FREE COMMUNICATIONS II

Platelets: Metabolism.

ENHANCEMENT OF PLATELET ACTIVITY BY INHIBITION OF ADENYLATE CYCLASE. E.W. Salzman, D.E.

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Induction of the platelet response to ADP and many other agonists is accompanied by reduction from basal level of cyclic AMP (cAMP). The Squibb compound 22536 (9-(tetrahydro-2-furyl)-adenine), an inhibitor of lung adenylate cyclase (Harris et al. Fed. Proc. 34:617, 1975), reverses the inhibition of platelet function and prevents elevation of platelet cAMP by drugs that stimulate adenylate cyclase, including PGE₁, PGD₂ and adenosine. It reduces basal and PGE₁- or NaF-stimulated adenylate cyclase activity and enhances the inhibition of basal activity induced by epinephrine. SQ22536 reduces basal cAMP levels but does not initiate the release reaction or platelet aggregation. It does, however, increase the effect on cAMP of platelet stimulants such as ADP and epinephrine and enhances serotonin release and aggregation induced by ADP, epinephrine, collagen, thrombin, arachidonic acid, endoperoxide PGG₂, centrifugation, and rewarming after chilling. Enhancement of platelet activity by SQ22536 in citrated PRP is demonstrable only over a narrow range of agonist concentrations where primary aggregation without release is transformed to complete aggregation with release. SQ22536 does not enhance platelet stimulation by vasopressin, serotonin, or the calcium ionophore Lilly A23187; these substances activate platelets without lowering cyclic AMP, unlike the stimuli listed above. In heparinized PRP, ADP-induced platelet aggregation is accompanied by serotonin release in the presence (but not in the absence) of SQ22536. These results suggest that reduction of cAMP may be involved in the initiation of release in platelets conditioned by a variety of phenomena, including primary aggregation.

ROLE OF CYCLIC AMP IN PLATELET FUNCTION: EVIDENCE FROM INHIBITION OF ADENYLATE CYCLASE IN INTACT PLATELETS BY ADENOSINE ANALOGUES. R.J. Haslam, M.M.L. Davidson and J.V. Desjardins. Department of Pathology, McMaster University, Hamilton, Ontario, Canada.

Adenosine exerts independent stimulatory and inhibitory effects on the adenylate cyclase activity of platelet particulate fractions (Haslam & Lynham, 1972). Two adenosine analogues, 9-(tetrahydro-2-furyl)adenine (SQ 22536) and 2',5'-dideoxyadenosine (DDA) have now been found to show marked non-competitive inhibitory activities only. Basal and PGE₁-stimulated adenylate cyclase activities were inhibited ~50% and ~70% respectively by 100 µM SQ 22536 and ~60% and ~80% respectively by 100 µM DDA. Both compounds also inhibited adenylate cyclase in intact platelets, when this was measured as the increase in cyclic [³H]AMP in platelets labelled with [³H]adenine and then incubated with papaverine. At the concentrations tested (10–500 µM), neither SQ 22536 nor DDA induced platelet aggregation or potentiated aggregation and release of [¹⁴C]5-HT induced by suboptimal concentrations of ADP, Arg⁸-vasopressin, arachidonic acid or collagen added to heparinized or citrated platelet-rich plasma. However, both compounds partially blocked the inhibition by PGE₁ or papaverine of aggregation induced by ADP or Arg⁸-vasopressin. From the concentrations exerting equal effects, DDA was ~3 times as potent in this regard as SQ 22536. Above 100 µM, the anti-inhibitory effects of both compounds decreased. The actions of these compounds in overcoming inhibition of aggregation by PGE₁ were correlated with decreases in platelet cyclic [³H]AMP in platelets labelled with [³H]adenine. The results show that cyclic AMP plays no role in the responses of platelets to aggregating agents unless the platelet cyclic AMP level is elevated above the resting level and confirm that the effects of PGE₁ on platelet function are mediated by cyclic AMP.