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Delta-9-Tetrahydrocannabinol: Metabolism and Disposition in Long-Term Marihuana Smokers

Abstract. *Radioactively labeled delta-9-tetrahydrocannabinol (Δ^9THC) administered intravenously to chronic marihuana smokers disappeared from the blood plasma with a half-life of 28 hours as compared to 57 hours for nonusers of marihuana. Apparent volumes of distribution did not significantly differ between the two groups. Within 10 minutes after administration of Δ^9THC, 11-hydroxy-Δ^9THC is present in the plasma of nonusers and chronic users. This metabolite was also present in urine and feces of nonusers and long-term marihuana smokers. In addition, polar metabolites were excreted in urine and feces of both groups for more than 1 week.*

Previous studies (*1*) have shown that ^{14}C-labeled Δ^9-tetrahydrocannabinol (Δ^9THC) persists in the plasma of human subjects for several days and is excreted in urine and feces for more than 8 days. The subjects in those experiments were normal volunteers who had no previous exposure to *Cannabis* preparations. We now report the effects of long-term marihuana smoking on the disposition and metabolism of [^{14}C]Δ^9THC.

Five male subjects (*2*), ranging in age from 21 to 27 years old, who professed smoking marihuana daily for a minimum of 1 year immediately before this investigation were used. The subjects appeared to be reliable and conscientious. Three were upper-level college students, and the other two were college graduates who were gainfully employed. None of the subjects used any other drugs or medications. The subjects were evaluated medically and psychiatrically before being considered for this study. They smoked marihuana as usual the evening before the study but did not during the study. On the morning of admission, 0.5 mg of [^{14}C]Δ^9THC was administered intravenously (*3*) and blood samples were drawn at intervals thereafter. Urine and feces were collected for 7 days after injection of the radioactive compound.

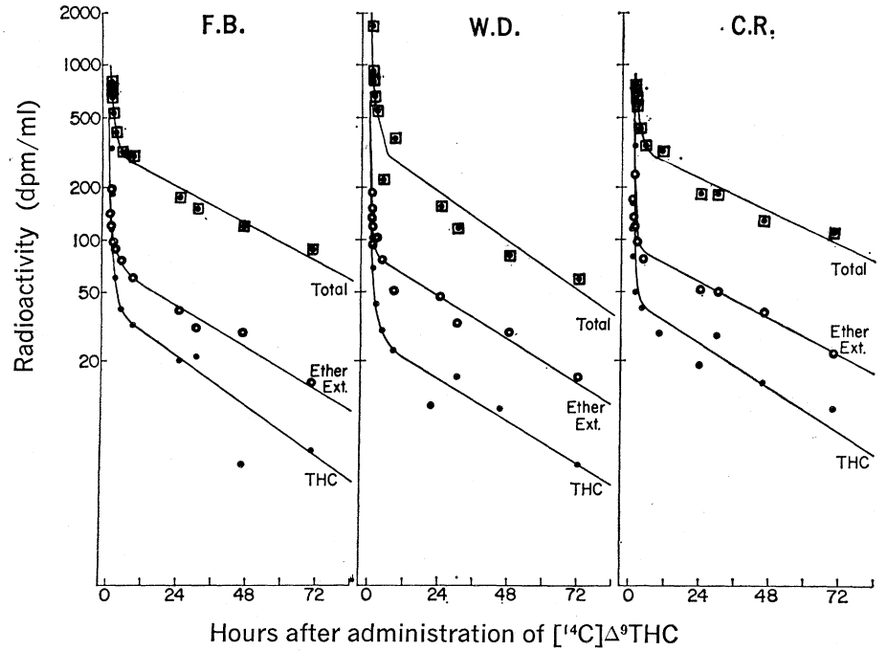

Fig. 1. Plasma levels of Δ^9THC, total radioactivity, and ether-extractable radioactivity after the intravenous injection of [^{14}C]Δ^9THC. Three long-term *Cannabis* users received 0.5 mg of Δ^9THC in 1 ml of ethanol. The radioactive solution was injected during an interval of 1 minute into the tubing of a rapidly flowing intravenous infusion of 5 percent dextrose in water. At intervals, blood samples were drawn from the opposite arm into syringes containing heparin. Plasma was assayed for Δ^9THC, total radioactivity, and ether-extractable radioactivity by liquid-scintillation spectrometry.

Intravenous administration of Δ^9THC (0.5 mg) to nonsmokers was devoid of any pharmacological effect. In contrast and admittedly not under well-controlled experimental conditions (since no placebos were administered) all of the long-term marihuana smokers (although told that a nonpharmacological dose of THC was to be given) reported effects that lasted for as long as 90 minutes. One subject stated that he "felt a familiar feeling" reminiscent of the effects of marihuana. The dose of Δ^9THC given to these subjects was in the range of 5 to 7 μg/kg. Kiplinger *et al.* (*4*) have shown that long-term marihuana smokers are able to obtain pharmacologic effects from smoking a marihuana cigarette which delivers a dose of Δ^9THC in the order of 6.25 μg/kg.

Unchanged Δ^9THC was determined in blood plasma by extraction at *p*H 7.4 with four volumes of heptane containing 1.5 percent isoamyl alcohol (*1*). The residual plasma was then extracted with ether to assay less polar metabolites. The more polar metabolites remained in the aqueous phase. The radioactivity was determined by liquid scintillation spectrometry and corrected for quenching by use of internal standards. The recovery of Δ^9THC added directly to plasma or urine was 95 ± 5 percent.

As in the previous study (*1*), the disappearance of Δ^9THC from plasma appeared to occur in at least two phases (Fig. 1). The initial phase was rapid and was followed by a slower phase, which had a half-life ($t_{1/2}$) of 28 hours (Fig. 1 and Table 1). This second phase was considerably more rapid than that found in nonsmokers ($t_{1/2}$ = 57 hours). Chromatography of the apparent Δ^9THC in the heptane extract of plasma obtained from chronic users had the same R_F as authentic Δ^9THC (*5*). In addition, small amounts of 11-OH-tetrahydrocannabinol were present

in the plasma at times when the pharmacologic effects of marihuana had been reported to be manifest (*6*). Total radioactivity and ether-extractable radioactivity had rates of disappearance from plasma similar to those seen for the Δ^9THC. Considerable quantities of metabolites of Δ^9THC (including 11-OH-tetrahydrocannabinol) were present as soon as 10 minutes after drug administration.

Radioactivity in the urines of smokers differed significantly from that of nonsmokers. In the long-term users of marihuana, more than 30 percent of the administered radioactivity was excreted in the urine during the first week (Fig. 2), in contrast to an average of about 22 percent in nonusers. In both groups most of the administered radioactivity was excreted during the first 2 days. About 40 percent of the radioactivity was recovered from the feces of these long-term users during the 7-day collection period. Although there was a significant difference between the urinary excretion of users and of nonusers, the cumulative excretion of total radioactivity (urine and feces) did not differ significantly (Fig. 2).

The apparent volumes of tissue distribution for the users and nonusers were calculated in an attempt to explain the increased rate of Δ^9THC decline in the plasma of chronic marihuana users (Table 1). The fact that no significant difference was found indicated a similar distribution of the radioactive Δ^9THC in both groups of subjects. The relatively high volume of distribution for Δ^9THC suggested that of a drug which is bound in tissues (extravascular sequestration) (*7*). This is consistent with the data on the disposition of Δ^9THC obtained in animals (*8*). It seems likely that the difference in the blood plasma half-lives between the two groups may be the result of an increased rate of metabolism of the Δ^9THC in the long-term marihuana users rather than a difference in its distribution in the tissues. Repeated administration of certain drugs enhances their metabolism in man and animals (*9*). In the case of Δ^9THC this would be of considerable importance since one of the metabolites (11-OH-tetrahydrocannabinol) has been reported to be at least as active as, or more active than, the parent drug (*10*). 11-OH-Tetrahydrocannabinol accounts for nearly 25 percent of the injected Δ^9THC; abotu 20 percent of it appears in the feces. Since this compound is probably further metabolized, this represents a minimum value.

Table 1. Fate of Δ^9THC and apparent volume of distribution (AVD) in long-term users and nonusers of *Cannabis*.

Patient	Half-life of Δ^9THC in plasma (hours)			AVD Δ^9THC (liters)
	Total	Ether	Δ^9THC	
	Nonusers (1)			
R.L.	78	67	49	498
S.M.	82	53	66	516
W.R.	42	42	52	439
R.N.	74	51	60	1179*
$\bar{X}$	69 ± 9†	53 ± 5†	57 ± 4‡	658 ± 174
	Chronic users			
W.D.	26	28	29	742
F.B.	34	30	24	498
C.R.	40	34	29	453
R.R.	25	26	29	474
L.J.	25	30	27	818
$\bar{X}$	30 ± 3†	30 ± 1†	28 ± 1‡	597 ± 76

*Patient not included in (*1*). †$P < .01$ (significant). ‡$P < .001$ (highly significant).

Negligible amounts of unchanged Δ^9THC were found in the urines from both groups, indicating complete transformation in the body. Comparison of the urinary and fecal metabolites during the first 2 days did not reveal any qualitative differences in the metabolism of the Δ^9THC between the two groups. The major urinary metabolites had the characteristics of more polar compounds.

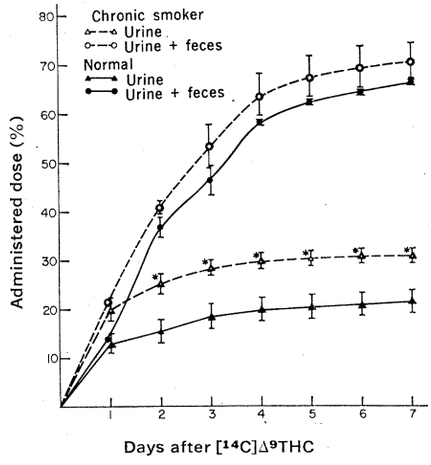

Fig. 2. Comparison of the cumulative excretion of radioactivity in chronic marihuana users and nonusers after intravenous injection of [^{14}C]Δ^9THC. Three chronic users and three nonusers were studied. Urine and feces were collected for at least 7 days after the intravenous administration of Δ^9THC. Urine and feces were frozen until analyzed. The feces were suspended in three volumes of methanol, and the suspension was shaken vigorously for 10 minutes on a mechanical shaker. The material was centrifuged, and a portion of the methanol extract was assayed for total radioactivity. Urine was assayed directly for total radioactivity by liquid-scintillation spectrometry. Radioactivity in the feces is represented by the difference between total radioactivity and urinary radioactivity. Significant differences are indicated (*).

The "reverse tolerance" observed in chronic users of marihuana could be the consequence of induction of enzymes which convert Δ^9THC to a more active or more stable metabolite. It could also be due to cumulative effects of repeated administration, to increased receptor sensitivity to Δ^9THC or its metabolites, or to a learned and heightened response to the effects of Δ^9THC.

LOUIS LEMBERGER
Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014, and *Pharmacology-Toxicology Program, National Institute of General Medical Sciences, Bethesda*
NORMAN R. TAMARKIN
Division of Drug Treatment and Research, Veterans Administration Hospital, Washington, D.C. 20422
JULIUS AXELROD
IRWIN J. KOPIN
Laboratory of Clinical Science, National Institute of Mental Health

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2. Subjects, as they became available, were admitted to the Clinical Center, National Institutes of Health, on the morning prior to the infusion of the drug and were discharged at the termination of the study.
3. The [^{14}C]Δ^9THC was obtained from the Research Triangle Institute (Research Triangle Park, North Carolina) (sample No. JWW-IV-17; specific activity 17.5 mc/mg, 5.5 mc/mmole). Purity was shown to be greater than 98 percent by chromatography. The sterile and pyrogen-free radioactive material in ethanol was prepared under sterile conditions in single-dose vials by the National Institutes of Health Radiopharmacy.
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5. Samples of plasma from the first hour, from the remainder of day 1, and from days 2 and 3 were pooled and extracted with four volumes of heptane containing 1.5 percent alcohol. The extract was evaporated to dryness at reduced pressure, redissolved in a small volume of ethanol, applied to an Eastman silica-gel chromatogram sheet and developed in a hexane-acetone (3 : 1) system. Authentic Δ^9THC and 11-OH-Δ^8THC were cochromatographed with the heptane extract. The sheet was cut into 1-cm strips, from the origin to the solvent front, and placed in vials containing scintillation solution; radioactivity was determined by liquid-scintillation spectrometry.
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How Does the Striate Cortex Begin the Reconstruction of the Visual World?

Abstract. *The striate cortex transforms the topographic representation of visual space in the lateral geniculate body into a Fourier transform or frequency representation at the complex cell level via the intermediary simple cell stage of "strip integration." Each of these three stages contains essentially the same amount of information, which expresses a conservation of information principle; however, the form of the information is changed. In the transform domain, invariant descriptions of visual objects can be derived to serve as the basic sets required for pattern recognition and memory. We believe that our experimental and theoretical findings are fundamental for understanding the functional organization of the striate cortex.*

Thirty years ago Lashley (*1*) considered the problem of how we see an object as the same object regardless of its position and apparent size. He considered the problem of "stimulus equivalence" as the most elementary problem of cerebral organization and doubted that any progress toward a genuine understanding of nervous integration would be achieved until this problem was solved.

In searching for some invariant description of a visual object, the physiologist is confronted by neurons all along the visual pathways which respond to many variations in stimulus parameters by increases or decreases in firing rate. Kuffler (*2*) and others (*3*) have found that the receptive fields of retinal ganglion cells are organized in a concentric manner; "on" center cells are excited as a function of the size, position, and relative brightness of a test spot within a circular "center" and are inhibited by stimulation over a concentric "surround." Cells with "off" centers and "on" surrounds are oppositely affected. In the lateral geniculate body the receptive field organizations are also concentric, but the topographic representation of visual space becomes more discrete (*4*).

Hubel and Wiesel have shown that layers IIIb and IV of the striate cortex of cats (*5, 6*) and monkeys (*7*) contain sets of "simple" cells that receive information via the geniculo-calcarine radiations and are either excited or inhibited by slits of light selectively oriented and placed in the visual field. Within the cortex each region of visual space is " . . . represented over and over again in column after column, first for one receptive field organization and then another" (*6*). It has not been known what particular advantages are gained by such geometrical and angular organization of the receptive fields, nor how the brain processes the received data to provide invariant descriptions of visual objects at any moment in time.

We carried out experiments in an attempt to find any invariant properties of simple and complex cell responses (in terms of cell-firing rate and response latency) as we varied such stimulus parameters as size, position, and relative brightness. We recorded from 19 cats, each initially anesthetized with sodium thiopental (30 mg/kg, intraperitoneally) with supplemental small doses of Brevital as required. Significant eye movements were prevented by slow intravenous drip of gallamine triethiodide and succinylcholine chloride (*8*). Respiration was maintained with a Harvard pump. Atropine sulfate (4 percent) was used for mydriasis and cycloplegia. Phenylephrine HCl (10 percent) enabled retraction of the nictitating membrane. Corneal contact lenses were selected with the aid of a streak retinoscope to focus each eye at 1.5 m, where a blackboard holding a mat white poster board was placed. A 4-mm artificial pupil was placed before each eye to limit light transmission to the center of the lens.

Light stimuli of various sizes and shapes were projected onto the board from a Leitz Prado universal projector with the aid of a rotatable slit device (*5*). A Compur 3 electronic shutter permitted delivery of rectangular pulses of light for set durations, and the diaphragm settings were changed to produce light stimuli of variable intensity. Background and stimulus light intensities were measured by using an SEI exposure meter. Tungsten microelectrodes were used for extracellular recording (*5*). Recordings were taken from the right striate cortex, and stimuli were presented to the left eye with the right eye covered. In presenting stimuli to one eye, we have reduced the general problem of binocular vision to that of resolving a two-dimensional brightness distribution. A Synax histogram computer 100 (Synax Biomedical) was used to construct poststimulus histograms either on-line or from tape-recorded data.

After each receptive field was mapped, ten stimuli were presented at 5- to 10-second intervals for a number of stimulus sizes and positions, and at each of a number of intensity steps covering a range of 2 logarithmic units above background. For any fixed size of spot or slit within the excitatory field center of simple cells, or in any position across the receptive field of complex cells, the neuronal firing rate was found to increase linearly with the logarithm of the relative light intensity (Fig. 1A). Complex cells respond maximally to slits of a specified width and orientation equally well in all positions across the receptive field (*6*). Elongation of a spot or slit length within the field center of a simple cell or along the preferred direction of a complex cell also caused increases in firing rate, as expected (*6*). However, because of the dual dependence of firing rate upon both relative brightness and area, the data from a single simple cell cannot provide a unique representation of either size or brightness.

Further processing must be carried out until a "reconstruction" (by which we mean the derivation of an invariant description of a visual object) has been achieved in some set of neurons. This information may then serve as a unique determinant for further concept elaboration, comparison with the memory, or other behavior. The data set available at the simple cell stage (Fig. 1B) essentially (*9*) corresponds to data sets