0712

DEPRESSED RESPONSIVENESS TO ADRENALINE IN PLATELETS FROM APPARENTLY NORMAL HUMAN DONORS - A FAMILIAL TRAIT.
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Decreased responsiveness to adrenaline has been observed in 5 out of approximately 150 apparently normal unrelated human donors. In 4 donors, familial studies have shown that this trait is inherited. Three of the donors, as well as their affected relatives, exhibit depressed responsiveness to collagen and vasopressin but normal responsiveness to ADP and thrombin in association with the decreased responsiveness to adrenaline. The other two affected donors exhibit normal responsiveness to most other agonists although in one instance depression of responsiveness to vasopressin and absence of a secretory response to ADP may be associated with the decreased adrenaline response.

Normal responsiveness can be restored in all instances either by incubating the platelet-rich plasma at 20°C or by addition at 37°C of a low concentration of the divalent cation ionophore, A-23187. No such effect results from addition of an adenylate cyclase inhibitor. All affected platelets have normal ATP and ADP contents, cholesterol to phospholipid ratios, and composition of the phospholipid classes. Mixing experiments demonstrate the absence of a circulating inhibitor of platelet function and suggest that the defect resides in the platelets. We conclude that depressed responsiveness of human platelets to adrenaline may result from a defect in Ca^{2+} mobilisation to the cytosol. The observed selectivity in the agonists affected may indicate that the stimulus-response coupling pathways converge at the level of an increase in cytosolic Ca^{2+} concentration.

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RECONSTITUTION OF PF1 IN PLATELETS FROM FACTOR V-DEFICIENT DONORS AS A FUNCTION OF AVAILABLE PF3.
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Reconstitution of membrane-associated Factor V-like activity (PF1) in human platelets isolated from severe F.V-deficient donors was assessed following incubations in citrated normal platelet free plasma. Coagulant activities were measured using: a one-stage prothrombin time, the Stypven time and a modified KAPTT in which the kaolin particles were removed from the plasma prior to recalcification. The supernatant from 3x frozen-and-thawed lysed normal platelets was used as a standard for 100% PF1 and 100% PF3. Normal platelets gel filtered or centrifuge-washed in the presence of adenosine, theophylline and PGE_1 had <1% available PF1 and PF3, whereas platelets from severe F.V-deficient donors isolated by the same procedure had no PF1 and the same amount of PF3. The supernatant from 3x frozen-and-thawed lysed F.V-deficient platelets also had no PF1 but had 100% total PF3. When gel filtered, PF1-deficient platelets were incubated in normal plasma, they acquired about 1% PF1 which did not change following freezing-and-thawing. By contrast, PF1-deficent platelets washed in the absence of these inhibitors had 15-20 times more available PF3 and acquired about 15-20 times more total PF1 after incubation in normal plasma. When either the crude frozen-and-thawed lysed membrane supernatant from these PF1-deficient platelets (100% available PF3) or a partially purified membrane-rich fraction from this supernatant was incubated with normal plasma, then 100% reconstitution of PF1 was achieved. PF1 was also reconstituted in a purified system using all-or-none binding when the PF3-containing lipid-protein particles secreted by platelets, upon collagen induced aggregation, were incubated with purified human F.Va. Following incubation, these particles had the same amount of PF1 as the PF3-containing particles from normal platelets. It is apparent that in human platelets a correlation exists between the amount of available PF3 and the capacity to reconstitute PF1.

0714

THROMBOCYTOPATHY IN CHRONIC MYELOCYTIC LEUKEMIA: A POSSIBLE DEFECT IN THE RESPONSE TO THROMBOXANE A_2.
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Platelet functions, adenine nucleotide contents and arachidonic acid (AA) metabolism have been studied in a chronic myelocytic leukemia patient with slight thrombocytosis and a mild bleeding tendency. Platelet aggregation with 5 μM ADP was completely reversible. Platelet aggregation as well as ATP release induced with AA and collagen was defective. Only high concentrations of AA (≥2 mM) induced slight aggregation with its complete reversal. Normal platelets suspended in patient's plasma were aggregated by AA but patient's platelets in normal plasma were not, showing the abnormality to be in patient's platelets per se. ^{14}C-Serotonin uptake by the platelet and adenine nucleotide (ADP and ATP) contents in the platelet were normal, excluding a possibility of storage pool deficiency. Normal activities of cyclo-oxygenase and lipoxygenase pathways in patient's platelets were demonstrated both by thin-layer radiochromatographic analysis of lipid products obtained by incubating [1-^{14}C]AA with the platelet (Blood 1979;54:1258) and by the determination of thiobarbituric acid-reactive substances produced by the incubation of AA with the platelet (Thromb. Haemost. 1979;42:245). Normal biological activity of AA metabolites produced by patient's platelets was shown by strong irreversible platelet aggregation produced by the addition of normal citrated platelet rich plasma (PRP) to a reaction mixture in which patient's washed platelets had been incubated with AA at 37°C for 30 sec. Only slight aggregation with its reversal was observed when patient's PRP was added to a reaction mixture in which thromboxane A_2 (TXA_2) had been generated by the incubation of AA with the microsomal fraction prepared from normal platelets, while irreversible aggregation was produced when normal PRP was added in similar experiments. These results suggest that abnormal platelet functions in this patient are due to a defective platelet response to TXA_2.