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Vessel Wall: Cellular Interaction in Experimental Models.

A NEW MODEL FOR ANTIPLATELET DRUG DISCOVERY. R.N. Saunders, T.S. Burns, E.R. Waskawic and M.R. Stelzer. Searle Laboratories, Skokie, Illinois, U.S.A.

Circulating platelet aggregates (CPA) have been observed by Wu and Hoak (Lancet 2: 294, 1974) in the blood of patients with transient ischemic attacks, acute myocardial infarction and acute peripheral arterial insufficiency. We have discovered that retired breeder (RB) male rats have spontaneous CPA which respond to therapy with clinically proven antiplatelet drugs. CPA are described as the ratio of the platelet count from blood drawn into a citrate/formalin solution compared to the platelet count from blood drawn into a citrate solution. A platelet aggregate ratio (PAR) of 1.0 is indicative of the absence of CPA. The PAR of 24 virgin male rats (0.94 $\pm$ .02, S.E.M.) was significantly greater ($P < 0.01$) than that of 34 male RB rats (0.77 $\pm$ .02)-indicating the presence of increased CPA in the RB rats. Acetylsalicylic acid (ASA) and sulfinpyrazone (S) have been successfully used clinically in patients with CPA and transient ischemic attacks (Stroke 6: 521, 1975). RB rats treated with ASA or S (100 mg/kg/day, i.g. for 8 days) demonstrated significantly ($P < 0.01$) increased PAR of 0.88 $\pm$ 0.02 and 0.99 $\pm$ 0.02 respectively. In vitro responses of RB platelets in citrate-treated platelet-rich plasma to adenosine diphosphate (0.4 µM to 3 µM/10^9platelets) and collagen (420 µg to 1470 µg/10^9 platelets) were similar in sensitivity to platelets from virgin rats. This suggests that the hyperactivity of RB rat platelets expressed as CPA is related to an increased aggregate stimulation in vivo. The results indicate that the male RB rat may be a useful model for the preliminary evaluation of therapeutically useful antiplatelet agents.

MORPHOLOGIC PLATELET CHANGES DURING THROMBUS FORMATION IN THE RAT. R.Wiedemann, W.Weichert and K.Breddin. Department of Angiology, Medical Center, University Frankfurt a.M., Germany.

The film presents observations in small mesenteric vessels (diameter 10-20 µm) of the rat using high power Nomarski optics. Under stasis conditions platelets appear as flat discs. Leucocytes are often seen creeping slowly along the intact vessel wall. Vascular lesions are produced with a focused laser beam (Hadron 513 biolaser). Immediately after the lesion platelets stick to the site of the microburn either in their native disc like shape without apparent morphologic changes or with protrusions. Within seconds these platelets swell and form protrusions. After 3 - 10 min, depending on the size of the lesion the vessel is occluded by a platelet thrombus. Platelets undergo further swelling. Later the thrombus is partially or completely swept away and the vessel is recanalized. Irreversible fusion of platelets is rarely observed. New, usually smaller thrombi form at the damaged vessel wall. The morphologic platelet changes observed differ markedly from the changes observed during aggregation in vitro. After injection of a new antithrombotic substance (Bay G 7565) the adhesion of platelets to the damaged area is remarkably diminished. The few platelets which adhere to the site of injury show the same swelling and transformation like in untreated animals. The film demonstrates that it is possible to investigate morphologic changes of single platelets during thrombus formation. It seems possible to adapt this model for the in vivo study of antithrombotic drugs.