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Topical Δ^9-tetrahydrocannabinol in hypertensive glaucomas

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Marihuana smoking is accompanied by significant decreases in both blood and intraocular pressures (IOP) (Crawford & Merritt 1979; Merritt et al 1980). Δ^9-Tetrahydrocannabinol (Δ^9-THC), one of 64 cannabinoids found in marihuana, lowers both the IOP and blood pressure in animals (Green et al 1978) through its peripheral vasodilator properties. To investigate these effects, we needed to identify a concentration of topical Δ^9-THC that would have no hypotensive effect in hypertensive glaucoma subjects, and allow identification of strength of the drug that would produce ocular, but not systemic, hypotensive effects.

After informed consent, seven black and one caucasian (7 female, 1 male, mean age 65 years) adult hypertensive glaucoma subjects were admitted to the Clinical Research Unit. All had received prior therapy for both open angle glaucoma and essential hypertension. Three subjects (five eyes) had undergone prior filtration procedures for uncontrollable open angle glaucoma.

The preparations were made by measuring the appropriate amount of Δ^9-THC from ethanolic solution. The ethanol was evaporated using a stream of bacteriologically filtered nitrogen. The vehicle (light mineral oil, U.S.P. containing 0·0025% propyl paraben, and 0·005% methyl paraben, U.S.P.) was added to volume and the solutions agitated. The solutions were then filtered through a Polytef sterilizing filter into 10 ml glass vials. Polytef stoppers were fitted to the vials and the aluminium cap crimped. All operations were performed under a laminar flow hood such that no preparation contacted plastic or rubber. Preparations were stored at room temperature (20 °C) in the dark.

Each subject sat quietly for 15 to 20 min while heart rate and blood pressure measurements were made every 5 min. The IOP was then measured with applanation tonometry and these data were designated control. One eye of each subject was randomly selected to receive cannabinoid while the fellow eye received vehicle alone. The method of drop instillation was the same for each compound and 0·1 ml was administered using tuberculin syringes as follows:

(1) Two drops were instilled on to the superior conjunctival cul-de-sac and wiped down over the cornea by manual blinking while the patient looked down.

(2) The subject was then instructed to look up, and two drops were then placed on the lower cul-de-sac holding the lower lid from the globe.

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Cannabinoids in light mineral oil concentrate in the cornea (Green et al 1977) such that this method of topical instillation allows for maximum bioavailability of active agent. The theoretical maximum amount of cannabinoid that could be absorbed was 100 and 50 μg from the 0·1 and 0·05% solutions respectively. Two patients were tested with 0·01%, three with 0·05%, and three received 0·1% Δ^9-THC. Two subjects received both the 0·05% and 0·1% with at least 48 h intervening between sessions. The blood pressures, heart rate and IOP were measured by observers who were unaware of the treatment

Topical 0·01% Δ^9-THC produced no change in blood pressure, heart rate or IOP in the two subjects tested with this concentration. The 0·05% Δ^9-THC decreased the IOP a mean ($\pm$s.e.m.) 4·8 + 2·8 mm Hg in the treated eye and 6·8 $\pm$ 2·5 mm Hg in the fellow eye at 3 h. The 0·1% Δ^9-THC decreased the IOP 5·4 $\pm$ 2·6 mm Hg in the treated eye at 5 h with the maximum fall of 5·2 $\pm$ 2·8 mm Hg occurring in the fellow eye at 1 h. IOP's returned to control 8 to 9 h after 0·05%, but not after 10 h with 0·1% Δ^9-THC. There was a 12 mm Hg decrease in systolic blood pressure 6 h after 0·1 ml of 0·1% Δ^9-THC, though no hypotensive effect was documented after 0·05%. There was no significant change in heart rate after either concentration. There were no adverse local effects after single dose instillation in the cannabinoid or vehicle treated eyes. No adverse psychic, or cardiovascular effects occurred after topical Δ^9-THC in these 8 hypertensive glaucoma subjects.

Initial smoking studies utilizing Mexican marihuana containing 2% and 2·8% Δ^9-THC showed no difference between those two concentrations in either the intraocular or blood pressure lowering effects (Crawford & Merritt 1979; Merritt et al 1980). These observations suggested that the cardiovascular effects (tachycardia and postural hypotension) predominate when marihuana is smoked and that these properties mitigate against its wide-spread therapeutic use in elderly glaucoma patients.

We, therefore, designed this dose-ranging study to identify a concentration of Δ^9-THC that had no demonstrable effect on either heart rate, intraocular or blood pressures. The two least potent concentrations (0·05 and 0·1%) were then applied in light mineral oil to one eye randomly selected. Hypertensive glaucoma patients seem sensitive to the hypotensive effects of marihuana (Crawford et al 1978) hence, the decrease in systolic blood pressure (12 mm Hg) after 0·1% in our hypertensive subjects deserves confirmation in expanded

studies. The contralateral hypotensive effect in the untreated fellow eye in our hypertensive subjects has been documented in animals (Green et al 1978) and suggests that the pressure lowering effect of Δ^9-THC is through systemic (cardiovascular and/or central nervous) rather than locally mediated effects within the eye. Before the full therapeutic potential of the cannabinoids are realized, further research should identify the ocular-active cannabinoid which would have minimal cardiovascular and psychologic effects so that local delivery systems of this cannabinoid may be devised.

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Effect of GABAergic drugs on dopamine catabolism in the nigrostriatal and mesolimbic dopaminergic pathways of the rat

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Nigrostriatal and mesolimbic (mesocortical) dopaminergic neurons are involved in the regulation of muscle tone, extrapyramidal motility and general motor function, and are often affected in abnormal movement disorders (Hornykiewicz 1975) and psychotic disturbances (Stevens 1979). γ-Aminobutyric acid-utilizing (GABAergic) neurons are thought to interact with these dopaminergic systems and to regulate their activity (Fuxe et al 1975; Moore & Wuerthele 1979). There is good evidence for GABAergic neurons in both the nerve terminal and somatodendritic regions of the nigrostriatal dopaminergic pathway, viz. corpus striatum (Obata & Yoshida 1973; Bernardi et al 1976; Bartholini & Stadler 1977) and substantia nigra respectively (Precht & Yoshida 1971; Fonnum et al 1974; Hattori et al 1975; Ribak et al 1976). The role of GABAergic neurons in relation to the mesolimbic dopaminergic pathway is not as well elucidated, but the amino acid may similarly regulate the activity of these dopaminergic neurons both in the nucleus accumbens (Woodruff et al 1976; Pycock et al 1978; Beart et al 1980) and in the ventral tegmental area (Fonnum et al 1977; Wolf et al 1978; Walaas & Fonnum 1980). In Huntington's chorea a deficit of GABAergic neurons results in dopaminergic overactivity and consequent choreiform movements (Bird & Iversen 1974). The general involvement of GABA as an inhibitory neurotransmitter implies that GABAergic drugs could be of clinical importance in disorders such as Huntington's chorea, neuroleptic-induced tardive dyskinesias and epilepsy (Bartholini 1980; Meldrum 1978).

To analyse brain GABA-dopamine interactions we have examined the influence of several GABAergic drugs on the nigrostriatal and mesolimbic dopaminergic systems by studying drug-induced changes in the concentrations of the important dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) (Roffler-Tarlov et al 1971). Alterations in the concentration of DOPAC represent a biochemical index of dopaminergic nerve activity and increases in DOPAC concentration are seen with increases in dopaminergic nerve impulse flow and vice-versa (Roth et al 1976).

Male Sprague-Dawley rats (150–250 g) were injected with drugs either intraperitoneally (2 ml kg^{-1}) or intravenously (1 ml kg^{-1}) into the tail vein. The following drugs were studied, picrotoxin (1 & 10 mg kg^{-1}, i.p., 60 and ca 15 min respectively), bicuculline (2 & 18 mg kg^{-1}, i.p., 60 min and ca 40 s respectively), 3-mercaptopropionic acid (15 & 90 mg kg^{-1}, i.p., 30, and ca 8 min respectively), aminooxyacetic acid hemi-hydrochloride (36 mg kg^{-1} of base, i.p., 60 min), 4-aminohex-5-ynoic acid (γ-acetylenic GABA 75 mg kg^{-1}, i.p., 240 min), nipecotic acid hydroxymethylpivalate oxalate (50 mg kg^{-1} of base, i.p., 60 min) and guvacine hydrobromide (40 mg kg^{-1} of base, i.v., 60 min). When convulsant doses were employed (picrotoxin, bicuculline and 3-mercaptopropionic acid) rats were killed at the onset of convulsions. Drugs were dissolved in 0·9% NaCl (saline) except for 4-aminohex-5-ynoic acid (distilled water) and bicuculline (1·1 equivalents of hydrochloric acid), and adjusted to pH 7·4 where appropriate. Corpus striatum, substantia nigra, nucleus accumbens and the ventral tegmental area were dissected as previously described (Beart & Gundlach 1980). Dissected brain areas were homogenized in 5 or 10 volumes of ice-cold 0·1 M hydrochloric acid, 0·1% EDTA and stored overnight at − 20 °C. Homogenates were centrifuged at 10 000 *g* for 5 min at 4 °C and portions of supernatants were assayed for DOPAC by a radioenzymatic assay employing catechol-*O*-methyltransferase and [^{3}H]-S-adenosyl methionine (Amersham) in which DOPAC is

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