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Clinical studies on the disposition and metabolism of Δ^9-THC and their correlation with its pharmacologic effects

Plasma levels of ^{14}C-Δ^9-THC declined in a biphase manner after its intravenous administration to non-users, or chronic users of marihuana. The $t_{1/2}$ of the second phase was 56 h in non-users and 27 h in chronic users. Urinary excretion of radioactivity was significantly greater in users than non-users. However, total radioactivity excreted in urine and feces did not differ significantly. 11-Hydroxy-THC was present in plasma within 10 min and was excreted in urine and feces. 8,11-Dihydroxy-THC was also excreted in feces. The major urinary metabolites in man appear to be acidic and very polar, perhaps being identical to the metabolites present in rabbit urine (Agurell, *et al. Biochem. Pharmacol.*, 1970). After oral ingestion of a pharmacologic dose of ^{14}C-Δ^9-THC, the psychologic effects had their onset within 30 to 60 min, reached their peak at 2 to 3 h, and had a duration of 4 to 6 h. Plasma radioactivity correlated well, with the psychologic effects increasing to a peak at about 3 h then gradually declining. The finding that at the peak "high" unchanged Δ^9-THC plasma levels account for only a relatively small percentage of total radioactivity is consistent with the hypothesis that 11-OH-Δ^9-THC or some other metabolite is responsible for the pharmacologic activity. After the inhalation of a marihuana cigarette containing ^{14}C-Δ^9-THC, plasma levels of radioactivity were initially high and then gradually declined. The psychologic effects were manifested within 6 to 12 min and were largely dissipated by 3 h, at which time the plasma levels of radioactivity had decreased considerably.

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The role of vehicles in cannabis application and interaction between cannabis and central active drugs

The administration of cannabis compounds is complicated by the extreme insolubility in aqueous media. We applicated a single dose of cannabis resin (containing 10 mg/kg THC, 9 mg/kg cannabinol, 20 mg/kg canna-

bidiol, 1 mg/kg unknown substances) i.p. in different vehicles to male rats in order to get some information about the influence of these agents. Onset of hypothermia was rapid in propylene glycol (30 Vol. %) and polyethylene glycol (60 Vol. %) and somewhat delayed in cremophor (10 %). No decrease in body temperature was observed after cannabis in rape oil. Cannabis in rape oil enhanced hexobarbitone sleeping time up to four days following a single injection. Using the other vehicles the effect lasted two days at most. Similar the route of administration is of interest. Experiments are in progress to determine pharmacological response by different routes.

Interaction of cannabis with other drugs seems to be important in view of polytoxicomania. We studied the effect of cannabis given one hour prior i.p. on the LD_{50} of various agents (see table). LD_{50} values are estimations by the method of Speerman and Kärber. Cannabis enhances the toxicity of morphine and pentobarbitone, decreases the toxicity of *d*-amphetamine sulfate. Almost no effect can be detected in ethanol LD_{50}. The effect on amphetamine toxicity is less pronounced after 8 day-pretreatment with cannabis.

	Control LD_{50} 1 h after 10 % cremophor 0.2 ml/100 g	LD_{50} 1 h after i.p. application of cannabis extract (25 % Δ^9-THC) 40 mg/kg = 10 mg/kg THC	80 mg/kg = 20 mg/kg THC
d-Amphetamine sulfate, s.c.	17 mg/kg	54 mg/kg	66 mg/kg
Pentobarbitone, s.c.	108 mg/kg	73 mg/kg	64 mg/kg
Morphine sulfate, s.c.	159 mg/kg	94 mg/kg	67 mg/kg
Ethanol, p.o.	10.9 g/kg	8.4 g/kg	8.6 g/kg

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Effects of some cannabinols on biosynthesis of brain amines and on pituitary response in the rat

Δ^9-Tetrahydrocannabinol (Δ^9-THC), Δ^8-tetrahydrocannabinol (Δ^8-THC) and dimethylheptyltetrahydrocannabinol (DMHP) were injected i.p. into male albino rats (190—220 g body weight) as suspensions in physiological saline containing 6.5 % Tween 80. The effects of single injections (10—30 mg/kg) on catecholamine biosynthesis and on serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations were studied in the