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Effects of (—)Δ^9-Trans-Tetrahydrocannabinol in Man

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It has long been thought that tetrahydrocannabinols are responsible for most of the psychological effects of hashish and marihuana (LOEWE, 1944 and 1950). WOLLNER, MATCHETT and LOEWE (1942) isolated a physiologically active fraction by distillation but the exact structure of this material could not be established. Advances in the chemistry of the tetrahydrocannabinols have now established that (—)-Δ^9-*trans*-tetrahydrocannabinol[1] (GAONI MECHOULAM, 1964) and *l*-Δ^8-*trans*-tetrahydrocannabinol[2] (HIVELY, *et al.*, 1966) occur in hashish. It is the purpose of this communication to report that (—)-Δ^9-*trans*-tetrahydrocannabinol (hereafter termed Δ^9-THC) which was free of the Δ-8 isomer has marihuana-like activity in man. Although tetrahydrocannabinols have been tested in humans in the past, so far as the authors know, this is the first demonstration of hashish-like activity of a tetrahydrocannabinol of *known* chemical structure in man. In addition, we wish to report that the relative potencies of tetrahydrocannabinols can be assayed quantitatively in man and that Δ^9-THC is more potent when smoked than when taken orally.

Δ^9-THC was isolated from hashish by countercurrent distribution as previously described (KORTE, HAAG and CLAUSSEN, 1965). Its structure and purity was proved by chemical measurements and by infrared and nuclear magnetic resonance spectroscopy.

Δ^9-THC (and other materials) was then studied in man at the Addiction Research Center. Subjects were healthy former opiate addicts who were serving sentences for violations of the United States Narcotic Laws. All had been abstinent from all drugs for months before serving

[1] This compound was also designated Δ^1-3,4-*trans*-tetrahydrocannabinol by GAONI and MECHOULAM (1964).

[2] Also termed *trans*-Δ^6-tetrahydrocannabinol by HIVELY *et al.* (1966).

as subjects in the experiments. All these patients had used marihuana by smoking and were familiar with the effects of that crude drug. Δ^9-THC was dissolved in 95% ethanol in appropriate concentrations. When the drug was given orally, the appropriate dose was diluted with 15 cc of cherry syrup. No more than 4 ml of alcohol was ingested. Cherry syrup containing an equivalent amount of alcohol served as a "placebo", When the drug was to be smoked it was deposited in the middle third of a tobacco cigarette and the cigarette dried overnight. Placebo cigarettes prepared by injecting an identical amount of alcohol into the cigarettes. Cigarettes were smoked by deep inhalation in 15 min or less. More than 40 different subjects received Δ^9-THC in a number of experiments. Originally the subjects were not told that the drug was expected to have marihuana-like effects but they soon identified it as being similar to marihuana. Subjects participated in experiments no oftener than once weekly in order to minimize the chances of development of any possible tolerance.

Patients were housed in a special ward so the experimental environment was as constant as possible. Observations were made at appropriate intervals twice before and several times after ingestion or smoking of the drugs. Observations included determinations of resting pulse rate, systolic and diastolic blood pressure, respiratory rate, pupillary size and threshold for elicitation of the knee jerks after the patients had rested 10 min in bed. Subjective psychological effects were studied by means of a special questionnaire administered before and at appropriate intervals after the drug.

In an assay experiment comparing the relative potencies of Δ^9-THC orally and by smoking and by oral ingestion, the same 10 subjects received in randomized order a placebo and the following doses of Δ^9-THC: 120 mcg/kg orally, 480 mcg/kg orally, 50 mcg/kg by smoking, and 200 mcg/kg by smoking.

Data were analyzed by the paired t-test or by analysis of variance for both peak effects and for areas under time action curves. Subjective responses were assessed by counting the number of questions answered positively that were not answered positively before the drug at each observation time after the drug. The total number of positive responses over the entire observation period were also calculated.

Effects of Δ^9-THC

Regardless of the route of administration, Δ^9-THC caused no significant changes in pupillary size, respiratory rate, systolic and diastolic blood pressures or threshold for elicitation of the knee jerk. Pulse rates at rest were consistently elevated. Patients developed injection of the conjunctivae after larger doses. Effects of doses of 120 mcg/kg orally

or 50 mcg/kg or smoking were recognized by all patients as being similar to those of marihuana. In addition patients frequently stated that the effects of the drug were "something" like those of LSD-25 or cocaine. Changes in mood, usually euphoric, were consistently reported. Other changes included alterations in sense of time and in visual and auditory perception (usually described or keener). With doses of 300—480 mcg/kg orally or 200—250 mcg/kg by smoking, marked distortion in visual and auditory perception, depersonalization, derealization and hallucinations, both auditory and optical occurred in most patients. Δ^9-THC, therefore, is a psychotomimetic drug and its psychotomimetic effects are dependent on dose. In occasional individuals, psychotic episodes may occur with low doses ("idiosyncratic" reactions). Under the conditions listed above, the reaction to the same dose of Δ^9-THC is reproducible in the same individuals on different occasions. In 15 patients the mean difference in the maximal increase in peak pulse rate between the first and second trials of the same dose of tetrahydrocannabiol was -6.6 beats per min with a standard error of ± 3.75 ($t = 2.25$; $p > .05$). The mean difference in the total number of positive responses on the questionnaire was -3.26 ± 3.77 ($t = 1.7$; $p > .05$). These differences are not significant statistically.

In the assay experiment, potency of Δ^9-THC after smoking calculated from changes in the peak pulse rate was 2.6 times that after oral ingestion (95% confidence limits, 1.3—5.1). In the case of responses on the questionnaire, Δ^9-THC was 3.0 times as potent when smoked as when taken orally (95% confidence limits, 1.8—5.1). Analysis of variance showed that the data in this experiment met requirements for parallelism and regression for a valid assay. The variance between subjects was significant, pointing up the importance of using each subject as his own control in an assay.

The reasons for the greater potency of Δ^9-THC by smoking are unknown but might include more rapid absorption, less detoxification because of not passing directly through the liver via the portal veins and possible conversion of Δ^9-THC to a more active substance by heat. Taylor *et al.* (1966) have reported that Δ^9-THC is converted to the Δ^8 isomer by heat. On the other hand, Claussen and Korte (1967) studied the possible conversion of Δ^9-THC to Δ^8-THC when cannabis was smoked in a machine. No evidence of such conversion was found. Additional work is necessary.

The data referred to above show that it is possible to assay the relative potencies of substances causing marihuana-like effects in man. The fact that the same relative potencies were obtained using pulse rates (an "objective" measure) and responses on a questionnaire (a "subjective" measure) lends confidence to the validity of the assay technic.

In addition to quantitative information, qualitative information can be obtained both from the patient's statements as to similarity of subjective effects and from the pattern of the symptoms reported. The chief advantage of assays in humans is, of course, that the subjective effects of such drugs can be assessed only in man. Since the mental effects of substances found in hashish and marihuana are of paramount interest, assay of these materials in man is, sense, more specific than the dog ataxia test (WALTON, 1938; LOEWE, 1944), and the corneal areflexia test of GAYER (1928).

Tetrahydrocannabinol synthesized according to the method of ADAMS and BAKER (1940) yields a mixture of at least two isomers which have been obtained in pure form (KORTE and SIEPER, 1964; CLAUSSEN and KORTE, 1966). A sample of the $\Delta^{6a.\,10a}$ isomer, which constitutes the largest portion of this material, produced no effects under our condition in doses ranging up to 400 mcg/kg by smoking.

Synthetic cannabidiol dimethyl ether (KORTE, DLUGOSCH and CLAUSSEN, 1966) and cannabichromene (CLAUSSEN *et al.*, 1966; GAONI and MECHOULAM, 1966) also produced no effects in doses ranging up to 2.5 mg/kg orally. It is interesting that MECHOULAM and GAONI (1966) found cannabichromene active in the dog ataxia assay.

In patients tolerant to 1.5 mcg/kg of LSD-25, no cross tolerance to Δ^9-THC (250 mcg/kg by smoking) was observed in an experiment using 10 patients. This indicates that, although both Δ^9-THC and LSD-25 are psychotomimetics, they probably act by different mechanisms. In addition the mental effects of the two drugs are somewhat different.

Complete details will be published later.

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