Tuesday, July 14, 1981

Poster Presentations

Platelets – XIII

Inhibitors, Activators, Chemiluminescence
11:00–12:30 h

Grand Ballroom Lobby Boards 266–277

0450


Several attempts have been made to dissociate the inhibitory effects of aspirin on platelet and vascular cells, but no definite results have been obtained. Other drugs, presumably acting on cyclo-oxygenase, are therefore being investigated for their relative inhibitory effect on platelet and vascular prostaglandin synthesis.

The present study was performed in male CD-1 mice. Itanoxone (chloro-2’-diphenyl)-4-oxo-4 methylene 2-butyric acid, a newly developed, hypolipidemic and hypouricemic compound with moderate anti-inflammatory activity, showed a short-lived, dose-dependent (20-200 mg/kg, orally) apparent competitive inhibition of platelet MDA stimulated by either thrombin or arachidonic acid. Repeated doses did not result in any cumulative effect. At doses which completely blocked MDA production, itanoxone also inhibited thrombin-stimulated thromboxane B2 production in platelets but had no measurable effect on vascular prostacyclin generation measured both by a bioassay and a radiolmmunoasay of its stable derivative 6-Keto-PGF1α. Pretreatment with itanoxone partially prevented the inhibitory effect of aspirin on both platelet and vascular prostaglandin synthesis. This suggests that itanoxone - like aspirin - acts at the level of cyclo-oxygenase but has much greater selectivity on the platelet enzyme.

This pharmacological activity is of great theoretical interest for potential use of this compound as an anti-thrombotic drug.

0451


Adenosine is a vasodilator, and also inhibits platelet aggregation apparently by acting at an external membrane receptor to increase levels of platelet cyclic AMP. Certain analogues of adenosine retain activity as vasodilators, and also inhibit platelet aggregation by raising levels of platelet cyclic AMP. NECA is an extraordinarily potent vasodilator, so its effects on human platelet function were tested.

NECA (1 µM) inhibited human platelet aggregation induced by ADP, 5-HT, thrombin and adrenaline more powerfully than adenosine (1 µM). NECA, even at micromolar concentrations, was 5 to 10 times more potent than adenosine as an inhibitor of aggregation induced by ADP (5 µM or 200 µM) or adrenaline (200 µM). NECA (K1 = 0.95 µM) caused increases in levels of platelet cyclic AMP, which could be competitively inhibited by theophylline (K1 = 8 µM), an adenosine receptor antagonist. However, here NECA was only about 1.3 times more potent than adenosine (K1 = 1.2 µM). The effects of NECA, like those of adenosine, were completely stereospecific, the L enantiomer of NECA being inactive. NECA (30 µM) did not prevent inhibition of PGF2α-stimulated adenylate cyclase by ADP (5 µM).

NECA is the most potent analogue of adenosine yet tested on human platelets, and is the first example of a 5’ modification to retain significant inhibitory potency.