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Mechanisms of collagen-induced bronchoconstriction and thrombocytopenia in the guinea-pig

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Circulating platelets are not required for bronchoconstriction due to the thromboxane A2 precursor arachidonic acid (AA), but are needed for bronchoconstriction by ADP and ATP (Lefort & Vargaftig, 1975). We have now investigated the correlation between bronchoconstriction (Holmes, 1977) and thrombocytopenia due to the standard platelet aggregating agent collagen (Horn Chemical, Munich). Pentobarbitone anaesthetized guinea-pigs were prepared for recording of pulmonary resistance (bronchoconstriction) to inflation. All injections were given intravenously. Platelets were counted from arterial blood automatically, and *in vitro* platelet aggregation was studied by the turbidimetric technique in citrated platelet-rich plasma. Collagen (50–300 μg/kg) induced dose-related bronchoconstriction accompanied by thrombocytopenia, with a peak of 60 ± 21 (% drop in platelet counts ± s.d.) within 3 min for 300 μg/kg. Higher amounts of collagen killed the animals from irreversible bronchoconstriction and hypotension. Aspirin and indomethacin (1 and 5 mg/kg respectively) inhibited bronchoconstriction, but caused a statistically insignificant reduction in thrombocytopenia. Drugs which failed to interfere with the effects of collagen were (mg/kg): cyproheptadine (0.5), atropine (1), mepyramine (2), soybean trypsin inhibitor (20), carboxypeptidase (5, enough to suppress bronchoconstriction by bradykinin), ADP (infused at 1 mg kg^{-1} h^{-1}, enough to inhibit bronchoconstriction and thrombocytopenia by ATP and by ADP itself), and the Künitz trypsin inhibitor (100,000 u/kg). This ruled out a role for histamine, serotonin, acetylcholine and bradykinin in collagen-induced bronchoconstriction. Failure of platelet desensitization with ADP to inhibit bronchoconstriction suggested that platelets are not involved directly, but platelet antiplasma (Vargaftig & Lefort, 1977) suppressed bronchoconstriction. Guinea-pig platelets are aggregated by complement-derived peptides (Benner, Schumacher & Glassen, 1975; Grossklaus, Damerau, Lemgo & Vogt, 1976), and the complement component Clq is a collagen-like glycoprotein (Müller-Eberhard, 1975). Since immune platelet depletion presumably is complement-dependent, complement activation was thought of as a mechanism of action of collagen *in volvo*. The complement-depleting agent carrageenin (Davis, 1965), infused for 30 min at 1 mg/kg, prevented bronchoconstriction and thrombocytopenia by collagen, but not by AA, and failed to block thrombocytopenia or *in vitro* aggregation of platelets collected at the end of the infusion. A platelet site of action for collagen-induced bronchoconstriction is suggested, but complement-derived peptides may be involved also, and trigger generation of thromboxane A2, thus explaining effectiveness of aspirin and of indomethacin.

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