Distribution of tritiated-1-Δ^9-tetrahydrocannabinol in rat tissues after inhalation

Recent controlled studies of marihuana administration to man indicate several unusual pharmacological actions, including a change from mild sedative and euphoric action at low dose, to hallucinogenic effect at high dose; a greater potency when administered by inhalation than by ingestion; and reverse tolerance in that habitual users experience a greater effect per unit dose than naive subjects (Isabell, Gorodetzsky & others, 1967; Hollister, Richards & Gillespie, 1968; Weil, Zinberg & Nelson, 1968).

We have now examined the biological distribution and retention of ^{3}H-Δ-9-tetrahydrocannabinol (Δ^9-THC) administered by inhalation.

^{3}H-Δ^9-THC (13·5 mg, 3370 μCi) (Idänpään-Heikkilä & others, 1969) in light petroleum (30–60°) was injected into a half length cigarette which was then mounted on wire at the bottom of a large vaccuum desiccator. The cigarette was ignited, the desiccator plate was replaced, followed by male Sprague-Dawley rats, 200–250 g, and the desiccator top. After a 15 min exposure to the smoke the animals were transferred into housing cages and decapitated after a 20 min, 8, 24, 72 h, or 7 day interval. All tissues were homogenized in water and 0·1 ml of the homogenate from each tissue in a 10 ml medium containing POP and POPOP was assayed for tritium with a liquid scintillation spectrometer. All samples were corrected for tritiated water, if formed *in vivo* from the ^{3}H-Δ^9-THC, by allowing a duplicate sample to dry in a counting vial before being subjected to liquid scintillation assay. The tissue distribution of ^{3}H-Δ^9-THC in rats at various time intervals is shown in Table 1.

Table 1. *Distribution of radioactivity in rat tissues following inhalation of* ^{3}H-Δ^9-THC

Tissue	Ratio of radioactivy (μCi/g) in each tissue to that in brain				
	20 min	8 h	24 h	72 h	7 days
Brain	1·0	1·0	1·0	1·0	1·0
Lungs	8·1	5·3	3·9	1·7	1·0
Liver	1·9	1·4	1·2	1·3	1·0
Kidneys	2·4	1·3	1·2	1·7	0·7
Adrenals	2·1	0·5	0·4	0·3	0·7
Spleen	0·9	0·8	0·7	1·0	0·7
Testis	1·9	0·8	0·8	1·0	1·0
Muscle	2·0	0·3	0·3	0·3	0·7
Fat	1·3	0·5	0·4	0·3	0·7
Salivary Glands	5·8	—*	—*	—*	0·7
Urine†	3·2	3·1	1·3	0·3	0·7
Jejunum	5·6	1·7	1·3	1·3	0·3
Ileum	0·9	3·2	2·0	1·7	0·7
Colon	0·6	4·2	3·8	2·0	1·0

* Samples not taken.
† Sample obtained from the bladder.

The results are expressed as the ratio of radioactivity (μCi/g) in each tissue to that in the brain. As early as 20 min a high accumulation of Δ^9-THC or metabolites, or both, were found in the lungs, salivary glands, jejunum, urine, kidneys, adrenals, muscle, liver, and testis in decreasing order of radioactivity. The extremely high concentration in the lungs was most likely due to the site of administration of the compound. However, the retention of Δ^9-THC in the lungs was obvious, as the radioactivity remained high at 24 h. During the interval between 20 min and 8 h, concentrations in the liver decreased to half, while levels in the brain and kidneys

declined more slowly. Subsequently, tissue concentrations in the brain, liver, and kidneys were maintained constant throughout a period from 8 to 72 h. On the 7th day, an equally high concentration was still found in the brain, lungs, and liver. A high accumulation in the jejunum at 20 min indicated a possible role for biliary excretion and reabsorption of Δ^9-THC or metabolite, or both. Increase of concentrations in the ileum and colon at the later times coincided with the findings of Agurell, Nilsson & others (1969) that the major route of elimination of Δ^9-THC in the body is in the faeces.

The concentrations of radioactivity peaked and fell in all tissues except brain. The decline from the initial brain level at 20 min (0·041 μCi/g) was less than 25% after seven days (0·032 μCi/g). Possibly enough Δ^9-THC or an active metabolite is retained in the brain to account for increased effect per unit dose when smoked habitually.

Unchanged Δ^9-THC (30 to 40% of the total radioactivity), was identified in the lung at 20 min by thin-layer chromatography (TLC) (n-hexane: diethyl ether, 4:1, Silica Gel G) and by a positive colour reaction using *o*-dianisidinetetrazolium chloride spray. Unchanged Δ^9-THC was estimated to be 10 to 20% at 8 and 24 h. The small amount of physical material in the other tissues at all time intervals limited analysis to TLC utilizing a carrier. (Standard Δ^9-THC (red oil) provided by Dr. Sciliagno of the National Institute of Mental Health and synthetic Δ^9-THC provided by Dr. Hines of Hoffman-LaRoche were used as carriers.) Approximately 40% of the radioactivity in the brain at 20 min represented Δ^9-THC; this value had only decreased to 30% at 24 h. In this study, we were unable to further characterize the presence of Δ^9-THC by gas chromatography because of the interference of impurities extracted from the tissues.

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Texas Research Institute of Mental Sciences, Houston, Texas 77025, *U.S.A.*

BENG T. HO
G. EDWARD FRITCHIE
PATRICIA M. KRALIK
LEO F. ENGLERT
WILLIAM M. MCISAAC

Department of Pharmacology, University of Helsinki, Siltavuorenpenger 10, *Helsinki* 17, *Finland.*

JUHANA IDÄNPÄÄN-HEIKKILÄ

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