Thursday, July 16, 1981

Poster Presentations

Prostaglandins – I

11:00–12:30 h

Kenora Room Boards 113–123

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THE CYCLIC-AMP-LOWERING EFFECT OF PGE2 AND OF THE PGH2 ANALOG, U46619. B. Martin and C. Bonne. Centre de Recherche sur les Maladies de la Rétine INSERM FRA N°45, Paris.

We have recently reported that PGE2 counteracted the anti-aggregating action of PGE1 and of other PG by inhibiting the adenylate cyclase system. But this effect is not due to the interference with anti-aggregating PG receptors. In this study, the mechanism of action of the c AMP-lowering effect of PGE2 has been further investigated.

Suspensions of aspirin-washed human platelets were incubated for 1 min at 37°C in the presence of papaverine (0.5mM) with PGE1, PGE2, U46619, a chemical analog of PGH2, 13-azaprostanoic acid, a specific antagonist of TxA2, either alone or in various associations. The c AMP concentration was determined by protein binding assays in platelet extracts. PGE2 (150nM) and U46619 (1μM) inhibited the rise in c AMP induced by PGE1 (30nM). On the other hand, when 13-azaprostanoic acid (50μM) was added to the incubate, the inhibitory effects of these compounds were suppressed.

These results support the conclusion that TxA2 and U46619 act on a unique receptor which triggers the c AMP-lowering effect and suggest that PGE2 antagonizes the anti-aggregating PG through interaction with this receptor.

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EFFECT OF NOVEL PGE_1 ANALOGUE (OP-1206) ON THE PLATELET FUNCTIONS. T. Kitani, M. Nakagawa, Y. Maeda, T. Kawamura, M. Watada, H. Yoshikawa, Y. Hino and H. Ijichi. Second Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.

PGE_1 is one of prostaglandins which inhibit platelet functions and has vasodilating activity similar to PGI_2. Newly developed PGE_1 analogue (OP-1206) was supplied for the clinical evaluations on oral administration. This research was performed to analyze the effect of orally administrated PGE_1 analogue on platelet functions and to evaluate the usefulness on the thromboembolic disorders. Comparing with PGI_2, this analogue demonstrated the similar inhibitory activity on the platelet aggregation in vitro study. Oral administration of OP-1206 on the patients with thromboembolic disorders showed the dose-dependent inhibition on platelet aggregation and adhesiveness. This activity continued for 180 min (max at 120 min). Daily oral administration (20μg and 30μg t.i.d.) was continued for two weeks and its effect on blood pressure, heart rate, ADP induced platelet aggregation, platelet adhesiveness and platelet c-AMP level were evaluated. Both of administration doses caused remarkable depression of platelet aggregation, increment of c-AMP level in the platelet and mild suppression on the platelet adhesiveness. Blood pressure was decreased, but heart rate remained unchanged. Clinical improvement of symptoms were observed in the patients with deep vein thrombosis or angina pectoris. These results emphasize the effectiveness and usefulness of this orally administrated PGE_1 analogue against the prevention and treatment of thromboembolic disorders.

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BINDING AND METABOLISATION OF PGI_2 BY ERYTHROCYTES. Ch. Willems, J.A. van Mourik, H.V. Stel and W.G. van Aken. Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam.

Prostacyclin (PGI_2) is rapidly hydrolysed in aqueous solution at neutral pH. Previously we have reported that PGI_2 is stabilized by plasma components; yet PGI_2 is rapidly metabolized in vivo. These findings prompted us to study the fate of PGI_2 upon incubation in whole blood. The data on the distribution of PGI_2 between blood cells and plasma indicate that PGI_2 not only binds to platelets but also to erythrocytes. The kinetics of binding were studied in more detail by incubating [3H] PGI_2 at 37°C with washed erythrocytes resuspended in autologous plasma. Binding of [3H] PGI_2 plateaued within 2 min. and was concentration dependant. The binding of [3H] PGI_2 was not influenced by PGE_1 or 6 keto $PGF_{1\alpha}$. [3H] 6 keto $PGF_{1\alpha}$ showed no substantial binding to erythrocytes when compared with [3H] PGI_2. Upon repeated incubation of [3H] PGI_2 with erythrocytes less binding occured than would have been expected from time and concentration dependancy. The latter finding is explained by the demonstration of breakdown of [3H] PGI_2 - most likely into [3H] 6 keto-$PGF_{1\alpha}$ - and by measurements of the biological activity of PGI_2. Although metabolisation of PGI_2 complicates the evaluation of binding kinetics it could be shown, by using inhibition of platelet serotonin release, that erythrocytes and platelets compete for PGI_2. Binding of PGI_2 to erythrocytes and subsequent metabolisation explains the apparent lability of PGI_2 in whole blood. It is to expected that under physiological conditions erythrocytes suppress the effectiveness of PGI_2 to act as a circulating platelet inhibitor.