure and resistance to blood flow in the mesenteric, renal, and hindquarters vasculature, suggesting that in that species PAF lowers blood pressure by reducing total peripheral resistance. In the dog, in contrast, systemic PAF administration elevates total peripheral resistance, and reduced cardiac output accounts for the blood pressure–lowering effect. Elevation of total peripheral resistance in response to systemic PAF administration in the dog appears to be secondary to pressor systems activation, since PAF given by direct intra-arterial administration causes dilation in the femoral vasculature and has no effect on coronary vascular resistance.

The finding that PAF is a potent renal vasoconstrictor assumes added importance when taken in combination with results of a series of studies demonstrating that PAF is synthesized in the kidney and released systemically. PAF is found in blood of normal human subjects and rats, but it is undetectable after bilateral nephrectomy, suggesting that the kidney is the major source of circulating PAF and that PAF is released from the kidney under basal conditions. The concentration of PAF in blood of intact subjects ranged from 0.2 ng/ml in humans to 1.8 ng/ml in rats. In the present study, PAF produced sustained renal vasoconstriction when infused at 2 μg/min into an average renal arterial plasma flow of 150 ml/min, which should have resulted in a plasma PAF concentration of approximately 13 ng/ml. Thus, PAF can affect renal hemodynamics at plasma concentrations 10 to 100 times greater than those found under basal conditions. In the isolated, perfused rat kidney, PAF release into the renal venous effluent has been demonstrated to occur in response to calcium ionophore. PAF has also been found in urine of normal humans, but it is not known whether urinary PAF is derived from that in the circulation or arises from direct intrarenal synthesis and addition to the tubular fluid.

In addition to the evidence that PAF is released systemically from the kidney under basal conditions, other reports suggest that, in at least one circumstance, the kidney releases sufficient PAF to produce profound systemic cardiovascular effects. In rats with two-kidney, one clip Goldblatt hypertension, removal of the renal artery clip results in a rapid lowering of blood pressure, and in the release into the renal venous effluent of a substance that lowers blood pressure of normal rats. Muirhead and colleagues demonstrated the presence of PAF in renal venous effluent from the unclipped kidney and proposed that it is released from renal medullary interstitial cells, having previously shown that renal interstitial cells manufacture PAF, that they normally contain large lipid granules, and that they undergo degranulation following renal artery unclipping. The hypothesis that PAF is the vasodepressor released from the unclipped kidney is that responsible for the blood pressure lowering is supported by the recent finding that pretreatment with a specific PAF antagonist largely prevents the blood pressure–lowering effect of renal artery unclipping.

### Table 2. Renal Venous and Arterial Whole Blood Platelet Density During Sustained, PAF-Induced Renal Vasoconstriction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control - 5 min</th>
<th>PAF infusion + 5 min</th>
<th>PAF infusion + 10 min</th>
<th>PAF infusion + 15 min</th>
<th>PAF infusion + 20 min</th>
<th>PAF infusion + 25 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBF (ml/min)</td>
<td>215 ± 12</td>
<td>183 ± 14*</td>
<td>182 ± 12*</td>
<td>186 ± 11*</td>
<td>223 ± 16</td>
<td>220 ± 15</td>
</tr>
<tr>
<td>APD (x 10^-3 platelets/μl)</td>
<td>1.65 ± 0.31</td>
<td>1.60 ± 0.31</td>
<td>1.50 ± 0.20</td>
<td>1.42 ± 0.21</td>
<td>1.69 ± 0.26</td>
<td>1.60 ± 0.18</td>
</tr>
<tr>
<td>RVPD (x 10^-5 platelets/μl)</td>
<td>1.53 ± 0.28</td>
<td>1.85 ± 0.42</td>
<td>1.56 ± 0.22</td>
<td>1.55 ± 0.26</td>
<td>1.58 ± 0.20</td>
<td>1.77 ± 0.25</td>
</tr>
<tr>
<td>(A-RV)PD</td>
<td>0.12 ± 0.06</td>
<td>-0.25 ± 0.24</td>
<td>-0.06 ± 0.04</td>
<td>-0.14 ± 0.07</td>
<td>0.11 ± 0.18</td>
<td>-0.17 ± 0.07</td>
</tr>
</tbody>
</table>

Values are means ± SEM. No. of minutes indicates time before and after initiation of PAF infusion. RBF = renal blood flow; APD = arterial blood platelet density; RVPD = renal venous blood platelet density; (A-RV)PD = arterial-renal venous blood platelet density difference.

*p < 0.05, compared with control value.
reported that renal artery unclipping in one-kidney, one clip hypertensive rats caused a lowering of blood pressure that was accompanied by reduction of cardiac output and elevation of total peripheral resistance, a pattern of effects also observed during PAF infusion. They further noted that after unclipping plasma volume was decreased and hematocrit was increased, changes also reported to occur following PAF infusion.

Taken together, these findings provide strong evidence that PAF is released from the kidney under basal conditions and that following renal artery unclipping the kidney releases sufficient PAF to produce systemic effects. Given the potent renal vasoconstrictor action of PAF demonstrated in the present study, this conclusion raises the possibility that, at least under some circumstances, intrarenal PAF levels could affect renal vascular resistance.

Although an unequivocal conclusion regarding the mechanism by which PAF causes renal vasoconstriction cannot be drawn on the basis of available information, the following considerations are relevant to that mechanism. First, the renal vasoconstrictor effect of PAF was not diminished by angiotensin II receptor blockade, by α-adrenergic receptor blockade, by serotoninergic receptor blockade, or by treatment with a cyclooxygenase inhibitor. In addition, examination of renal venous blood did not reveal intrarenal platelet aggregation during continuous intrarenal arterial infusion of a vasoconstrictor dose of PAF. Thus, PAF-induced renal vasoconstriction is a direct, primary effect that does not involve aggregation of platelets, release of angiotensin II or norepinephrine, or production of renal vasoconstrictor metabolites of arachidonic acid by the cyclooxygenase pathway. Second, alprazolam blocked the renal vasoconstrictor effect of PAF at an estimated concentration similar to that found to competitively inhibit dog platelet activation by PAF. In addition, alprazolam blockade of the renal vasoconstrictor effect of PAF did not alter vasoconstrictor responses to angiotensin II or norepinephrine, implying that at least one component in the mechanism by which PAF causes renal vasoconstriction is unique for PAF and not common to the mechanisms of action of other vasoconstrictors.

Treatment with the cyclooxygenase inhibitor meclofenamate not only failed to reduce the renal vasoconstrictor effect of PAF but actually resulted in a marked enhancement of both the magnitude and duration of that effect. Prostaglandin synthesis inhibition similarly enhances renal vasoconstrictor actions of other agents, such as angiotensin II and norepinephrine, which stimulate renal synthesis of vasodilator prostaglandins. PAF has also been shown, both in the intact kidney and in cultured mesangial cells, to stimulate production of vasodilator prostaglandins. Schlondorff et al. reported that prostaglandin synthesis inhibition potentiated PAF-induced contraction of mesangial cells, and that addition of prostaglandin E₂ partially reversed the contractile response to PAF. As has been proposed to account for the enhancement of other renal vasoconstrictor agents, the increased magnitude and duration of the renal vasoconstrictor effect of PAF in meclofenamate-treated rats may be the expression of inhibited formation of intrarenal dilator prostaglandins that normally are synthesized in increased amounts in response to PAF and offset a portion of its constrictor action.

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