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NIACIN-INDUCED PROSTACYCLIN (PGI_2) GENERATION AND THE SEARCH FOR THE IDEAL DOSE OF ASPIRIN. J. A. Jakubowski and D. Deykin. Boston VA Medical Center and Boston University School of Medicine, Boston, MA, U.S.A.

We have previously reported that chronic administration of 80 mg/day of enteric-coated aspirin (ECA) in three divided doses of 27 mg each day for 7 days produced over 90% inhibition of platelet thromboxane production. What we wanted to know was whether that dose of aspirin spared PGI_2 production. We developed a sensitive plasma assay for PGI_2 (measured as 6-keto-PGF_{1a}). We confirmed the reports of others that normal plasma levels are very low, less than 2 pg/ml. We selected niacin as a provocative challenge to raise plasma levels of PGI_2 to test the ability of a given aspirin regimen to spare or suppress PGI_2 production in vivo. In 5 normal subjects an oral dose of 3 mg/kg of niacin produced a 3-fold rise in 6-keto-PGF_{1a} from 0.86 to 2.64 pg/ml. A dose of 5 mg/kg produced a rise to 6.6 pg/ml. Administration of 325 mg of regular aspirin/day for 7 days completely abolished niacin-induced elevation of plasma PGI_2. The lowest dose of ECA that we have found effective in suppressing platelet thromboxane production in vitro, 80 mg/day in divided doses of 27 mg three times a day for 7 days, also completely suppressed niacin-induced elevation of PGI_2. Our data do not support the hyypothesis that a very low dose of ECA selectively suppress platelet thromboxane production but spares generation of PGI_2.

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PROSTACYCLIN AND THROMBOXANE A_2 GENERATION IN VIVO IN MAN - EFFECT OF LOW DOSE ASPIRIN. P.A. Kyrle (1), H.G. Eichler (2), K. Lechner (1). Division of Hematology and Blood Coagulation (1) and Division of Clinical Pharmacology (2), I.Department of Medicine, Vienna, Austria.

The effect of a low-dose aspirin regimen on platelet and vascular prostaglandin metabolism was studied in vivo in man. In a double-blind placebo-controlled cross-over study, 7 healthy male volunteers were treated with aspirin (35 $mg.day^{-1}$) or placebo for 7 days. After a washout period of 2 weeks, the subject were crossed to the alternate treatment. 12 hours after the last dose of aspirin or placebo formation of thromboxane A_2 (TxA_2) and prostacyclin (PGI_2) was measured in blood emerging from a standardized injury of the microvasculature made to determine bleeding time. TxA_2 and PGI_2 were measured as their stable degradation products, thromboxane B_2 (TxB_2) and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$), using radioimmunoassay procedures. When subjects were treated with placebo, there was a rapid and substantial generation of both TxA_2 and PGI_2 at the site of platelet-vessel wall interaction. This was reflected by an increase of TxB_2 from 2.8±1 ng/ml and of 6-keto-$PGF_{1\alpha}$ from 38.6±14.6pg/ml in the first minute to 4.5±0.6 ng/ml TxB_2 and 154±50 pg/ml 6-keto-$PGF_{1\alpha}$ after 4 minutes. Low-dose aspirin caused a significant inhibition of both TxA_2 and PGI_2 generation in bleeding time blood as represented by 65-92% and 81-84% inhibition of TxB_2 and 6-keto-$PGF_{1\alpha}$, respectively throughout the 4 minute study period. We conclude that (a) rapid activation of both platelet prostaglandin metabolism and vascular PGI_2 biosynthesis occurs at the site of platelet-vessel wall interaction and (b) low-dose aspirin results in a significant inhibition of platelet and vascular cyclo-oxygenase activity. Thus, our data fail to confirm the concept of a differential effect of low-dose aspirin on platelet and vascular prostaglandin synthesis in vivo in man.

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1-^{14}C-ARACHIDONIC ACID INCORPORATION INTO THE LIPIDS OF RAT AORTA.EFFECT OF EXHAUSTION ON PGI2 PRODUCTION. V.Martinez-Sales, J.Valles, M.T.Santos and J.Aznar. Research Center. Hospital "La Fé". Valencia. Spain.

Prostacyclin (PGI2) production in rat aortic rings incubated in Tris-buffer decreases with time.It has been shown that this decrease is not dependent on the total arachidonate concentration in the arterial lipids, and it has been suggested that it may be due to a partial enzymatic inactivation of cyclooxygenase and / or PGI2-synthethase. However, there is a possibility that although the total 1-^{14}C-arachidonate (AA*) incorporation increases with exhaustion, this incorporation into the different lipid fractions may be different before and after the exhaustion process.In this study we evaluate this possibility by assessing the incorporation of AA* into rat aorta lipids in control samples and after 180 min exhaustion in 10mM Tris-buffer saline pH=7.4 or human plasma. In addition 6-keto-PGF1 (6K) formation from endogenous AA was also evaluated in the above mentioned experimental conditions by RIA. The results show that this 6K production is drastically reduced by the exhaustion in Tris-buffer (91%) and to a lower extent in arteries exhausted in plasma (52%). With regard to AA* incorporation into the total lipid fractions, it was found that in control arteries 67% was incorporated in phospholipids (PL),19% in triglycerides (TG) and 4.2% in esterified cholesterol. The AA* incorporation into the different PL was: 31% in phosphatidyl-choline (PC), 28% in P-ethanolamine (PE), 25% in P-serine+P-inositol, 8% sphingomyeline and 6% lisolecitine.When the arteries are exhausted in Tris-buffer the AA* incorporation decreases in TG and increases in total PL when compared to control samples. Additionally, a very significant increase of AA* in PE and a decrease in PC were found. In plasma-exhausted samples the AA* incorporation into the arterial lipids shows the same trend as in Tris-buffer exhausted samples, although these differences were lower in the former when compared to the control. When rat aortic rings are exhausted in Tris-buffer there is a remarkable reduction in PGI2 production and an alteration in the AA* incorporation into the arterial lipids.Plasma has a protective effect on rat aorta during the exhaustion process.

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INFLUENCE OF GLUCOSE AND INSULIN OF PROSTACYCLIN SYNTHESIS IN CULTURED TROPHOBLAST CELLS. I.Rákóczi, Gy. Gerő, J.Demeter and I. Gáti. Department of Obstetrics and Gynecology, Postgraduate Medical University, Budapest, Hungary.

It is known that placental cells can produce prostacyclin /PGI_2/. At present, the physiological role of trophoblast PGI_2 production can only be speculative. PGI_2 produced by trophoblast may help to prevent the platelet aggregation and thrombosis in spiral arteries and it can also explain the maintance of, and blood flow through, the spiral arteries during endovascular trophoblast invasion in early pregnancy. It has been previously shown that increased glucose concentrations in the incubation fluid can inhibit the formation of PGI_2 by rat aortic rings. The aim of present investigation was to study the effect of glucose and insulin on the generation of PGI_2 by trophoblast obtained from early pregnancy. Trophoblast tissue was obtained immediately from surgical termination of first trimester pregnancy /9 specimens/. Trophoblast was cultured using the method of Jogee et al. Cells obtained from trypsinization were cultured at a density of $2x10^5$ cells/ml in medium 199 containing 10% horse serum. Glucose /5.5, 16.5 and 33mmol/l / and insulin /10^3, 10^4 and 10^6mU/l / were added to culture and the effect on 6-oxo-PGF_2 production over a 24hr incubation was assessed. Control cultures were incubated without glucose and insulin. The concentration of 6-oxo-PGF_2 in culture supernatans were measured by specific radioimmunoassay /^{3}H-6-oxo-PGF_1 , RIA-kit, New England Nuclear, USA /.There was a significant decrease in 6-keto-$PGF_{1\alpha}$ production by trophoblast cells incubated with increased glucose concentrations /16.5 and 33 mmol/l / compared to controls / $p<0.001$/. In contrast, insulin in growth medium did not have any effects on the PGI_2 production. These data suggest that high concentrations of glucose inhibit PGI_2 production by cultured trophoblast cells. This decreased PGI_2 synthesis may impair the blood supply of trophoblast which could play a role in the development of congenital anomalies in pregnant women with poorly controlled diabetes mellitus in the first trimester of pregnancy.