Role of Platelet-Activating Factor in Renal Function in Normal Rats and Rats with Bilateral Ureteral Obstruction (43291)

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Abstract. **Platelet-activating factor (PAF) is a powerful vasodilator with important effects on kidney function. It has been suggested that the renal effects of PAF are mediated by thromboxane A_2 (TxA_2). We examined the effect of PAF on renal function in sham-operated rats and rats that had undergone unilateral release of bilateral ureteral obstruction (BUO) of 24-hr duration, a condition in which the synthesis of TxA_2 is increased. To eliminate systemic hemodynamic changes, PAF was infused directly into the left renal artery using the lowest dose that affected renal function (2.3×10^{-13} moles/min). Infusion of PAF significantly decreased the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in normal rats and rats with BUO. Normal (sham-operated) rats pretreated with an inhibitor of TxA_2 synthesis also had a significant decrease in GFR after administration of PAF (ERPF also decreased, but not significantly). Rats with BUO pretreated with an inhibitor of TxA_2 synthesis had significantly greater basal GFR and ERPF (increases of 72 and 171%, respectively) than untreated BUO rats. Administration of PAF to the former group further increased GFR and ERPF (by 37 and 39%, respectively; $P < 0.001$). The role of endogenous PAF was evaluated by administering a specific PAF receptor antagonist. Sham-operated rats pretreated with high doses of the PAF receptor antagonist had significantly higher mean arterial pressure values than normal untreated rats, and had no decrease in GFR and ERPF during PAF infusion. Rats with BUO pretreated with the PAF antagonist had a significant, dose-dependent decrease in basal GFR and ERPF. These data suggest that endogenous PAF has a vasodilatory role in obstructive nephropathy. No significant differences in eicosanoid excretion in the urine corrected per GFR were observed during infusion of PAF in any of the groups examined. In BUO rats with intact TxA_2 synthesis, exogenous administration of PAF decreased renal function, presumably through further increases in the production of TxA_2. However, when TxA_2 production was inhibited, PAF administration increased GFR and ERPF, presumably due to its unopposed vasodilatory properties. The data suggest an important role of PAF in the hemodynamic changes seen in obstructive nephropathy.** [P.S.E.B.M. 1991, Vol 198]

Obstruction of the urinary tract decreases the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) and causes multiple abnormalities of renal tubular function (1, 2). Three vasoconstrictors—angiotensin II, thromboxane A_2 (TxA_2) (3), and antidiuretic hormone (4)—have an important role in the decrease of GFR and ERPF observed after unilateral release of bilateral ureteral obstruction (BUO) of 24-hr duration. The production of both thromboxane B_2 (TxB_2), the stable metabolite of TxA_2, and angiotensin II is increased in animals with BUO (1, 2). The production of TxA_2 is markedly increased in the obstructed kidney due to its release by infiltrating leukocytes (5) and greater synthesis by cells intrinsic to the kidney (6). Inhibition of angiotensin II and TxA_2 synthesis (3), or the use of antagonists of the V_1 receptor of antidiuretic hormone (4) prior to obstruction, increases GFR and ERPF in postreleased kidneys. Other substances with vasodilatory properties, such as prostaglandin E_2, also influence renal hemodynamics after release of obstruction (7).

Received February 20, 1991. [P.S.E.B.M. 1991, Vol 198]
Accepted May 8, 1991.

0037-9727/91/1981-0572$3.00/0

Platelet-activating factor (PAF) is found in the renal medulla, inflammatory cells, platelets, endothelial cells, and isolated glomeruli (8). The effects of infusing PAF on renal function have been examined in dogs, rabbits, and rats (9, 10). When infused systemically, PAF decreases ERPF and GFR (9). However, since systemic PAF lowers blood pressure, the decrease in renal function may be secondary to this effect. In normal rats, administration of PAF stimulates eicosanoid production by the kidney in a dose-dependent manner, and it has been suggested that TxA_2 release mediates some of the renal effects of PAF (9).

The overall hemodynamic state in BUO is reflective of vasoconstriction, which appears to be determined by the imbalance between increased synthesis or activation of vasoconstrictors and, probably, decreased activity and/or synthesis of vasodilators. In this study, we examined the role of endogenous and exogenous PAF, a potent vasodilator, in the renal hemodynamics of rats in which BUO of 24-hr duration was unilaterally released. The experiments were performed in rats in which synthesis of TxA_2 was either left intact or inhibited. The potential contribution of endogenous PAF to renal hemodynamics was evaluated by pretreating the animals with a PAF receptor antagonist prior to obstruction.

Methods

Animals and Chemicals. Female Sprague-Dawley rats (mean weight 210.4 ± 3.7 g) were obtained from Sasco, Inc. (Omaha, NE). After arrival, the animals were housed five or six to a cage, fed a standard rat chow diet containing 22.8% protein (Ralston Purina, St. Louis, MO), and given water *ad libitum*. Experiments were performed no sooner than 7 days after arrival of the animals.

Platelet-activating factor (Sigma Chemical Co., St. Louis, MO) was dissolved in 70% ethanol, divided into 6000 ng/50-μl aliquots, and stored at −20°C until use. On the day of the experiment, the ethanol was evaporated under a nitrogen stream and PAF was redissolved in normal saline to a final concentration of 6 ng/ml for administration to rats, as described below. The PAF receptor antagonist L-659,989 (a gift from Drs. J. Chabala and T. Doebber, Merck, Sharp & Dohme Research Laboratories, Rahway, NJ) was dissolved in 70% ethanol, divided into aliquots of 1 mg/250 μl, and stored at −10°C for oral administration to rats, as described below. L659,989 is a potent and highly selective competitive inhibitor of the binding of [^{3}H] PAF to its receptors in platelet membranes from humans and rabbits. It exhibits equilibrium inhibition constants for PAF binding that are at least 1–2 orders of magnitude lower than those of other available PAF antagonists (11). On the day of administration, the PAF receptor antagonist aliquot was diluted 20-fold in distilled water prewarmed at 20–40°C and vortexed prior to administration. The rats were given the total amount using a stomach tube (Perfektum, New Hyde Park, NY). The thromboxane synthase inhibitor OKY-046 was a gift from ONO Pharmaceuticals (Osaka, Japan). Inulin was purchased from Sigma and *para*-aminohippuric acid (PAH) was purchased from Merck, Sharp & Dohme (West Point, PA).

Surgical Procedures. *Bilateral ureteral obstruction.* This procedure was performed in 26 rats by ligating both ureters at the junction of the lower one third and upper two thirds through a small midline suprapubic incision, under ether anesthesia. The rats were returned to their cages without food or water and were studied 24 hr later. Sham-operated rats had their ureters manipulated, but not ligated.

Renal artery catheterization. A heparinized catheter (PE-10) with a calculated external diameter of 0.009 in. was placed into the left renal artery through the femoral artery. This catheter was used exclusively for the infusion of PAF, as described below.

Experimental Groups. Four groups of sham-operated rats (Groups 1 to 4) and four groups of rats with BUO (Groups 5 to 8) were studied (Table I). The protocol in each group consisted of two baseline clearance periods of 20 min each, followed by a constant infusion of PAF (2.3×10^{-13} moles/min, delivered in normal saline) into the renal artery using a pump (Harvard Apparatus, South Natick, MA). After equilibration (10 min), there was a second set of two 20-min clearance periods. Groups 1 (sham-operated rats) and 5 (BUO rats) received no prior treatment. The rats from Groups 2 and 6 were pretreated with 20 mg/kg body wt of subcutaneous OKY-046, a selective inhibitor of thromboxane synthesis (3), twice a day for 2 days prior

Table I. Different Groups of Rats Studied

Sham-operated rats, pretreated as indicated and according to the PAF protocol after operation	
Group 1 (n = 6)	No pretreatment
Group 2 (n = 6)	Pretreated with the thromboxane synthase inhibitor OKY-046
Group 3 (n = 6)	Pretreated with 1 mg/kg body wt of the PAF receptor antagonist L-659,989 12 hr prior to study
Group 4 (n = 5)	Pretreated with 5 doses of 5 mg/kg body wt of the PAF receptor antagonist L-659,989 prior to study
Rats with bilateral ureteral obstruction, pre-treated as indicated, and according to the PAF protocol after BUO	
Group 5 (n = 12)	No pretreatment
Group 6 (n = 5)	Pretreated with OKY-046, as in Group 2
Group 7 (n = 4)	Pretreated with the PAF receptor antagonist, as in Group 3
Group 8 (n = 5)	Pretreated with the PAF receptor antagonist, as in Group 4

to clearance studies. The rats from Groups 3 and 7 were pretreated with 1 mg/kg body wt of the PAF receptor antagonist L-659,989 orally 12 hr prior to study. The rats of Groups 4 and 8 were pretreated with 5 mg/kg body wt of L-659,989 twice a day for 2 days prior to, then just before, clearance studies.

Clearance Studies and Blood Pressure Determinations. Standard clearance studies were performed, as described previously (3). Briefly, under light ether anesthesia, catheters were inserted into the tail vein, the right femoral artery, the left ureter, and the left renal artery. The rats were secured in plastic holders and, 2 hr after recovery from anesthesia, were studied in the awake state. Awake rats were used to facilitate comparison with previous studies conducted in our laboratory and also to minimize hemodynamic changes resulting from anesthesia. A priming dose of inulin designed to produce plasma levels of 70–150 mg/dl and PAH calculated to produce plasma levels of 1–2 mg/dl was infused in 0.6 ml of normal saline over a 3-min period. This was followed by a sustained infusion delivered at 40 μl/min that contained sufficient inulin and PAH to maintain constant plasma levels of these compounds. Following an equilibration period of at least 60 min, and approximately 4 hr after unilateral release of the obstruction, two consecutive 20-min collections of urine and blood were obtained for estimation of GFR by inulin clearance and of ERPF by PAH clearance. At the completion of the baseline periods, an infusion of PAF (2.3×10^{-13} moles/min) was started and 10 min later another set of two 20-min collections of urine and blood was obtained for the same determinations described above. Blood pressure was recorded throughout the experiment using the catheter placed into the right femoral artery and connected to a Harvard Apparatus (WECO VT-1; Winston Electronic Co., Millbrae, CA).

Analytic Studies. Thromboxane B_2 levels were determined in urine samples collected in prechilled tubes before and during the administration of PAF using a specific radioimmunoassay. The TxB_2 antiserum was prepared in our laboratory and its cross-reactivity and details of the radioimmunoassay have been reported previously (12). All determinations were done in duplicate. Inulin levels were determined using the anthrone method (13) and PAH was measured by a modification of the method of Smith *et al.* (14).

Calculations and Statistics. Inulin and PAH clearances were calculated using standard formulas. For each rat, the values of the two baseline clearance periods were averaged and compared to the average of the two experimental clearance periods obtained during the continuous administration of PAF. The same was done for thromboxane excretion in the urine. A paired Student's *t* test was used to compare, within each group, the changes in blood pressure and renal function during the infusion of PAF. Intergroup comparisons were performed by means of analysis of variance. Differences were considered significant when $P < 0.05$.

Results

The values for mean arterial pressure (MAP) before and during the administration of PAF in sham-operated rats and BUO rats are depicted in Figure 1. No significant changes in systemic blood pressure were observed during the direct infusion of PAF into the renal artery. On the other hand, sham-operated rats pretreated with high doses of the PAF receptor antagonist (Group 4) had significantly higher MAP than the other three groups of sham-operated rats. Rats with BUO (Groups 5 through 8) had significantly higher MAP values than sham-operated rats. Rats with BUO given high doses of the PAF receptor antagonist (Group 8) had slightly higher, but not significantly different, values for MAP, compared with untreated BUO rats (Group 5).

No significant differences in hematocrit values were observed among the eight groups of rats. There were no significant changes in hematocrit or heart rate during administration of PAF (data not shown).

The values for GFR and ERPF for the eight groups of rats are shown in Table II. In sham-operated rats not pretreated (Group 1) and BUO rats not pretreated (Group 5), there was a significant decrease in GFR and ERPF during the infusion of PAF. Pretreatment of sham-operated rats with a thromboxane synthase inhibitor (Group 2) did not prevent a significant decrease in GFR after PAF administration, although the decrease in ERPF observed was not significant. Baseline values

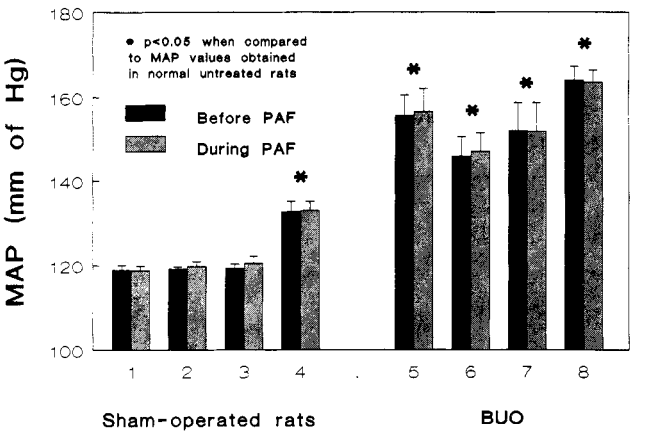

Figure 1. Values for mean arterial pressure in eight groups of rats before (closed bars) and during (hatched bars) infusion of PAF into the renal artery. There were no significant changes in MAP during the infusion of PAF. However, sham-operated rats pretreated with high doses of a specific PAF-receptor antagonist (Group 4) had significantly greater values for basal MAP than sham-operated rats not pretreated (Group 1). Rats with BUO (Groups 5 through 8) had significantly higher values for basal MAP than normal rats (Groups 1 through 4). Asterisks represent significant differences for MAP when compared with sham-operated rats not pretreated (* $P < 0.05$). The composition of the groups and the protocols followed are described in Table I.

Table II. Values for GFR and ERPF in Eight Groups of Rats[a]

	GFR (ml/min/kg body wt)		ERPF (ml/min/kg body wt)	
	Before PAF	During PAF	Before PAF	During PAF
Sham-operated rats				
Group 1	6.4 ± 0.6	4.5 ± 0.6[b]	19.0 ± 2.3	13.8 ± 2.2[b]
Group 2	5.7 ± 0.2	4.3 ± 0.5[b]	19.6 ± 1.9	15.4 ± 2.9
Group 3	7.5 ± 0.8	5.3 ± 0.8[b]	21.4 ± 1.9	12.1 ± 1.8[b]
Group 4	5.2 ± 0.3	5.3 ± 0.4	20.5 ± 1.6	21.6 ± 2.9
Rats with bilateral ureteral obstruction				
Group 5	1.1 ± 0.1	0.7 ± 0.1[b]	2.1 ± 0.2	1.4 ± 0.2[b]
Group 6	1.9 ± 0.2	2.6 ± 0.2[b,c]	5.7 ± 0.5	7.9 ± 0.8[b,c]
Group 7	0.6 ± 0.1	0.5 ± 0.2[d]	1.9 ± 0.5	1.7 ± 0.7
Group 8	0.2 ± 0.1	0.2 ± 0.1[d]	0.6 ± 0.2	0.5 ± 0.3[d]

[a]Values are expressed as mean ± SE in each group of rats. In normal (sham-operated) animals, values are calculated for one kidney. In rats with bilateral ureteral obstruction, values were obtained after unilateral release of bilateral ureteral obstruction of 24-hr duration. Composition of the groups is the same as that for Table I.
[b]$P < 0.05$, for intragroup comparisons between values obtained before and during infusion of PAF.
[c]$P < 0.05$, for intergroup comparisons to values obtained before infusion of PAF in the untreated obstructed rats.
[d]$P < 0.05$, for intergroup comparisons in values obtained before administration of PAF in the obstructed groups pretreated with L-659,989.

for GFR and ERPF in sham-operated rats receiving the receptor antagonist of PAF (Groups 3 and 4) were not significantly different from those observed in sham-operated rats not pretreated (Group 1). However, the group of rats that received the lower dose of the PAF receptor antagonist (Group 3) still had a significant decrease in GFR and ERPF during the infusion of PAF. Pretreatment with higher doses of the PAF-receptor antagonist (Group 4) prevented this decrease. In rats with BUO (Groups 5 through 8), basal GFR and ERPF values were significantly less than in sham-operated rats (Groups 1 through 4). Rats with BUO pretreated with an inhibitor of thromboxane synthesis (Group 6) had significantly greater basal GFR (72% greater) and ERPF (171% greater) than obstructed rats not pretreated (Group 5). Infusion of PAF to rats of Group 6 increased GFR by 37% and ERPF by 39%. Rats with BUO pretreated with lower doses of the PAF receptor antagonist (Group 7) had a significant decrease in basal GFR but not in ERPF, when compared with the basal values obtained in BUO rats not pretreated (Group 5). Rats with BUO given high doses of the PAF receptor antagonist (Group 8) had significantly lower basal GFR and ERPF than BUO rats not pretreated (Group 5). There were no significant changes in GFR or ERPF after administration of PAF in rats with BUO given the PAF receptor antagonist (Groups 7 and 8). Rats with BUO given the lower dose of the PAF receptor antagonist (Group 7) had significantly greater GFR and ERPF than rats with BUO given the higher doses of the antagonist (Group 8).

Figure 2 depicts the percentage changes in GFR during the infusion of PAF as compared with basal values in the different groups of rats. In rats given high doses of the PAF receptor antagonist (Groups 4 and 8), there was no significant change in GFR during infusion of PAF. Only rats with BUO pretreated with an inhibitor of thromboxane synthesis (Group 6) had an increase in GFR during infusion of PAF. All other groups, except 4 and 8, had a decrease in GFR during infusion of PAF.

The excretion of TxB_2 in the urine for seven of the eight groups of rats is summarized in Table III. A laboratory accident prevented the determination of thromboxane in the urine of rats of Group 3. After the infusion of PAF, there were no significant changes in the excretion of TxB_2 expressed either in absolute values (not shown) or after correction per milliliter of inulin clearance. However, the excretion of TxB_2, corrected per GFR, in the urine of BUO rats not pretreated (Group 5) was significantly greater than that of sham-operated rats (Group 1). Rats given the inhibitor of thromboxane synthesis (Groups 2 and 6) had significantly lower excretion rates of TxB_2 in urine than untreated rats of the corresponding groups (Groups 1 and 5). Sham-operated rats given the high dose of the PAF receptor antagonist (Group 4) had significantly lower excretion rates of TxB_2 in the urine than sham-operated rats not pretreated (Group 1). No significant changes in thromboxane excretion per milliliter of inulin clearance were observed in rats with BUO treated

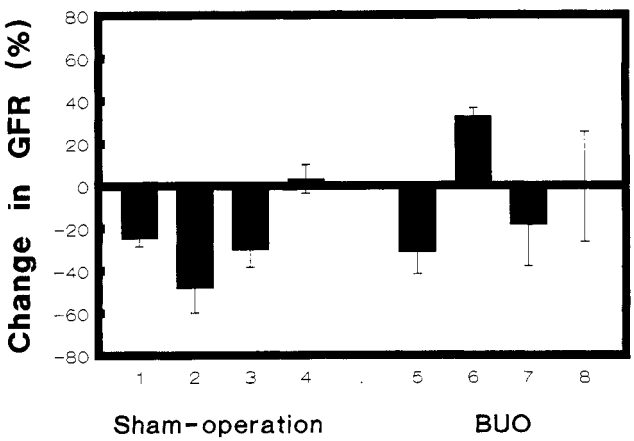

Figure 2. Percentage changes in GFR values during infusion of PAF into the renal artery in eight groups of rats. For each rat, the percentage change in GFR during the infusion of PAF was calculated and the values for the group were averaged. Negative bars represent a decrease in GFR (Groups 1, 2, 3, 5, and 7). There were no significant changes in GFR during infusion of PAF in the rats that received the high dose of the PAF receptor antagonist (Groups 4 and 8). There was a significant increase in GFR after PAF infusion in rats with BUO pretreated with an inhibitor of thromboxane synthesis (Group 6). The composition of the groups is given in Table I.

Table III. Thromboxane B_2 Excretion in the Urine before and during PAF Administration[a]

	pg/ml of C_{in}	
	Before PAF	During PAF
Sham-operated rats		
Group 1	5.4 ± 1.4	5.6 ± 1.1
Group 2	0.01 ± 0.002[b]	0.002 ± 0.001
Group 4	0.01 ± 0.03	0.01 ± 0.001
Rats with bilateral ureteral obstruction		
Group 5	19.1 ± 2.8[b]	43.6 ± 19.3
Group 6	2.3 ± 0.8[c]	1.8 ± 0.6
Group 7	30.9 ± 6.1	20.4 ± 12.9
Group 8	57.7 ± 40.7	61.8 ± 29.6

[a]Values are mean ± SE in each group of rats. Values are the average of the two results obtained for each sample. Composition of the groups is the same as that described in Table I.
[b]$P < 0.05$ when compared with values obtained in normal rats.
[c]$P < 0.05$ when compared with values obtained in BUO rats not pretreated.

with the PAF receptor antagonist (Groups 7 and 8), as compared with BUO rats not so treated (Group 5).

Discussion

The effect of systemic administration of PAF on renal function has been examined previously in normal animals. Friedlander *et al.* (15) and Hebert *et al.* (16) reported a significant decrease in urine flow and GFR after the intravenous administration of PAF. However, significant hypotension occurred after the administration of PAF, making it difficult to dissociate a potential direct effect of PAF on renal function from the systemic hemodynamic changes it induced. Other reports are also complicated by the hemodynamic effects that occur after systemic administration of PAF, including hypotension, hemoconcentration, and shock (9), all of which affect renal function. On the other hand, one group of investigators, Badr *et al.* (10), did report a dose-dependent reduction in GFR and RPF in the absence of hypotension or hemoconcentration in normal anesthetized rats after aortic administration of PAF.

In the present study, PAF was infused directly into the renal artery of awake rats at a dose that did not induce changes in systemic blood pressure, heart rate, or hematocrit values. The amount of PAF used was the minimum necessary (2.3×10^{-13} moles/min) to induce changes in renal function without producing systemic effects. The results confirm that the intrarenal administration of PAF at a dose that does not induce systemic hemodynamic changes decreases GFR and ERPF in both normal rats and rats with BUO. We are not aware of any other study that has examined renal function in awake rats after the constant infusion of PAF directly into the renal artery. It is highly unlikely that the decrease in renal function observed in normal rats and in BUO rats after PAF administration is due to platelet aggregation. Rat platelets do not aggregate when exposed to PAF *in vitro*, although they aggregate normally when ADP is added (17). The decrease in renal function after administration of PAF was prevented by pretreating sham-operated rats (Group 4) with high doses of a PAF receptor antagonist. This pretreatment also significantly increased basal MAP, suggesting that endogenous PAF may play a role in regulating systemic blood pressure. In rats with BUO pretreated with the PAF receptor antagonist (Groups 7 and 8), no decrease in GFR or ERPF was observed after the infusion of PAF. However, basal values for GFR and ERPF were already markedly decreased, so that the lack of effect of PAF on GFR and ERPF in these two groups of rats is difficult to interpret.

Since renal perfusion pressure, as a function of MAP, was constant in our experiments, the decrease in GFR found after infusion of PAF could be due to one or more of the following: (i) increased renal vascular resistance, predominantly of the afferent arteriole; (ii) a decrease in the ultrafiltration coefficient (K_f) due to contraction of mesangial cells; and (iii) a decrease in renal vascular resistance secondary to dilatation of the efferent arteriole, with a fall in intraglomerular capillary pressure. There is controversy in the pertinent literature as to whether changes in renal vascular resistance occur with doses of PAF that do not affect MAP. Badr *et al.* (10) reported increased vascular resistance in both pre- and postglomerular vessels after PAF administration. There was a fall in K_f, suggesting a decrease in the glomerular capillary surface available for filtration, presumably as a consequence of mesangial cell contraction (10). In contrast, Schwertschlag *et al.* (18) reported that PAF infusion decreased renal vascular resistance in the isolated perfused rat kidney. Similar findings have been reported in *in vivo* studies. Siren and Feuerstein (19) found a decrease in renal vascular resistance after the intravenous administration of 0.1–3 nmol/kg body wt of PAF in rats, with a greater response (38% decrease) seen with the 1.0 nmol/kg dose. Gerkens (20) also reported a decrease in renal vascular resistance in the isolated perfused rat kidney during PAF administration that was dependent on the presence of albumin.

The effects of PAF on renal function may be mediated by changes in thromboxane A_2 production. We found no significant changes in thromboxane excretion during PAF administration to sham-operated rats. This may be due to the small dose of PAF (subpicomolar range) used. In addition, the excretion of thromboxane in the urine may not truly reflect the changes in renal production, since the levels of this eicosanoid in renal venous blood were not measured. It is also possible that PAF administered in this manner has a direct effect on renal function through mechanisms unrelated to thromboxane production by the kidney. Direct effects of PAF on mesangial cell contraction and K_f independ-

ent of eicosanoid(s) are possible. In support of this postulate is the report by Kester *et al.* (21), who observed a direct increase in $[Ca^{2+}]_i$ after incubation of mesangial cells with PAF.

It is possible that the effect of PAF on renal function of normal rats may not be mediated through thromboxane A_2. In normal rats pretreated with an inhibitor of thromboxane synthesis (Group 2; see Table II), basal excretion of TxA_2 in the urine was significantly reduced; however, GFR and ERPF still decreased after the infusion of PAF. This observation differs from the results reported by Badr *et al.* (10). However, our study differs from theirs in two ways: we used a smaller dose of PAF and we used animals in the awake state. Previous studies by Terragno *et al.* (22) demonstrated an 8-fold increase in the basal excretion of eicosanoids in the urine of anesthetized dogs when compared with conscious dogs, suggesting an increase in eicosanoid production in acutely stressed animals.

The results of our studies in sham-operated rats confirm a decrease in GFR and ERPF during intrarenal administration of PAF, at doses that do not modify MAP. Although the mechanism(s) underlying this effect is not evident, it appears that the decrease in renal function is not mediated through TxA_2, since inhibition of the synthesis of this eicosanoid did not prevent the fall in GFR and ERPF.

The hemodynamic changes seen in obstructive nephropathy have been a subject of considerable investigation in this and other laboratories (1–4). In the present study, we observed a decrease in GFR and ERPF beyond that caused by BUO itself after the intrarenal infusion of PAF (Group 5). This effect was observed in the absence of changes in blood pressure, heart rate, or hematocrit. Although the excretion of TxB_2 in the urine was increased in these animals after PAF administration, this increase did not achieve statistical significance.

The response observed after PAF administration to BUO rats treated with a thromboxane synthase inhibitor prior to obstruction (Group 6) is of interest. Basal values for GFR and ERPF after release of obstruction were 70 and 170% greater in these rats than in BUO rats not pretreated (Group 5; see Table II). This is consistent with our previous report that inhibition of thromboxane synthesis during BUO increases GFR and ERPF (3). In rats of Group 6, GFR and ERPF increased further, by 37% and 39%, respectively, after the infusion of PAF. The administration of PAF to BUO rats pretreated with an inhibitor of thromboxane synthesis unmasked a potent and significant vasodilatory effect. Since prostaglandin E_2 and 6-keto-PG $F_{1\alpha}$ excretion in the urine was unchanged in these animals during the administration of PAF (data not shown), we suggest that in the setting of prior thromboxane synthase inhibition in rats with BUO, the administration of exogenous PAF has a vasodilatory action that is not mediated through an increase in vasodilatory eicosanoids and is not counterbalanced by an increased production of the vasoconstrictor thromboxane A_2.

The fact that PAF infused at subpicomolar concentrations induced marked changes in renal function unrelated to either hemodynamic systemic changes or to eicosanoid generation suggests that PAF could act directly through a specific receptor, or through the renal generation of other mediators. The predominant effect of PAF when thromboxane synthesis is inhibited appears to be vasodilatation. Of interest in this respect is the demonstration by Kamata *et al.* (23) that very low doses of PAF (10^{-11} moles/min) induced vasodilatation of resistance vessels through the release of endothelium-derived relaxing factor.

A putative role for endogenous PAF as a vasodilatory agent in the obstructed kidney is derived from results in BUO rats treated with a selective PAF receptor antagonist prior to study. In these rats (Groups 7 and 8), basal values for GFR and ERPF were decreased more than those of BUO rats not pretreated (Group 5; see Table II). The decrease in renal function was greater in the rats that received the higher dose of the antagonist (Group 8). These results suggest a dose-dependent inhibition of the vasodilatory action of PAF in this model. Also, the finding of an increase in MAP in normal rats pretreated with 5 mg/kg body wt of the selective PAF receptor antagonist, L-659,989 (Fig. 1), supports a vasodilatory effect of PAF *in vivo*.

The effect of intrarenal administration of PAF on renal function *in vivo* after ureteral obstruction has not been studied in detail before. Weissmann *et al.* (24) studied the effect of PAF administration (100 ng as a bolus) in the isolated perfused rabbit kidney after unilateral ureteral obstruction of 72-hr duration. PAF caused a dose-dependent increase in the release of prostaglandin E_2 from the hydronephrotic kidney. However, no measurements of GFR or ERPF were reported. Furthermore, Weissmann *et al.* used a dose of PAF that in our hands produced hypotension and hemoconcentration even if administered intrarenally (data not shown). The same group reported evidence that suggested that PAF stimulates the release of prostaglandins from the hydronephrotic kidney in the rabbit and that this effect could be inhibited by using specific PAF receptor antagonists acting principally through inhibition of TxA_2 synthesis (25). Our results indicate that in the presence of inhibitors of thromboxane synthesis, PAF administration increased GFR and ERPF in rats with BUO (Group 6). Furthermore, we observed a decrease in GFR and ERPF after pretreatment with the PAF receptor antagonist. There are differences between the two protocols that may explain the discrepant results obtained. First, we studied rats, in which, unlike in rabbits, platelet aggregation does not occur after PAF

administration. Second, we performed clearance studies with animals in the awake state. Third, we infused the PAF at a constant rate instead of giving it as a bolus. Fourth, we infused the minimal dose of PAF needed to induce changes in renal function.

Taken together, our studies in rats with BUO suggest a vasodilatory role of PAF in obstructive nephropathy when the synthesis of TxA_2 had been previously inhibited. In normal rats with an intact pathway for TxA_2 synthesis, the administration of PAF induced a vasoconstrictor response, suggesting that a potential vasodilatory effect of low doses of PAF could have been obscured by the action of vasoconstrictor substances such as TxA_2.

The results of this study suggest that PAF plays an important role in the hemodynamic alterations seen after unilateral release of BUO of 24-hr duration, and that the role is related to the vasodilatory capacity of PAF. The results also demonstrate that PAF may be important in the maintenance of renal function after release of obstruction.

This work was supported by U.S.P.H.S. NIDDK Grants DK-09976, DK-07126, and DK-40321. We thank Pat Verplancke for her assistance in the preparation of the manuscript.

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