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Papaverine-like Pharmacological Properties of Rotenone

SIR,—Recent investigations showed papaverine and some structurally related compounds to be powerful inhibitors of oxidative phosphorylation (Santi, Ferrari and Contessa, 1963). A relation also seemed possible between the spasmolytic activity of papaverine-like drugs and their inhibition of the respiratory chain, thus explaining the similarity of effects elicited by anoxia, by some enzyme inhibitors and by papaverine, on the drug-induced contraction of intestinal smooth muscle. Under these experimental conditions it was observed (West, Hadden and Farah, 1951; Santi Contessa and Ferrari, 1963) that the isolated gut failed to give normal tonic responses to acetylcholine, histamine and $BaCl_2$ showing only an immediate, short-lasting contraction. This inability of smooth muscle to maintain tone was considered as "the first evidence of interference with energy production" (West, Hadden and Farah, 1951). For papaverine and allied drugs we pointed out that a similar effect may be elicited through a strong inhibition of electron-transfer reactions, between DPN and cytochrome b. The site of action is therefore the same as the one recognised for amytal (Ernster, Jalling, Low and Lindberg, 1955), rotenone (Ernster, Dallner and Azzone, 1963) and allyloxibenzamide (Bruni and Contessa, 1961). With regard to the selectivity of the action and to the degree of activity, among the inhibitors of oxidative phosphorylation rotenone appears as the one most closely related to papaverine (Ernster, Dallner and Azzone, 1963; Santi, Contessa and Ferrari, 1963). This similarity of biochemical properties prompted a pharmacological comparison between rotenone and papaverine. The purpose was to examine the reliability of the previously proposed hypothesis on the mechanism of action of papaverine.

In the present investigations on rotenone and papaverine we have studied the spasmolytic activity on isolated gut (guinea-pig ileum and rabbit duodenum); the vasodilator effect on the hind-limb of the dog, by recording the arterial femoral flow with a Shipley and Wilson rotameter; the effects on respiration and arterial blood pressure in rabbits and dogs.

Rotenone at final concentrations ranging from 10^{-8} to 10^{-9} (w/v) inhibits selectively the tonic response of intestinal smooth muscle to acetylcholine and histamine without preventing the immediate short-lasting contraction. Thus rotenone mimics the spasmolytic effect of papaverine, but its degree of activity is

much greater (about 100 times) and the myolytic effect is persistent and not readily abolished by washing.

When injected intra-arterially rotenone (15–20 μg.) elicits a remarkable vasodilator effect by increasing blood flow 70–80 per cent for a time of 120–150 sec.; papaverine shows a similar but weaker activity.

Rotenone exhibits a clear respiratory stimulant effect both when injected into the common carotid artery (15–20 μg. through the thyroid inferior artery) and when administered intravenously (15–25 μg./kg.); when given intravenously there is evidence of a short-lasting hypotensive effect resembling that elicited by papaverine.

The data so far obtained demonstrate a close resemblance between the pharmacological properties of rotenone and papaverine. Rotenone appears the more active compound in pharmacodynamic and biochemical properties. In respect to our previous investigations which led to the hypothesis that the spasmolytic effect of papaverine is related to the inhibition of oxidative phosphorylation, it is noteworthy that rotenone, the most selective inhibitor of oxidative phosphorylation till now recognised, exhibits papaverine-like activities (spasmolytic, vasodilator, respiratory stimulant effects). It seems reasonable to admit that other pharmacological properties of papaverine, like the respiratory stimulant one, are related to the inhibition of oxidative phosphorylation.

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