Pharmacological properties of tetrahydropapaveroline and their relation to the catecholamines

SIR,—Recent reports from this laboratory (Santi, Contessa & Ferrari, 1963; Santi, Ferrari & Contessa, 1964) have shown that papaverine is a powerful inhibitor of the aerobic oxidation of substrates linked to nicotinamide adenine dinucleotide (NAD) in rat liver mitochondria. The inhibition of oxidative phosphorylation which could be localised in the electron transfer step between NAD and cytochrome b might be important in understanding the mechanism of the spasmolytic effect of the drug. Since some effects of papaverine resemble those generally referred to stimulation of the so-called β-receptors of adrenaline, Santi (1963) has put forward a working hypothesis based on the possibility that the adrenaline-like drugs produce an impairment of cellular energy sources.

In this context, the conclusion by Holtz, Stock, & Westerman (1963) that a substance similar in structure to papaverine, tetrahydropapaveroline, could be formed by the condensation of the well-known precursor of adrenaline, dopamine, and dihydroxyphenylacetic aldehyde, is of interest.

We have confirmed the results of Holtz & others (1963) and we believe that the pharmacological properties of tetrahydropapaveroline are in themselves very interesting in as much as this drug behaves in some respects like papaverine, in others like the catecholamines and particularly, isoprenaline. Some pharmacological properties of the drug were described several years ago by Laidlaw (1910).

The spasmolytic activity of tetrahydropapaveroline, as seen on the isolated guinea-pig ileum, resembles that of eupaverin (1-benzyl-3-ethyl-6,7-dimethoxyisoquinoline) rather than that of papaverine. It differs from papaverine in not inhibiting mitochondrial respiration.

Tetrahydropapaveroline stimulates the myocardium as was seen *in vivo* by measuring the contractile strength by means of the strain gauge technique described by Boniface, Brodie & Walton (1953), as well as *in vitro* on isolated guinea-pig atria. The latter effect is antagonised by dichloroisoprenaline (DCI). The action of tetrahydropapaveroline on the heart is presumably important in understanding its pharmacological activities. In the dog, 0·1 mg/kg injected intravenously greatly increases the contractile strength of the heart and also its frequency. At 0·02 μg/ml, it has a positive inotropic and chronotropic action; a similar effect may be shown on isolated atria of the previously reserpinised guinea-pig. In dogs and cats, tetrahydropapaveroline reduces blood pressure at concentrations 20–30 times lower than papaverine and 50 times greater than isoprenaline. The hypotensive effect mainly concerns diastolic pressure, whereas the systolic values remain unchanged, the differential increasing accordingly. The decrease of blood pressure must be presumed to be due to a peripheral vasodilatation, since when 5–10 μg of the drug was introduced into the femoral artery, a strong increase of blood flow was measured with a Shipley-Wilson rotameter (1951). On the other hand, the vasodilator response of the blood vessels of the isolated rabbit ear according to the technique of Pissemski (1914) was present, although not intense. When administered intravenously to dogs and cats, the drug greatly stimulated respiration.

Tetrahydropapaveroline, similarly to adrenaline (Ussing, 1960), and in contrast to papaverine, increases the short circuit current of the isolated frog skin as measured by the technique of Ussing & Zerahn (1951), modified by Vescovini & Marro (1960). Finally, the drug injected intraperitoneally produces an increase in the plasma level of free fatty acids in rats; this effect is considered to be

specific for adrenaline and related drugs. The mobilisation by tetrahydropapaveroline of lipids from adipose tissue was also observed *in vitro*.

From these observations it is concluded that the drug acts like papaverine on respiration and like eupaverin on the isolated ileum whereas the pharmacological effects on isolated rat liver mitochondria, isolated mammalian heart or atria, blood vessels, free fatty acids and frog skin resemble those of the catecholamines and particularly isoprenaline. Whether tetrahydropapaveroline might play a role as a chemical transmitter in the central nervous system is the subject of current enquiry in our laboratories.

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