

INCREASED CIRCULATING 6-OXO-PGF_{1α} DURING ANGIOTENSIN II INFUSION IN MAN. K. Silberbauer and H. Sinzinger, 2nd Dept. Internal Medicine, University of Vienna, Austria.

Angiotensin II(A II) is able to stimulate phospholipase A₂. This enzyme initiates the arachidonic acid cascade. Previously we have shown that AII enhances the PGI₂ release from rat aortic rings and rat kidneys.

We, therefore, wondered if AII infusion in man might influence the plasma concentrations of 6-OXO-PGF_{1α} (RIA in unextracted plasma), the stable metabolite derived by non-enzymatic conversion from PGI₂. Fourteen patients with normal blood pressure, who were tested to assess left ventricular function by radionuclide angiography, received AII (2-1,5 μg/min for 15 minutes i.v.). During the rise of blood pressure (\bar{x} :125/80mmHg to 157/102mmHg) 6-OXO-PGF_{1α} increased significantly (2p<0.01). Fifteen minutes after AII termination the blood pressure returned to prevalues(\bar{x} :125/82mmHg) and 6-OXO-PGF_{1α} dropped. In one patient saralasin, a competitive inhibitor of AII, had no direct effect on 6-OXO-PGF_{1α} (0.1 μg, 1 μg and 10 μg saralasin/kg b.w./min, each dosage was infused for 15 minutes).

The released vasodilator PGI₂, as measured by 6-OXO-PGF_{1α} generated in the vessel wall and in the kidney, might antagonize the vasoconstriction caused by AII.

LOW AFFINITY PLATELET FACTOR 4/β-THROMBOGLOBULIN (LA-PF₄/βTG) ANTIGEN AND CIRCULATING PLATELET AGGREGATES DURING PROSTACYCLIN (PGI₂) THERAPY. J. Musiał, A. Szczeklik and R. Nizankowski. Department of Internal Medicine, Copernicus Academy of Medicine, Cracow, Poland.

We have found that continuous intraarterial infusion of PGI₂ alleviates rest pain and promotes healing of ischemic ulcers in patients with advanced arteriosclerosis obliterans. Since these effects could be related to the anti-platelet actions of prostacyclin, we studied serum levels of the platelet specific protein, a possible marker of platelet activation in vivo, named LA-PF₄/βTG, and compared it with those of serum circulating platelet aggregates. The former was assessed by radioimmunoassay, the latter by method of Wu and Hoak. Determinations were carried out in 16 patients with arteriosclerosis obliterans, initially and during the second day of intra-arterial infusion of PGI₂ in a mean dose of 6 ng/kg/min. This therapy led to an almost uniform fall in circulating platelet aggregates. In contrast, levels of LA-PF₄/β-TG antigen at the beginning of second day of the infusion /mean = 19.19 ng/ml, + S.D. = 8.97/ did not differ significantly from the initial values /mean = 23.59 ng/ml, + S.D. = 13.12/.

In conclusion: 1/ In our patients vascular disease did not produce any apparent increase in serum LA-PF₄/β-TG antigen levels; 2/ Infusions of PGI₂ did not affect basal levels of this platelet specific protein, while it markedly depressed the percent of circulating platelet aggregates.

INTERACTION BETWEEN HUMAN BLOOD PLATELETS AND POLYMORPHONUCLEAR LEUKOCYTES IN THE METABOLISM OF ARACHIDONIC ACID. J.J. Killackey, B.A. Killackey and R.B. Philp. Department of Pharmacology, University of Western Ontario, London, Ontario, Canada.

In a study of human polymorphonuclear leukocyte (PMN) prostaglandin (PG) biosynthesis from exogenous ¹⁴C-arachidonic acid (¹⁴C-AA), we found that combinations of platelets and PMN produced different TLC profiles of AA metabolites than either pure platelets or relatively pure PMN alone. Cells were separated from citrated whole blood by ficoll-sodium diatrizoate density gradient centrifugation. Washed platelets were prepared from citrated platelet-rich plasma. Cells were incubated with 30 μM ¹⁴C-AA for 15 m at 37°C in phosphate buffered saline with or without 2-10 mg/ml serum-treated zymosan (STZ). AA metabolites were extracted and measured by radio-thin layer chromatography compared to known standards. Under these conditions, washed platelets (1-5x10⁷) produced peaks of radio-activity corresponding to, in decreasing order, PGE₂, PGD₂ and thromboxane B₂ (TXB₂). 10 mg/ml STZ reduced the PGE₂ peak by 60%, inhibited the PGD₂ peak but did not alter the TXB₂ peak. Indomethacin (20 μM) inhibited all peaks under all conditions. Relatively pure PMN (1-5x10⁷) containing platelets in a ratio of 1:10 PMN metabolized small amounts of AA but this increased dramatically upon the addition of STZ. Although peaks of activity corresponded to TXB₂ and PGD₂ they were not inhibited by ASA (500 μM) or indomethacin (50 μM) but were inhibited by 5 μg/ml nordihydroguaiaretic acid. This suggests that they are lipoxygenase products. PMN samples containing platelets in a ratio of 1:3 PMN produced maximum activity corresponding to TXB₂ and this, in contrast to platelets or PMN alone was augmented upon addition of 10 mg/ml STZ. This increase was inhibitable with cyclooxygenase inhibitors. These results suggest that platelets and PMN interact in the presence of STZ and AA and this interaction may play a role in inflammation.

INHIBITION OF PLATELET AGGREGATION, MALONYLDIALDEHYDE AND THROMBOXANE FORMATION BY HYDROPEROXIDES OF ARACHIDONIC ACID. D. Aharony, J.B. Smith and M.J. Silver. Cardeza Foundation and Department of Pharmacology. Thomas Jefferson University, Philadelphia, PA 19107 U.S.A.

The arachidonate hydroperoxides 12-HPETE and 15-HPETE were biosynthesized from arachidonic acid using partially purified human platelet lipoxygenase or soybean lipoxygenase respectively, and isolated by thin layer chromatography. Both compounds inhibited the arachidonic acid-induced aggregation of washed human platelets, suspended in calcium-free Krebs Henseleit solution, in a dose dependent fashion at concentrations between 1 and 50 μM. No inhibition was seen with up to 100 μM of these hydroperoxides when platelet-rich plasma was used. 12-HPETE (in micromolar concentrations) inhibited the formation of both thromboxane B₂ (radioimmunoassay) and malonyldialdehyde (spectrophotometric assay) when washed platelets were incubated with arachidonic acid. The 12-hydroxide, 12-HETE also inhibited platelet aggregation and thromboxane formation, but was less potent than 12-HPETE. We suggest that arachidonate hydroperoxide generated in platelets via the lipoxygenase pathway modulates platelet aggregation induced by arachidonic acid by inhibiting thromboxane formation.