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DIFFERENTIAL EFFECT OF PLATELET-ACTIVATING FACTOR (PAF) RECEPTOR ANTAGONISTS ON PEPTIDE AND PAF-STIMULATED PROSTAGLANDIN RELEASE IN UNILATERAL URETERAL OBSTRUCTION*,†

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Abstract—Unilateral ureteral obstruction (UUO) results in increased renal resistance as well as in exaggerated prostaglandin (PG) release from the obstructed hydronephrotic kidney (HNK). We have reported previously that platelet-activating factor (PAF) dose-dependently stimulates the release of PGs from both the HNK and unobstructed contralateral kidney (CLK), with CLK release being 10% that of the HNK. In the present report, we studied the interaction of PAF with its receptor by examining the effects of PAF-receptor antagonists on the release of PGs from the isolated perfused rabbit HNK and CLK stimulated by PAF; angiotensin II (AII), and bradykinin (BK) were also used as agonists. In the HNK, kadsurenone (3 μM) inhibited PAF-stimulated PGE_2 and thromboxane B_2 (TxB_2) release by 28.2 and 62.5% respectively. CV-3988 (20 μM) and triazolam (5 μM) also preferentially diminished PAF-stimulated TxB_2 release. In addition, all three drugs significantly diminished BK- and AII-stimulated TxB_2 release, while CV-3988 was the only antagonist to affect peptide-stimulated PGE_2 release. While effective against agonist-stimulated PG synthesis, these drugs had no direct effect on arachidonic acid metabolism to PGs. Furthermore, in the CLK, CV-3988 had no effect on BK- or AII-stimulated PGE_2 release, whereas it totally inhibited PAF-stimulated release of PGE_2. These results show that PAF-receptor antagonists in the HNK preferentially inhibit TxB_2 release whether stimulated by PAF, AII or BK; in the CLK only PAF-stimulated PG release is affected. This biochemical difference may be of physiological significance and explain some of the functional differences between the HNK and CLK. Therefore, PAF may be an important mediator of some of the biochemical and functional changes associated with UUO.

Platelet-activating factor (PAF‖) is an endogenous biologically active phospholipid with a number of sites of synthesis and activity. In addition to its production by inflammatory cells, PAF synthesis and release have been demonstrated recently from the kidney [1]. Many of the pro-inflammatory actions of PAF may be mediated through interactions with arachidonic acid (AA) metabolism, suggesting a role for such an interaction in the tissue response to injury.

Unilateral ureteral obstruction (UUO) results in renal parenchymal injury as well as profound aberrations in hemodynamic parameters [2]. Alterations in endogenous and exogenous renal AA metabolism in the resulting hydronephrotic kidney (HNK), which include an enhancement of prostaglandin (PG) synthesis and an unmasking of thromboxane (TxA_2) synthesis, may be responsible for the hemodynamic defects associated with this condition [3].

Our previous findings have shown that PAF is a potent stimulus for PG release from the isolated perfused HNK and unobstructed contralateral kidney (CLK) [4]. In the present study, the interaction of PAF with its presumed receptor was studied by examining the effects of three structurally distinct specific PAF-receptor antagonists (kadsurenone [5], triazolam [6], and CV-3988 [7]) on PAF-stimulated PG release. These studies were carried out to examine the effects of these antagonists on PAF-stimulated PG release and to determine whether PAF-receptor antagonism may differentially affect the release of PGE_2 and TxB_2. In addition, the effects of these agents on peptide-stimulated PG release from the HNK and CLK were examined.

MATERIALS AND METHODS

New Zealand white male rabbits weighing between 2.3 and 3.0 kg were used in these experiments. The

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‖ Abbreviations: AA, arachidonic acid; AII, angiotensin II; BK, bradykinin; BSA, bovine serum albumin; HNK, hydronephrotic kidney; PAF, platelet-activating factor; PG, prostaglandin; PRP, platelet-rich plasma; Tx, thromboxane; and UUO, unilateral ureteral obstruction.

left ureter was aseptically ligated as previously described [4]. Seventy-two hours after obstruction, the animals were anesthetized, and a laparotomy was performed to expose the renal vessels. Both the renal artery and the renal vein of the HNK and CLK were cannulated with PE-90 tubing, and the kidneys were flushed through the renal artery cannula with 10 ml of heparinized saline.

After flushing, the kidneys were transferred to water-jacketed chambers (37°) and were perfused with oxygenated (95% O_2–5% CO_2) Krebs–Henseleit medium containing 0.25% bovine serum albumin (BSA) at a flow rate of 10 ml/min. Perfusion pressure was monitored continuously by a pressure transducer connected to a side arm of the renal artery cannulae, and preparations were only used in the period in which the baseline pressure remained constant. After a 3-hr equilibration period, the experimental protocol was begun. Aliquots of the renal effluent were collected over 5-min periods for radioimmunoassay (RIA) of prostaglandin E_2 (PGE_2) and TxB_2 before (basal) and after agonist stimulation (stimulated) as previously described [4]. All agonists were introduced as a 100 ng bolus (100 μl) into the renal artery cannula and flushed with 500 μl of the perfusion buffer. After this control period, antagonists were added to the perfusion medium and infused through the renal artery cannulae for 15 min. With antagonist infusion continuing, agonists were tested again. The appropriate vehicle was added to the perfusion medium during both the control and experimental periods to control for any effects of the vehicle on agonist-stimulated PG release. The recovery period consisted of a 30-min washout of antagonist followed by repeating the agonist stimulation. PAF, BK and AII were tested in each kidney before, during, and after PAF-antagonist; only one antagonist was tested in any kidney. The perfusions were carried out for a total of approximately 6 hr. This period of time has been used previously to study renal PG release by our laboratory and others [4, 8].

Renal cortical and medullary microsomes were prepared from 72-hr HNKs and CLKs as previously described [9] and incubated with 1 μg of [1-^{14}C]AA for 30 min in the presence or absence of the PAF-receptor antagonists or their vehicles. Incubations containing indomethacin (2 μg/ml) or OKY-046 (100 ng/ml) were also examined. Incubation mixtures were acidified and extracted, and PGs were separated by TLC and quantified by liquid scintillation counting [9].

Human platelet-rich plasma (PRP) was prepared as follows. Human blood was collected in 3.8% citrate (1 vol. for 9 vol. of blood). PRP was obtained after centrifugation of blood for 15 min at 1000 rpm (100 *g*). Incubations were carried out with stirring in a Chrono-log aggregometer. PRP (0.4 ml) was incubated in the presence or absence of PAF-receptor antagonists or their vehicles for 2 min prior to the addition of sodium arachidonate (400 ng). After 4 min, the reaction was terminated by adding an excess of cold RIA buffer, and the sample was immediately put on ice. TxB_2 in the sample was measured by specific RIA.

All experiments reported herein were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the NIH.

Statistics. All results are expressed as the means ± SEM of net PGE_2 or TxB_2 release per 5-min period of stimulation. The drug treatment period in each kidney was compared to the pre- and post-drug periods in that same kidney, and the P value was determined for the entire group receiving the same drug treatment. Comparisons were made using one-way analysis of variance or Student's *t*-test. Differences were considered significant at $P < 0.05$.

The following agonists and antagonists were used and were prepared as described. PAF (1-*O*-alkyl-2-acetyl-*sn*-glyceryl-3-phosphorylcholine), prepared from bovine heart lecithin, was obtained from Sigma (St. Louis, MO). An ethanol stock (100 μg/ml) was diluted in Krebs buffer to a concentration of 1 μg/ml. Angiotensin II (AII) and bradykinin (BK) (Sigma) were prepared as 1 mg/ml aqueous stocks and diluted to 1 μg/ml in Krebs buffer.

PAF-receptor antagonists. The doses of the PAF-receptor antagonists studied were chosen based on reported IC_{50} values for inhibition of PAF-stimulated platelet aggregation in platelet-rich plasma. Doses studied represent a doubling of the IC_{50} value for this effect [5–7].

Kadsurenone (supplied by T. Shen, Merck & Co.) 1 mg/ml solution in dimethyl sulfoxide (DMSO), was diluted in Krebs–BSA to a final concentration of 1 μg/ml (3 μM) (vehicle concentration of 0.1%).

CV-3988 (supplied by the Takeda Chemical Corp.), 12.4 mg/ml in saline, was diluted in Krebs–BSA to a final concentration of 12.4 μg/ml (20 μM) (vehicle concentration of 0.1%).

Triazolam (supplied by the Upjohn Corp.) 1.72 mg/ml solution in ethanol, was diluted in Krebs–BSA to a final concentration of 1.72 μg/ml (5 μM) (vehicle concentration of 0.1%).

RESULTS

In these experiments, three different PAF-receptor antagonists were found to have inhibitory actions on PAF-stimulated PG release from the isolated perfused HNK and CLK. In the HNK, each of the antagonists, at the dose studied, diminished PAF-stimulated Tx release. TxB_2 release by the HNK in the pre-drug time period was 52.9 ± 19.8 ng/5 min (stimulated = 57.7 ± 20.3 ng, basal = 4.8 ± 1.4 ng). CV-3988 (20 μM) decreased TxB_2 release to 4.5 ± 0.9 ng (stimulated = 7.7 ± 2.9 ng, basal = 3.2 ± 1.9 ng), representing a 95.0% inhibition (Fig. 1). In the post-drug period, net release of TxB_2 returned to 13.8 ± 7.5 ng (stimulated = 20.6 ± 8.0 ng, basal = 6.8 ± 2.0 ng). Kadsurenone (3 μM) also diminished PAF-stimulated Tx release, as did triazolam (5 μM), by 62.5 and 35.0% respectively (Figs. 2 and 3). PGE_2 release stimulated by PAF in the HNK was also affected by these drugs. CV-3988 inhibited PGE_2 synthesis by 92.0% (Fig. 1). Pre-drug PGE_2 release was 350.2 ± 130.0 ng/5 min (stimulated 401.6 ± 148.6 ng, basal = 51.4 ± 20.0 ng) as compared to 10.4 ± 13.1 ng in the presence of CV-3988 (stimulated 54.4 ± 17.4,

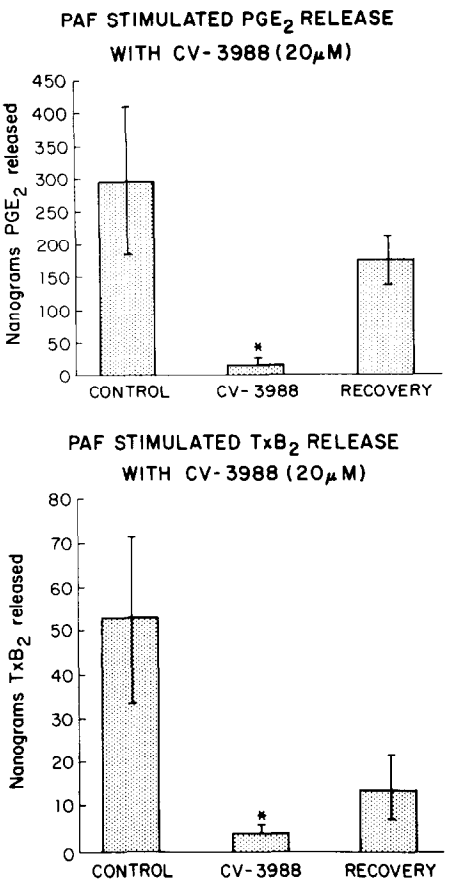

Fig. 1. Effect of CV-3988 on PAF-stimulated PGE_2 and TxB_2 release from the HNK. The top panel shows the release of PGE_2 stimulated by PAF (100 ng) before (control), during (CV-3988), and following (recovery) CV-3988 (20 μM) infusion. Control release represents the stimulated release with only drug vehicle in the buffer. Following the control period, CV-3988 was infused for 15 min, and release stimulated by the agonist (100 ng) was determined in the presence of drug. Recovery represents the agonist-stimulated release (100 ng) following a 30-min washout in which the kidney was perfused with fresh buffer containing only the drug vehicle. The bottom panel shows the release of TxB_2 stimulated by 100 ng PAF from the HNK in the presence and absence of 20 μM CV-3988. Values are means ± SEM (N = 6). Key: * significant reduction from control ($P < 0.05$).

basal = 44.0 ± 14.6) and 210.2 ± 114.3 ng (stimulated 324.0 ± 154.2, basal = 113.8 ± 45.9) in the post-drug period. Kadsurenone decreased PGE_2 release by 28.2% (Fig. 2). Triazolam was unique, in that it significantly inhibited PAF-stimulated TxB_2 release without inhibiting PGE_2 release (Table 1; Fig. 3).

In the CLK, CV-3988 reduced the release of PGE_2 stimulated by 100 ng PAF from 35.6 ± 13.4 ng/5 min to undetectable levels. Recovery to 45.2 ± 26.6 ng/5-min stimulus followed a 30-min washout (Fig. 4).

In addition to their effects on PAF-stimulated PG release, the PAF-receptor antagonists had an effect on peptide-stimulated PG release in the HNK. Both BK- and AII-stimulated TxB_2 release was affected by the receptor antagonists, although to a lesser extent than was PAF-stimulated release. CV-3988 decreased BK- and AII-stimulated TxB_2 release by 64.0 and 70.0% respectively (Table 1). Kadsurenone had a similar action and inhibited BK-stimulated release by 35.0% and AII-stimulated release by 31.9% (Figs. 5 and 6). Triazolam inhibited BK-stimulated TxB_2 release by 12.7%.

PGE_2 release stimulated by BK and AII in the HNK was not affected as greatly by the three antagonists. Kadsurenone and triazolam had no effect on the stimulated release of PGE_2 by these agonists. CV-3988, on the other hand, diminished BK- and AII-stimulated PGE_2 release by 37.0 and 54.1% respectively (Table 1).

Since the PAF-receptor antagonists were shown to affect PG release, and TxB_2 release in particular, the possibility was considered that these drugs might be affecting PG synthetic enzymes. Therefore, the effects of these drugs on PG synthesis from AA were measured directly. The conversion of radiolabeled AA by renal medullary microsomes was examined in the presence of PAF-receptor antagonists and their vehicles. None of these agents affected thromboxane synthesis, whereas both indomethacin and the specific Tx synthesis inhibitor OKY-046 specifically inhibited TxB_2 synthesis (Table 2). PGE_2 and $PGF_{2\alpha}$ synthesis was unaffected by all drugs except indomethacin (data not shown).

To test the effects of these drugs on AA metabolism in whole cells, we used human PRP prepared as described in Materials and Methods. The production of thromboxane from PRP incubated with AA (400 ng) in the presence of kadsurenone, triazolam or CV-3988 at the concentrations used in the perfused kidney was quantified by RIA. Samples to which only saline was added exhibited no detectable levels of TxB_2. In samples to which AA alone was added, the thromboxane concentration was 103.5 ± 30.2 ng/ml. In the presence of kadsurenone

Table 1. Percent inhibition of PGE_2 and TxB_2 release by PAF-receptor antagonists

Agonist	Antagonist	% Inhibition PGE_2	% Inhibition TxB_2
PAF (100 ng)	Kadsurenone (3 μM)	28.2*	62.5*
	Triazolam (5 μM)	0	35.0*
	CV-3988 (20 μM)	92.0*	95.0*
BK (100 ng)	Kadsurenone (3 μM)	0	35.0*
	Triazolam (5 μM)	0	12.7*
	CV-3988 (20 μM)	37.0*	64.0*
AII (100 ng)	Kadsurenone (3 μM)	0	31.9*
	Triazolam (5 μM)	0*	ND†
	CV-3988 (20 μM)	54.1*	70.0*

Krebs-perfused HNKs were stimulated with a bolus injection of each agonist prior to and following a 15-min period in which antagonists were added to the perfusion medium. PG release was measured by RIA (N = 6) for each agonist and antagonist, and the percent inhibition was calculated. See figures for control values.

* $P < 0.05$.

† Not determined.

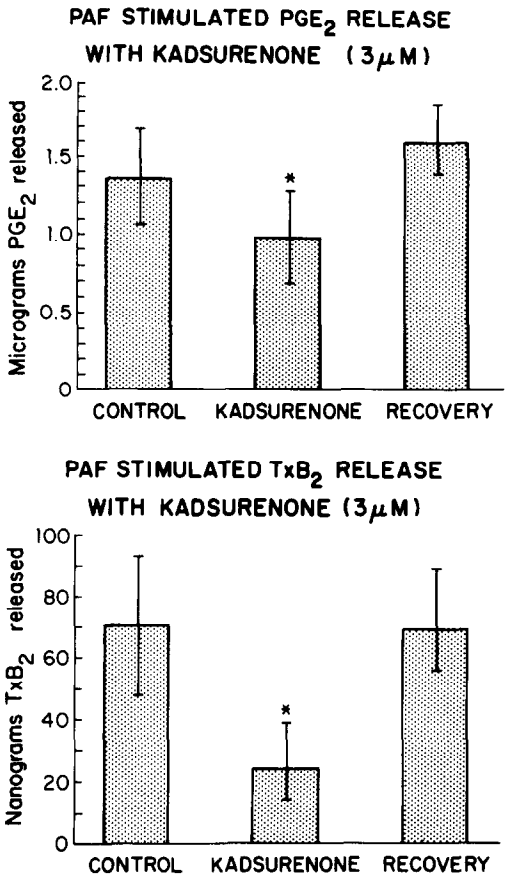

Fig. 2. Effect of kadsurenone on PAF-stimulated PGE_2 and TxB_2 release from the HNK. The same procedure was used as for Fig. 1 except that kadsurenone (3 μM) was studied. Values are means ± SEM (N = 6). Key: * significant reduction from control ($P < 0.05$).

Table 2. Thromboxane production by renal medullary microsomes in the presence of PAF-receptor antagonists

	TxB_2 produced from 1 μg AA (ng/mg protein)
Control	72.25 ± 11.1
OKY-046, 100 nM	9.9 ± 6.4*
Indomethacin, 2 μg/ml	1.8 ± 0.5*
Kadsurenone, 3 μM	67.2 ± 17.5
Kadsurenone vehicle	72.2 ± 9.8
CV-3988, 20 μM	70.0 ± 14.1
CV-3988 vehicle	72.9 ± 21.3
Triazolam, 10 μM	77.0 ± 6.0
Triazolam vehicle	81.7 ± 18.4

Medullary microsomal preparations were prepared from 72-hr obstructed kidneys as described in Materials and Methods. The conversion of [^{14}C]AA (1 μg) by the microsomal preparation following a 30-min incubation at 37° was compared in the presence and absence of PAF-receptor antagonists and their vehicles. In samples in which inhibitors were added, these drugs were preincubated with the microsomes prior to addition of ^{14}C-labeled AA. Products were extracted from the incubation mixture and separated on TLC as described. Results are expressed as ng TxB_2 produced per mg protein per 30-min incubation.

* $P < 0.05$, compared to control.

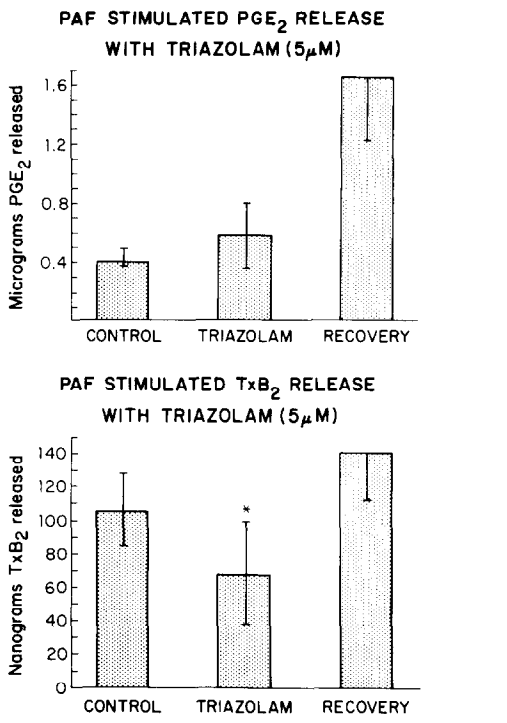

Fig. 3. Effect of triazolam on PAF-stimulated PGE_2 and TxB_2 release from the HNK. The same methods as described in the legend of Fig. 1 were used with the exception that Triazolam (5 μM) was examined. Values are means ± SEM (N = 6). Key: * significant reduction from control ($P < 0.05$).

(3 μM), CV-3988 (20 μM), and triazolam (5 μM). TxB_2 concentrations were 115.5 ± 42.3, 129.0 ± 31.9, and 143.3 ± 68.1 ng/ml respectively. These concentrations did not differ significantly from the vehicle controls which produced 144 ± 51.2 (DMSO), 99.0 ± 36.1 (saline), and 132.6 ± 21.5 ng/ml (ethanol) (N = 6).

Results of experiments in the CLK, which was perfused concurrently with the HNK, further demonstrated the specificity of the PAF-receptor antagonists. In the CLK, neither AII- nor BK-stimulated PGE_2 was affected by CV-3988 or triazolam in the same concentrations as were effective in the HNK (Fig. 4). For example, BK-stimulated PGE_2 release was 24.3 ± 9.0 ng/5-min stimulus during the control period. During the drug and recovery periods, PGE_2 release was 41.85 ± 16.5 and 81.92 ± 32.3 ng/5-min stimulus, respectively, demonstrating no inhibition of PGE_2 release by CV-3988. The slight increase in PGE_2 release with perfusion time has been noted previously [4]. The pattern was identical for AII-stimulated PGE_2 release (data not shown).

DISCUSSION

A myriad of interactions exists between the renin-angiotensin, prostaglandin, and kinin systems in the kidney [10]. In UUO, stimulation of the HNK by the effector molecules of the renin-angiotensin (AII)

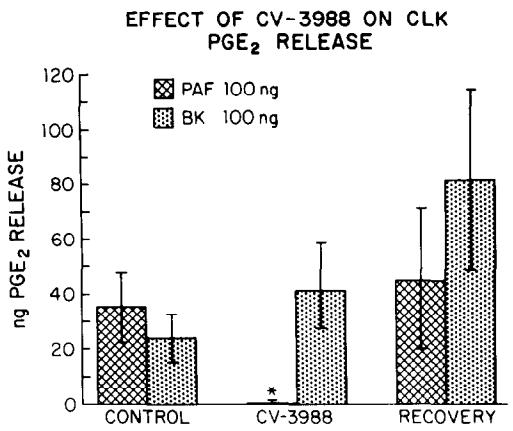

Fig. 4. Effect on CV-3988 on agonist-stimulated PG release from the CLK. CV-3988 at the same concentration (20 μM) as was studied in the HNK was examined in the CLK to determine its effect on agonist (100 ng) stimulated PGE_2 release. The same methods as were described for the HNK were employed for the CLK. Values are means ± SEM (N = 4). Key: * significant reduction from control ($P < 0.05$).

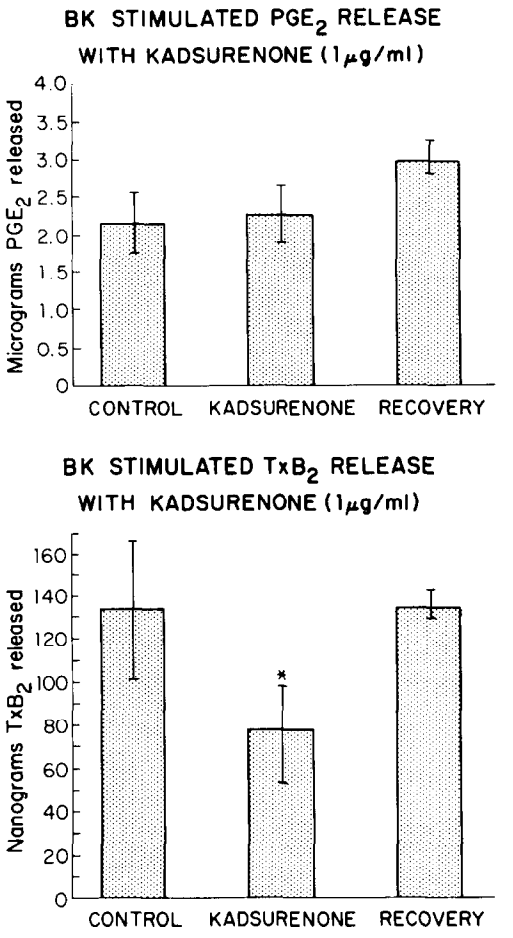

Fig. 5. Effect of kadsurenone on BK-stimulated PGE_2 and TxB_2 release from the HNK. Values are means ± SEM (N = 6). Key: * significant reduction from control ($P < 0.05$).

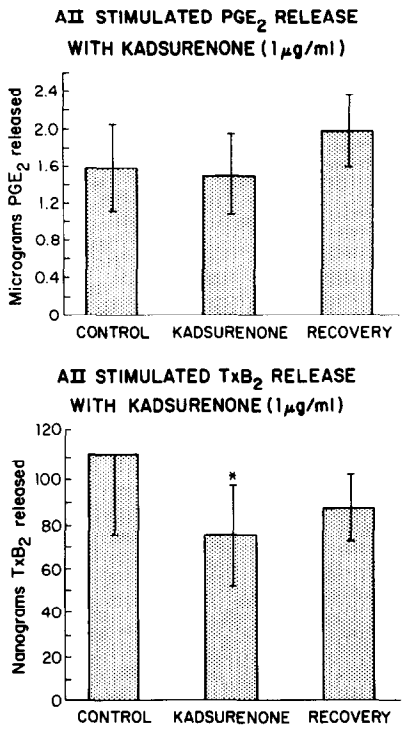

Fig. 6. Effect of kadsurenone on AII-stimulated PGE_2 and TxB_2 release from the HNK. Values are means ± SEM (N = 6). Key: * significant reduction from control ($P < 0.05$).

and kinin systems (BK) results in an exaggerated PG release. In addition, we have shown previously that PAF, which may also be released intrarenally, is a potent stimulus for renal PG release [4]. In these previous studies, it was found that intrarenal administration of PAF causes a stimulation of the release of PGE_2, TxB_2, $PGF_{2\alpha}$, and the PGI_2 metabolite, 6-keto-$PGF_{1\alpha}$ from the HNK and CLK. The HNK was found to release significantly more of all the compounds assayed than the CLK. This response is specific for PAF as neither vehicle nor the biologically inactive, structurally similar, lyso-PAF caused release of renal PGs. In addition, the release of $PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$ exhibits tachyphylaxis to a second PAF stimulus [4]. This observation of desensitization to PAF along with the finding of a structural requirement for PG release at position two of the PAF molecule suggested a specific receptor interaction. The finding, presented in this paper, that three structurally distinct PAF-receptor antagonists significantly inhibited PAF-stimulated PG release from the HNK is further evidence in support of this release being receptor mediated. Of particular interest is our finding that these drugs, at the doses administered, had a greater effect on Tx release than on PGE_2 release stimulated by PAF, suggesting the possibility of a differential site for PGE_2 and Tx synthesis within the HNK. These sites may include infiltrating mononuclear cells which have been found in the HNK cortex [11]. This finding is consistent with our previous observation of differential agonist-stimulated PGE_2 and TxB_2 release. Thus, by using

both agonists and antagonists, it is possible to dissociate TxB_2 and PGE_2 release. This may indicate the existence of differential sites of synthesis or coupling or receptors to synthetic enzymes which may differ in their accessibility to both the agonists and antagonists. The possibility also exists that these agents may alter the activity of thromboxane synthetase in addition to their PAF-antagonistic properties, thus preferentially inhibiting Tx release. However, our studies on the effect of these PAF-receptor antagonists on whole and broken cell preparations confirm that these drugs have no significant inhibitory action on PGE_2 or TxB_2 synthesis in these systems and suggest that the preferential effect of PAF-receptor antagonists to inhibit Tx release from the HNK would reflect their interaction with the PAF receptor and not with the enzymes of AA metabolism.

Kadsurenone, triazolam, and CV-3988 significantly altered AII- and BK-stimulated TxB_2 release in the HNK; since this inhibition is similar to that observed when PAF is the stimulus, the data suggest that interaction with the PAF receptor is important in this inhibition. It is possible that these peptides may stimulate the synthesis of PAF by activation of specific phospholipases. This possibility is supported by the fact that the glomeruli and renomedullary interstitial cells both have BK and AII receptors [12], and both have been shown to synthesize PAF in response to phospholipase activation by calcium ionophore [13]. Camussi *et al.* [14] have shown that human endothelial cells in culture release PAF following non-immunological stimuli such as AII and vasopressin in addition to ionophore. Prescott [15] has further demonstrated that thrombin, histamine and bradykinin can stimulate PAF synthesis by these cells.

While the hypothesis that the peptide hormones stimulate PAF production is attractive, it is conceivable that blockade of peptide-stimulated PG release by PAF antagonists represents non-specific effects of these drugs. For example, Nunez *et al.* [16] showed that in washed platelets, but not in platelet-rich plasma, CV-3988 inhibits both PAF- and AA-induced platelet aggregation. However, we were unable to show an effect of CV-3988 on AA metabolism in either platelet-rich plasma or microsomes. Furthermore, results of studies in the CLK demonstrated that only PAF-stimulated PGE_2 release was inhibited by PAF-receptor antagonists; peptide-stimulated PGE_2 release was not diminished significantly. This suggests that the inhibition of PG release in the HNK is not a non-specific effect of these drugs. Since both kidneys are treated identically and studied concurrently, it appears that there are biochemical differences in the CLK in response to AII or BK stimulation which may underlie the biochemical and physiological differences between these kidneys. Since differences in PAF release may be of importance, measurement of PAF release from these kidneys should be undertaken. However, the absence of PAF release into the effluent of the isolated perfused kidney would not invalidate the possibility that PAF is synthesized in response to peptide stimulation since many cell types, when stimulated to synthesize PAF, fail to release the PAF formed and maintain it intracellularly [15]. It is conceivable that PAF produced intracellularly is capable of associating with the cell membrane and activating phospholipases which result in the elaboration of PGs into the effluent.

The data presented herein are supportive of our previous findings which suggested that PAF, through a receptor-mediated process, stimulates the release of PGs from the kidney. Furthermore, the fact that the three PAF-receptor antagonists studied had a greater effect on Tx release than on PGE_2 release from the HNK is consistent with our hypothesis that PAF preferentially stimulates Tx release. The finding that triazolam can inhibit PAF-stimulated Tx synthesis without affecting PGE_2 release is significant in that it suggests that such antagonists can be used to preferentially dissect out the possible effects of PAF-stimulated Tx release and should prove valuable in better understanding whether different sites or receptors exist for stimulating PGE_2 and TxB_2 release and the role of AA metabolites in PAF bioactivity. These findings are supportive of the possibility that PAF-receptor antagonists affect stimulated Tx synthesis by a mechanism independent of inhibition of Tx synthetase.

The potent hemodynamic effects and the preferential stimulation of Tx release in the HNK suggest that the interaction of PAF and Tx may be important in the pathophysiologic response of UUO.

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