PATHWAYS OF THROMBIN-INDUCED AGGREGATION AND RELEASE WITH HUMAN AND RABBIT PLATELETS.
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There are at least 3 mechanisms involved in thrombin-induced aggregation and release: (1) released ADP, (2) formation of thromboxane A_2 and (3) a third mechanism(s). We have examined whether the third pathway is due to formation or release of a substance from platelets which affects other platelets. Washed human platelets were exposed to thrombin (2.5 u/ml) for 15 min at 37°C in the presence of indomethacin to block thromboxane A_2 formation. Platelets were removed by centrifugation and the thrombin neutralized with hirudin or DFP. Addition of the supernate to washed human platelets prelabeled with ^{14}C-serotonin caused platelet aggregation but release did not occur. Treatment of the supernate with apyrase, CP/CPK or dialysis abolished aggregation, indicating that the material was ADP. Thus, the mechanism by which thrombin induces aggregation and release with human platelets in the presence of agents which destroy ADP and block the formation of thromboxane A_2 is a direct effect of thrombin on platelets and does not involve a substance freed from platelets. In contrast, when washed rabbit platelets were treated with thrombin in the presence of indomethacin and the released ADP was removed, material remained in the supernate which caused aggregation and release from washed rabbit platelets but was without effect on washed human platelets. The activity of this material (MW > 10,000) was not abolished by dialysis or boiling. Therefore rabbit platelets differ from human platelets because they have a mechanism in addition to released ADP, thromboxane A_2 and the direct effect of thrombin on platelets that can cause aggregation and release.

NORMALIZATION OF PLATELET SURVIVAL IN AN EXPERIMENTAL MODEL AFTER PLATELET EXPOSURE TO THROMBIN IN VITRO OR ADP IN VIVO.
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It is generally assumed that when platelets are damaged during preparation, their subsequent survival in the circulation is decreased. We have examined the effect of exposure of platelets to stimuli such as thrombin and ADP prior to studying their interaction with either damaged vessel wall or in vivo aggregation by infused collagen. Catheters inserted in the abdominal aorta of rabbits produced marked vascular damage. This was associated with a significant shortening of platelet half life ($T\frac{1}{2}$) of homologous ^{51}Cr-labelled platelets ($T\frac{1}{2}$-18hrs: Control animals $T\frac{1}{2}$-34hrs). In contrast, the platelet half lives of platelets degranulated by thrombin in vitro and those harvested from donors treated with ADP in vivo were 23 and 30 hrs respectively. In vivo collagen-induced platelet aggregation of the thrombin degranulated and the ADP exposed platelets was also found to be significantly diminished when compared with those obtained from untreated control animals.

These results suggest that exposure of platelets to either exogenous or endogenous stimuli could possibly mask a reduction in platelet survival in thrombovascular disorders and its modification by drugs.

β-THROMBOGLOBULIN AND PLATELET SURVIVAL IN PATIENTS WITH ARTERIAL THROMBOEMBOLIC DISEASE.
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A previous study has reported raised plasma levels of a platelet specific protein β-thromboglobulin (β-tg) in some patients with arterial thromboembolism (AT), rheumatic heart disease (RHD) and prosthetic cardiac valves (PCV). Comparative studies of β-tg levels and platelet survival are now reported in similar patients. β-tg was measured by a radioimmunoassay and platelet survival using ^{51}Cr labelled autologous platelets. In normal individuals a correlation (r=0.91) has been demonstrated between the reciprocal of the plasma β-tg concentration and the platelet survival. In 5 patients with AT the mean platelet lifespan was 7.4 days (range 5.7-9.3) and this was similar to 7.9 days (5.5-10.3) in control subjects. The mean plasma β-tg concentration in the patients, however, was 108ng/ml (range 45-235) and this was significantly greater (p=0.05) than 30ng/ml (range 17-72) in normal individuals. To determine if a single measurement of β-tg is representative of subsequent estimations in patients with RHD and PCV, samples were collected at monthly intervals from normal subjects and patients. In 11 patients the mean level was 50ng/ml and the coefficient of variation of repeat samples was 28% (range 13-68), while in normals the mean plasma concentration was 19ng/ml with a coefficient of variation of 26% (range 13-48). Treatment with dipyridamole resulted in decreased levels of plasma β-tg in some patients. It is concluded that in normal subjects and in patients with RHD and PCV the plasma β-tg is remarkably constant. It is suggested that the plasma β-tg concentration may be a more sensitive index of platelet activation than shortening of the platelet mean lifespan.