Interactions between calcium and some mylotic agents on depolarized vascular smooth muscle

A mutual antagonism occurs between calcium ions and papaverine-like drugs, both on polarized and KCl-depolarized smooth muscle preparations (Ferrari, 1964; Ferrari & Gaspa, 1965; Toth, Ferrari & others, 1966; Ferrari & Carpenedo, 1968). In view of the essential role played by calcium in muscular contraction, such antagonism was considered of great importance in the mechanism of action of spasmolytics. However, besides the antagonism with calcium ions, papaverine and some derivatives exert other effects related to the mechanism of their spasmolytic action: in fact, these drugs strongly inhibit oxidative phosphorylation and elicit on isolated smooth muscle preparations similar effects to those induced by anoxia or by metabolic inhibitors (Santi, Contessa & Ferrari, 1963; Santi, Ferrari & Contessa, 1964). Also, these metabolic inhibitors are spasmolytic, the most closely related to papaverine being the fish poison rotenone: it has the same site of action in the respiratory chain as papaverine, it shares several pharmacological properties with papaverine but is more active both pharmacologically and biochemically (Santi, Ferrari & Toth, 1963; 1966). We have now compared on depolarized vascular smooth muscle the antagonism of rotenone, papaverine and some congeners by calcium ions.

The investigations were made by testing the effects of rotenone (0·33, 1·65 $\times$ 10^{-7}M), papaverine (1·17, 2·34, 4·68 $\times$ 10^{-5}M), eupaverin (1·17, 2·34, 4·68 $\times$ 10^{-5}M), aminopromazine (0·76, 1·52 $\times$ 10^{-6}M) and iproveratril (0·85, 1·70 $\times$ 10^{-7}M) on the vasoconstriction induced by $CaCl_2$ on the rabbit isolated ear preparation perfused with a depolarizing solution (Ringer KCl). After an initial perfusion (lasting about 20 min) with calcium-free Tyrode medium, the preparation was perfused with calcium-free KCl-Ringer. $CaCl_2$ was added subsequently and its concentration was gradually

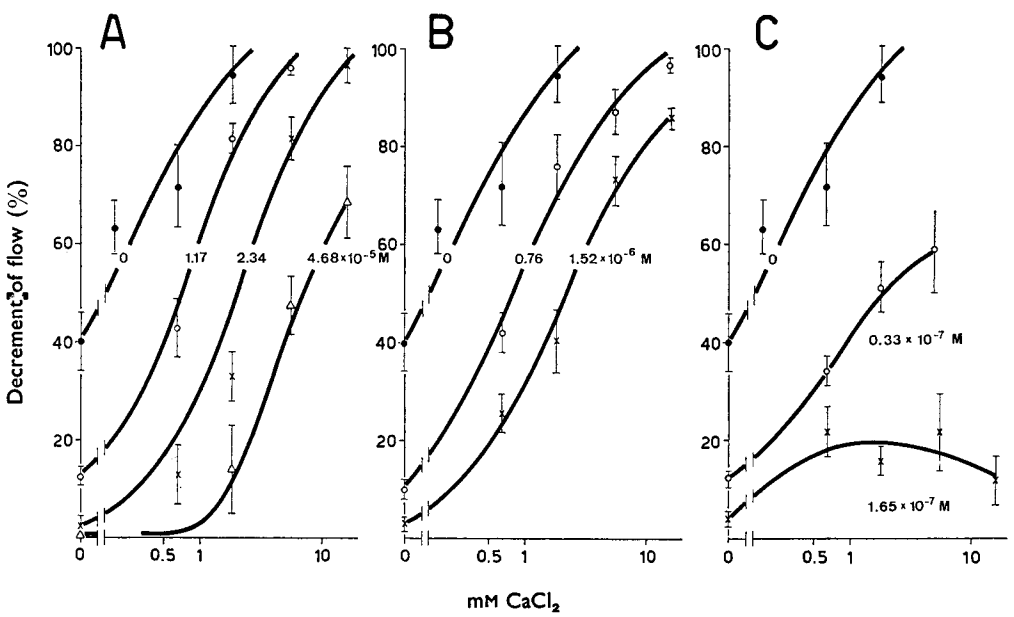

FIG. 1. Rabbit isolated ear perfused with KCl-Ringer at room temperature: cumulative log concentration-response curve for calcium ions in the presence of various concentrations of papaverine (in A), aminopromazine (in B) and rotenone (in C).

increased, every 3 min, following a cumulative sequence. In control experiments $CaCl_2$ concentrations ranged between 0 and 2mM; 2mM $CaCl_2$ constantly induced a complete vasoconstriction. In the presence of myolytic agents, higher $CaCl_2$ concentrations were employed and ranged from 0 to 16 mM. Flow values were recorded by means of a Jacquet drop-counter. The drugs were employed under continuous perfusion, in the presence of different calcium concentrations. Their effects were recorded after a 3 min perfusion and evaluated by van Rossum's method (1963).

Under these experimental conditions the drugs tested retain a clear vasodilating activity. The increase of calcium concentration poorly affects the myolytic activity of rotenone but fully counteracts the vasodilation induced by papaverine, eupaverin, aminopromazine and iproveratril: when plotted as % decrement of flow versus log $CaCl_2$ concentration, the results show (Fig. 1) that in the presence of papaverine or aminopromazine the dose-response curves assume a parallel displacement compared with the controls. The pattern of antagonism of eupaverin and iproveratril by calcium closely parallels that observed with papaverine and aminopromazine.

These findings suggest that, at least within a limited range of concentrations, the effects of papaverine-like drugs may be mainly ascribed to an impairment of calcium availability to the contractile system. Rotenone instead is not counteracted by calcium; this is consistent with the previous hypothesis that its myolytic activity should be entirely ascribed to metabolic inhibitory effects (Santi, Ferrari & Toth, 1966).

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September 23, 1969

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