A nucleotide with characteristic platelet aggregation and inhibition properties similar to 5-hydroxytryptamine

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The mechanism of the transient platelet aggregation response (PAR) of human platelets to 5-hydroxytryptamine (5-HT) is not well understood. We have found that adenyl-imidodiphosphate (AIP), a structural analogue of adenosine triphosphate (ATP), causes a reversible aggregation of human platelets, similar to that induced by 5-HT (Baumgartner & Born, 1968). A comparison has been made between AIP and 5-HT as inducers and as possible inhibitors of aggregation.

The extent of aggregation by AIP at a given concentration (50–100 μM) is related to the degree of PAR to 5-HT (10 μM) in the same platelet preparations. The higher the 5-HT response the greater the PAR to AIP. Another property shared by 5-HT is the fact that the transient PAR to AIP can be enhanced by short (40–60 s) preincubation with low (non-aggregating) concentrations (0.1–0.5 μM) of noradrenaline and adrenaline (Ball, Boullin & Glenton, 1977). Like 5-HT PAR, the transient PAR to AIP (50–100 μM) can be induced only once, and the platelets will not reaggregate again on further addition of the inducer. However, platelets that have aggregated reversibly to AIP, will respond by exhibiting reversible aggregation to the addition of 5-HT (10 μM). Similarity to 5-HT PAR was further strengthened by the observation that tetrahydro-β-carbolines and phenothiazines which strongly inhibit PAR to 5-HT were also potent inhibitors of PAR to AIP (Youdim, Oppenheim & Goldstein, 1978; Oppenheim, Youdim, Goldstein & Hefetz, 1978). AIP (50–100 μM), greatly enhances the first phase of adrenaline and nor-adrenaline responses, a time dependent phenomenon that is shared by 5-HT (Baumgartner & Born, 1968) and partly by ATP. AIP competitively inhibited both phases of PAR to adenosine diphosphate (ADP), however, it will inhibit only the second phase of PAR to adrenaline (10 μM) and nor-adrenaline (10 μM).

The second phase of aggregation response to ADP or adrenaline is usually related to release I, i.e. release of dense vesicle contents (Holmsen, 1975). Thus we may assume that AIP, in addition to being an aggregating agent can also be an inhibitor of release of 5-HT from storage vesicles. This possibility is presently being tested. AIP differs from ATP, adenosine monophosphate and adenosine because none of the latter compounds cause PAR at similar concentrations (50–100 μM). Since it is unlikely that a nucleotide derivative, such as AIP, will be taken up by intact platelets, one can envisage that the carrier for 5-HT uptake and its receptor for aggregation are different (Born & Michal, 1975). The lack of structural similarity between AIP and 5-HT suggests that the mechanism of reversible PAR to 5-HT may involve a nucleotide as an intermediate.

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The study of platelet aggregation in whole blood

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The invention by Born in 1962 of a turbidometric technique for measuring platelet aggregation proved to be of the greatest importance because it provided biological scientists with a tool for studying not only the mechanism of platelet aggregation *per se*, but also a host of other cellular activities which can be conveniently observed using platelets as a model system.

The main limitation of the Born aggregometer is that it only functions with translucent cell suspensions such as platelet rich plasma (PRP); in particular, it will not work in whole blood. This could be important in view of our recent finding (Blackwell, Flower, Russell-Smith, Salmon, Thorogood & Vane, 1978) that