Effect of Δ^9-tetrahydrocannabinol on experimental hypertension in rats

The cardiovascular effects of the chronic administration of (—)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC), the main active constituent of marihuana, have been studied in both normotensive and in hypertensive animals. Ho, An & others (1971) found that Δ^9-THC given for 5 to 6 weeks caused a small, but significant decrease, in the blood pressure of normotensive rats. Dewey, Jenkins & others (1972), however, found no significant change in the blood pressure of normotensive unanaesthetized dogs chronically administered Δ^9-THC. Nahas, Schwartz & others (1973) observed the development of tolerance to the hypotensive effect of Δ^9-THC in spontaneously hypertensive rats and Graham & Li (1973) noted a similar phenomenon with cannabis extract in normotensive rats. On the other hand, Birmingham (1973) found that the daily administration of Δ^9-THC to adrenal regeneration hypertensive rats for one week produced a persistent hypotension. We have assessed the influence of chronic administration of Δ^9-THC on the development of experimental hypertension in rats; the acute effect of Δ^9-THC on the systolic pressure and on the heart rate of a group of hypertensive rats was also determined.

Adult Sprague-Dawley male rats were used for inducing metacorticoid (Varma, 1967) and renal hypertension (Ayitey-Smith & Varma, 1970). The systolic blood pressure was determined by the tail-cuff method (Varma, 1967) and the heart rate was recorded by an electrocardiogram. (—)-*trans*-Δ^9-Tetrahydrocannabinol dissolved in ethanol (200 mg ml^{-1}) was obtained from the Department of National Health and Welfare, Canada and it was diluted in 70% ethanol in water to give the drug dose in 0·3 ml kg^{-1}; the same amount of 70% ethanol–water was given as control.

Δ^9-THC (1·5 mg kg^{-1}, i.p.) caused a significant decrease ($P < 0{\cdot}05$) in the systolic pressure and the heart rate of 10 rats hypertensive for 5 to 6 weeks and which had not received Δ^9-THC previously. The effects appeared within 15 min after injection and were significant at 60 min. Both the parameters returned to control level in 24 h. Nahas & others (1973) and Birmingham (1973) found a significant hypotensive effect of the initial injections of Δ^9-THC into hypertensive rats but in their animals the hypotensive effect persisted for more than 24 h. Cavero, Buckley & Jandhyala (1973) found that the duration of the hypotensive and the negative chronotropic effect of Δ^9-THC in anaesthetized normotensive dogs was dose-dependent.

When Δ^9-THC, 1 or 2 mg kg^{-1} (s.c.) was injected daily to 10 and 7 rats respectively (except on Sundays) for 3 to 5 weeks beginning on the day experimental hypertension was induced, the systolic pressure and the heart rate of the control (n=7) and treated rats did not differ at any time during the 3 to 5 weeks of observation; a comparable metacorticoid and renal hypertensive blood pressure level was recorded in both the groups. These results also support the observations of Nahas & others (1973) who observed a rapid development of tolerance to the hypotensive effect of 5 to 25 mg kg^{-1} of Δ^9-THC in hypertensive rats; they found that the blood pressures returned to the control levels 4 days after a daily oral administration of 5 mg kg^{-1} Δ^9-THC and continuation of the drug did not produce a hypotensive effect. However, our results again are at variance with those of Birmingham (1973) who observed a persistent and significant hypotension for a week after daily intraperitoneal injections of 3 mg kg^{-1} Δ^9-THC into hypertensive rats. Differences of dose may be responsible but the route used should not have influenced the results since Kreuz & Axelrod (1973) have shown the accumulation of Δ^9-THC and its metabolites after a single or repeated subcutaneous injections of an ethanol solution of ^{14}C-Δ^9-THC into rats and Sofia, Kubena & Barry (1974) have reported comparable pharmacologic effects of intraperitoneal and subcutaneous injections of Δ^9-THC into mice.

This work was supported by a Grant from the Department of National Health and Welfare, Canada.

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January 28, 1975

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Depot fluphenazine enanthate and decanoate: comparative rates of release in dogs

While many studies in man demonstrate the clinical efficacy of long-acting esters of fluphenazine, (Blachly, 1965; Keskiner, Simeon & others, 1968), there is scarcely any metabolic data in the literature that enables the quantitation of their slow-release from a depot (Ebert & Hess, 1965; Dreyfuss, Ross & Schreiber, 1971). Metabolic studies with these compounds in man have had only limited success owing to the small concentrations of drug or metabolites that are present at any time in the circulation (Schreiber & Grozier, 1973).

Two groups of five male purebred beagles, $\sim$ 10 kg, were given average doses of either [^{14}C] fluphenazine enanthate (4·92 μCi mg^{-1}) or [^{14}C] fluphenazine decanoate (4·84 μCi mg^{-1}), containing about 100 μCi of radioactivity. Both esters were formulated in sesame oil (*ca* 41 mg ml^{-1}) containing 1·6% benzyl alcohol and injected intramuscularly into the *biceps femoris* of the thigh muscle (0·5 ml of formulation for each 10 kg). The single dose of drug administered to dogs on the basis of body weight [1·89 $\pm$ 0·11 mg kg^{-1} for the enanthate (mean $\pm$ s.e.); 2·03 $\pm$ 0·04 mg kg^{-1} for the decanoate] was about 4 times that which would be administered to man clinically (DeWolfe, Barrell & others, 1971; Chacon & Harper, 1973). Samples of blood were taken periodically for 35 days; total urine and faeces were collected separately each day.

Plasma (0·8 ml) was dissolved in 4 ml of NCS solubilizer (Amersham, Searle) and counted in 15 ml of scintillation fluid containing, per litre of toluene, 5 g of 2,5-diphenyloxazole and 300 mg of 1,4-bis-2-(4-methyl-5-phenyloxazolyl)-benzene, using a Packard Tri-Carb liquid scintillation spectrometer, Model 3380. Quench correction was by automatic external standardization. Faeces were homogenized with 2–3 volumes of methanol, and 800 mg samples of the homogenate were combusted for counting in an oxidizer (Harvey Instrument Corp.). Samples of urine (1 ml) were counted directly in scintillation fluid (Bray, 1960).