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Effect of Intrarenal Infusion of Synthetic PAF-Acether in Dogs

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The effect of intrarenal infusion of PAF-acether was studied in dogs. PAF-acether infusions caused a dose-dependent decrease in glomerular filtration rate, renal blood flow and urinary flow and electrolyte excretion, without significant changes in mean arterial pressures. In addition, the higher doses used caused also increases in packed cell volume, and decreases in plasma proteins and leukocyte and platelet count, whereas the lower doses did not elicit those changes. These data suggest that PAF-acether causes an impairment in renal function which is in part mediated by vasoactive substances released from platelets and leukocytes.

Key words: PAF-acether, Renal blood flow, Glomerular filtration rate, Blood cell activation.

When initially described, PAF-acether was conceived as a mediator involved in inflammatory, immunologically-mediated reactions (3, 16). Later, a wider spectrum of actions has been defined, exceeding the functions originally proposed (17). At present, PAF-acether has been identified in different biological fluids, i.e. urine (20), saliva (5), amniotic fluid (10) and blood (8). Neutrophils (9), monocytes (9) and renal medullary interstitial cells (11) have been found to be capable of synthesizing and releasing PAF-acether. PAF-acether has also been recovered from the effluent of isolated kidneys perfused with ionophore (18). Recently, a significant role has been suggested for PAF-acether in shock (4), and potentially deleterious action on coronary circulation and myocardial function has been demonstrated (16, 20). In this case, the significance of PAF-acether as a compound mediating the liberation of vasoactive mediators (thromboxane A_2, leukotrienes) has been raised (12, 14). When PAF-acether is administered by intravenous (i.v.) route, it elicits a potent hypotensive response, with a fall in peripheral resistances and a reduction in cardiac output, both by altered myocardial performance and fall of

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circulating volume due to massive vasopermeability (4, 19).

The purpose of this paper was to study the effect of different doses of PAF-acether on the renal function of anesthetized dogs by direct infusion in the renal artery.

Materials and Methods

Nine male mongrel dogs, weighing between 25 and 35 kg were studied. Under pentobarbital anesthesia (40 mg/kg i.v.) and with artificial ventilation (Howard respirator), right femoral, brachial and renal (via spermatic vein) veins were cannulated.

A catheter connected to a pressure transducer (Grass) was introduced into the femoral artery. The left renal artery and the two ureters were exposed by a mid-abdominal incision. A magnetic flow probe (Nycotron) was placed around the left renal artery and a right-angle curved needle (23 gauge) was introduced into the same artery. Both urethers were also cannulated. Initially, 200 ml of 0.9 % saline were injected by the brachial vein for reposition of surgical losses, and a 250 ml/h infusion was maintained during all the experiment, to assure fluid replenishment. After completion of the surgical procedure, inulin (50 mg/kg i.v.) was infused in 10 min., and then a solution of 0,84 mg inulin/kg^{-1} min^{-1} in saline was continuously administered by the femoral vein. Graphical registration of arterial pressure and renal blood flow were obtained throughout the experiment. Animals were allowed to stabilize during one hour and after this time, a basal 20 min period was initiated with separated left and right ureter urine collection; blood samples were obtained from femoral artery and renal vein, in chilled glass tubes with sodium EDTA, at the end of the period. Then, PAF-acether infusion was started by the left renal artery to achieve an intrarenal concentration of about 10^{-8}M, with urine collection. After 20 min blood samples were obtained as in basal period.

The same procedure was repeated with PAF-acether concentrations of 10^{-7}, 10^{-6} and 10^{-5}M.

In blood from the femoral artery, packed cell volume, leukocyte and platelet count (Coulter) and Na, K, Cl and creatinine were measured (ASTRA 4 autoanalyzer). Na, K, Cl and creatinine were also measured in each urine sample. Data were analyzed statistically by the paired Student t test, considering $p < 0.05$ as significant.

Results

Data of basal values of separate renal function are shown in table I. No significant differences between left and right kidneys were observed.

Figure 1 shows the percent changes in mean arterial pressure and left renal blood flow with the different doses of PAF-

Table I. *Basal values of renal function.*

	Left kidney	Right kidney
GFR (ml/min)	16.7 ± 3.5	18.8 ± 3.2
RBF (ml/min)	98 ± 20	109 ± 20
FF (%)	17 ± 2	17 ± 2
U.V. (ml/min)	0.69 ± 0.1	0.97 ± 0.12
U_{Na} V (μEq/min)	76 ± 7	85 ± 7
U_K V (μEq/min)	42 ± 4	46 ± 4
U_{Cl} V (μEq/min)	69 ± 7	77 ± 7

Abbreviations: GRF: Glomerular filtration rate; RBF: Renal blood flow; FF: filtration fraction; U.V.: urine flow; U_{Na} V: urinary sodium excretion; U_K V: urinary potassium excretion; U_{Cl} V: urinary chloride excretion.

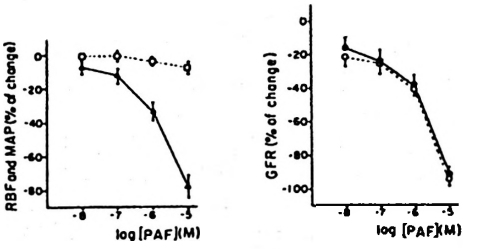

Fig. 1. *Changes in renal Blood Flow (RBF, ▲), Mean Arterial Pressure (MAP, □), Glomerular Filtration Rate (GFR, ○), in the infused and contralateral (●) kidneys, during the intrarenal infusion of platelet activating factor (PAF).* Data are mean ± S.E.M.

acether. It can be observed that mean arterial pressure did not change with the lower doses whereas it decreased slightly with the higher doses. RBF shows a dose-dependent response, with small decreases at lower dose and about an 80 % decrease with the higher dose. GFR shows a behaviour similar to that of RBF, without significant differences in either kidney. PAF-acether induced a decrease in filtration fraction for each dose assayed.

The percent changes in urinary electrolyte excretion, also show a dose-dependent response, which is similar to that of GFR (fig. 2).

No changes in packed cell volume, plasma protein or cell count were observed with the lower doses of PAF-acether, whereas with the higher doses, leukocyte and platelet count and plasma protein concentration decreased, increasing packed cell volume (table II).

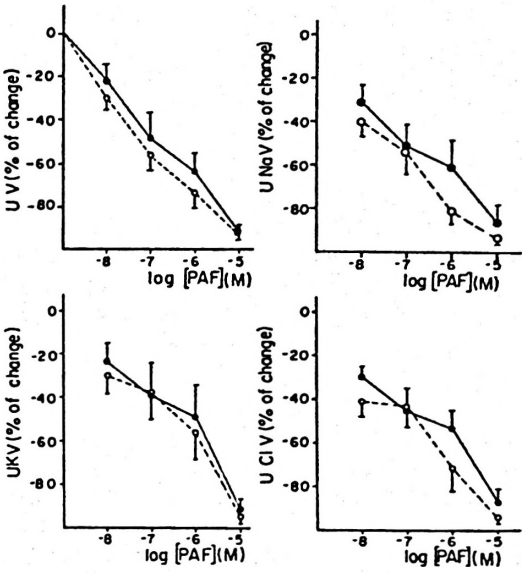

Fig. 2. *Changes in Urinary Flow (UV), urinary sodium excretion (UNaV), urinary potassium excretion (UKV), and urinary chloride excretion (UClV) in the infused and contralateral (●) kidneys during the intrarenal infusion of PAF.* Data are mean ± S.E.M.

Discussion

In the present study two different situations can be identified. First, with the lower PAF-acether doses neither systemic circulatory changes nor changes in platelets or leukocyte concentrations could be detected. Second, with the two higher doses, platelet and leukocytes fell significantly, and this was accompanied by

Table II. *Changes in blood cell count and plasma proteins with different doses of PAF (M).* Significant differences ($p < 0.05$) vs basal values. Results are expressed as mean SEM.

	Basal	10^{-8}	10^{-7}	10^{-6}	10^{-5}
Packed cell volume (%)	42.44 ± 3.9	40.08 ± 3.4	46.12 ± 2.83	46.79 ± 4.13	57.03 ± 6.1*
Leukocytes (µl-l)	7317 ± 1056	8180 ± 1402	7760 ± 1464	5133 ± 1144*	3500 ± 451*
Platelets (x 10^3 μl^{-1})	159.7 ± 31.24	172.6 ± 40.68	163.0 ± 36.6	68.66 ± 12.2*	59.8 ± 14.9*
Plasma (g · 100 ml)	4.83 ± 0.24	4.81 ± 0.18	4.66 ± 0.16	4.25 ± 0.19*	4.02 ± 0.31

changes in PCV and plasma proteins, suggesting increased vascular permeability and fluid extravasation, both effects already described for PAF-acether.

Regarding renal function, the parallel decrease in GFR and RPF observed with the two lower doses could be caused by the effect of PAF-acether per se on renal structures, whereas the almost complete abolition of glomerular filtration observed with the higher doses seems also to be caused by the intravascular volume contraction caused by fluid extravasation, as well as by the vasoactive substances released by platelets and leukocytes in response to PAF-acether (3, 13, 15, 17).

The fact that contralateral kidney also shows the effect of PAF-acether could be explained in several ways. First, a variable amount of PAF-acether injected into the renal artery could reach the contralateral kidney, avoiding the action of renal and plasma acetyl hydrolases in the first circulatory pass (6, 7). However, if this were the only cause, the effect in the contralateral kidney would presumably be less intense than in the infused kidney, which is not the case. The other possibility is that the effect of PAF-acether in the contralateral kidney is mediated by vasoactive mediators released from platelets and PMN, and perhaps other tissues. However, the exact mechanism of the effect of PAF on the contralateral kidney cannot be deduced from this study.

The mechanism by which PAF-acether directly causes severe reduction of RPF and GFR seems to be multifactorial: PAF-acether is able to constrict vascular smooth muscle (15), thus increasing renal vascular resistance; and PAF-acether can induce mesangial cell contraction (1, 2, 21) which can also decrease RPF and the ultrafiltration coefficient (Kf) and thus further reduce GFR. This can be supported by the reduction in the observed filtration fraction.

In conclusion, from the above results it may be deduced that PAF-acether can reduce severely the renal function. Thus, this substance could be considered as a potential important mediator of the renal failure accompanying shock, sepsis and other pathological situations which occur with activation of inflammatory pathways. However, the exact mechanisms of the renal action of PAF-acether should be defined in further studies.

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Resumen

Se estudia el efecto de la infusión intrarrenal del factor activador de las plaquetas (PAF) entre 10^{-8} y 10^{-6} mol/l, en la función renal en perros. La infusión de PAF induce una disminución de la tasa de filtración glomerular y del flujo sanguíneo renal, dependiente de la dosis, y que no se basa en una disminución de la presión arterial. Sólo las dosis más elevadas producen aumento en el volumen hematocrito y disminución en la concentración plasmática de proteínas, así como en el número de plaquetas y leucocitos. Los datos sugieren que la infusión de PAF induce una disminución de la función renal, que parece ser mediada, en parte, por substancias vasoactivas liberadas por plaquetas y leucocitos.

Palabras clave: PAF-aceter, Flujo sanguíneo renal, Tasa de filtración glomerular, Activador de plaquetas.

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