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METABOLIC DISPOSITION OF Δ⁸-TETRAHYDROCANNABINOL AND ITS ACTIVE METABOLITES, 11-HYDROXY-Δ⁸-TETRAHYDROCANNABINOL AND 11-OXO-Δ⁸-TETRAHYDROCANNABINOL, IN MICE

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ABSTRACT:

Metabolic disposition of Δ⁸-tetrahydrocannabinol (Δ⁸-THC), 11-hydroxy-Δ⁸-THC (11-OH-Δ⁸-THC), and 11-oxo-Δ⁸-THC was studied in mouse blood, liver, and brain. After administration of these cannabinoids at a dose of 10 mg/kg iv, the concentration in blood declined biphasically. The biological half-lives of the slower phases were 32, 12, and 6 min, respectively, for Δ⁸-THC, 11-OH-Δ⁸-THC, and 11-oxo-Δ⁸-THC. 11-OH- and 11-oxo-Δ⁸-THC were also eliminated faster from brain than is Δ⁸-THC. The peak levels of 11-OH- and 11-oxo-Δ⁸-THC in brain were, however, higher (10.64 and 4.25 μg/g, respectively) than that of Δ⁸-THC (3.48 μg/g) at 0.5 min after the iv injection (10 mg/kg). These results indicate that 11-OH- and 11-oxo-Δ⁸-THC are distributed more readily from blood to brain in mice than is Δ⁸-THC, and explain the greater pharmacological activity of these metabolites, as reported previously. It was also interesting to note that a much higher level of 11-OH-Δ⁸-THC (3.27 μg/g) was found in brain than in liver (0.74 μg/g) and blood (0.29 μg/ml) at 15 min after the injection of 11-oxo-Δ⁸-THC (10 mg/kg, iv). In this case the levels of 11-OH-Δ⁸-THC were always higher than those of 11-oxo-Δ⁸-THC. The results suggest that 11-OH-Δ⁸-THC may play an important role in the pharmacological effects of 11-oxo-Δ⁸-THC. In additional experiments, SKF 525-A (25 mg/kg, ip) inhibited the metabolism of 11-OH-Δ⁸-THC to 11-oxo-Δ⁸-THC, supporting the previous suggestion that this oxidation, as well as the 11-hydroxylation of Δ⁸-THC, is mediated by the microsomal mono-oxygenase system.

The metabolism of Δ⁸-THC[1] or Δ⁹-THC, the active component of marihuana, has been investigated by a number of groups (1–5). They suggested that the oxidation at 11-position (fig. 1) is very important, because it is a major metabolic pathway of THC in mammals (6–10). The 11-hydroxy metabolite was first identified as a major metabolite of THC, and the pharmacological activity of this metabolite was then demonstrated by several workers (11–16). Recently, we also reported that the pharmacological effects of 11-OH- and 11-oxo-Δ⁸-THC were greater in potency and more rapid in onset than those of Δ⁸-THC (17, 18). These results suggest that the metabolites may be more active than the parent compound. In connection with these pharmacological findings, Schou *et al.* (19) reported that the penetration of 11-OH-Δ⁹-THC into brain was faster than that of Δ⁹-THC after intracarotid injection in rats. Perez-Reyes *et al.* (20) also found that the brain levels of 11-OH-Δ⁹-THC were four times higher than those of Δ⁹-THC in mice. On the contrary, the duration of effect of 11-OH-Δ⁹-THC was shorter than that of Δ⁹-THC in man, although both compounds were equally potent (15). These results suggest that 11-OH-Δ⁹-THC is metabolized or eliminated from the central nervous system more quickly than Δ⁹-THC.

It is thus of interest to study the penetration and retention in brain of mice of those active metabolites in comparison with those of Δ⁸-THC for understanding of the pharmacological activity of Δ⁸-THC. In the present paper, we wish to report the detailed metabolic disposition of Δ⁸-THC, 11-OH-Δ⁸-THC, 11-oxo-Δ⁸-THC, and Δ⁸-THC-11-oic acid in mouse blood, brain, and liver, in order to understand the pharmacological effect of Δ⁸-THC. Furthermore, the effect of SKF 525-A on the metabolism and distribution of these active intermediates was studied.

[1]Abbreviations used are: THC, tetrahydrocannabinol; 11-OH-THC, 11-hydroxytetrahydrocannabinol; ECD, electron-capture detector.

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Materials and Methods

Male ddN mice weighing 20–25 g were used throughout the experiments. The animals were allowed to take food and water *ad lib.*, and room temperature was set at 22–24°C. Δ⁸-THC, 11-OH-Δ⁸-THC, 11-oxo-Δ⁸-THC, and Δ⁸-THC-11-oic acid were prepared by the methods reported previously (17). Each of the cannabinoids except for Δ⁸-THC-11-oic acid was suspended in saline containing 1% Tween 80 and injected iv into mice (1, 5, and 10 mg/kg) through the tail vein, over a period of 3 sec. Each group consisted of four mice and the injection volume was 0.1 ml/10 g of body weight. Cannabinoids were injected between 9 and 12 a.m. in all experiments. SKF 525-A, a generous gift of Smith Kline & French Labs. (Philadelphia, Pa.), was administered at a dose of 25 mg/kg ip 30 min before the injection of cannabinoids. Mice were killed by cervical fracture at 0.5, 1, 5, 15, 30, and 60 min after the injection. Blood was quickly collected by cardiac puncture and brain and liver were then removed. Δ⁸-THC and its metabolites were quantitated by ECD-gas chromatography, after extraction with acetone, purification by thin-layer chromatography, and conversion to the corresponding heptafluorobutyrates as described previously (21). Gas chromatograms were recorded with a Shimadzu model GC-6A gas chromatograph equipped with a ^{63}Ni-ECD at 195°C. A glass column, 1.0 m × 3 mm, packed with 1% XE-60 on Chromosorb W, 60–80 mesh, was used. Nitrogen was used as the carrier gas with a flow rate of 60 ml/min. The retention times of the heptafluorobutyrates of Δ⁸-THC, 11-OH-Δ⁸-THC, 11-oxo-Δ⁸-THC, and Δ⁸-THC-11-oic acid methyl ester were 2.3, 4.2, 5.8, and 6.8 min, respectively, under the conditions described above.

Results

Elimination of Δ⁸-THC, 11-OH-Δ⁸-THC, and 11-Oxo-Δ⁸-THC from Blood. After iv injection of Δ⁸-THC, 11-OH-Δ⁸-THC, or 11-oxo-Δ⁸-THC at doses of 10 mg/kg, the concentration of these

compounds in blood declined rapidly within the first few minutes and slowly thereafter (fig. 2). The half-life of the rapid phase was about 0.5 min for all these cannabinoids, whereas those of the slow phase were 32, 12, and 6 min, respectively, for Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC. The result indicates that the elimination rate from blood of mice decreases in the order 11-oxo-Δ^8-THC > 11-OH-Δ^8-THC > Δ^8-THC.

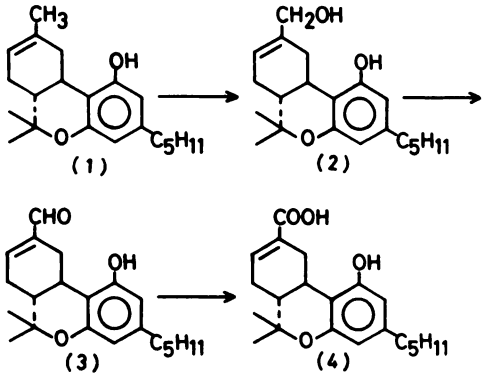

FIG. 1. *Metabolic pathway of Δ^8-THC at the 11-position.*

(*1*), Δ^8-THC; (*2*), 11-OH-Δ^8-THC; (*3*), 11-oxo-Δ^8-THC; (*4*), Δ^8-THC-11-oic acid.

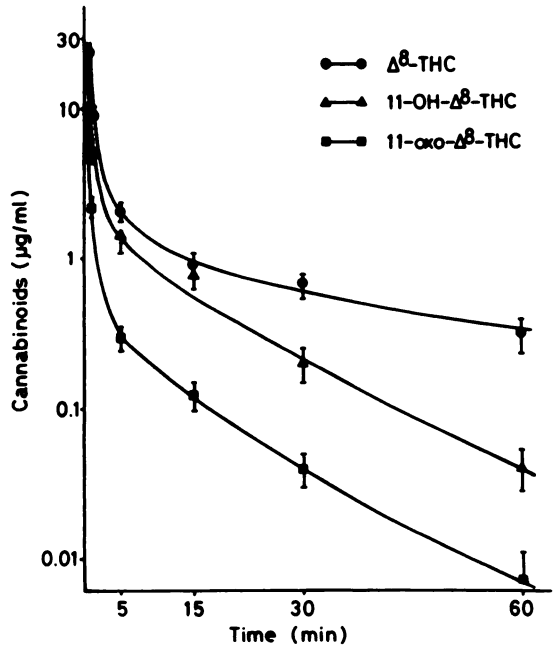

FIG. 2. *Elimination of Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC from blood of mice following iv administration.*

Each point represents the mean ± SE for four mice.

Penetration and Retention of Δ^8-THC, 11-OH-Δ^8-THC, and 11-Oxo-Δ^8-THC in Brain. In the same group of animals used in the above experiments, the contents of unchanged cannabinoids in the brain were also determined at the same time intervals after the injections. As indicated in table 1, Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC penetrated the brain rapidly, and their peak levels were attained within 0.5 min after the iv injection. It is very interesting to note that the brain levels of 11-OH-Δ^8-THC were three times higher than those of Δ^8-THC, whereas the blood levels of 11-OH-Δ^8-THC were lower than those of Δ^8-THC.

Table 2 shows the brain/blood ratio of the concentration of cannabinoids at several time intervals after the iv injection. The result indicates that the ratios rose markedly with time because of a slower elimination of these cannabinoids from the brain than those from blood.

Penetration of Δ^8-THC, 11-OH-Δ^8-THC, and 11-Oxo-Δ^8-THC into Brain at Different Doses. Higher levels of 11-OH-Δ^8-THC in brain were also found 5 min after the iv injection of doses of 1, 5, and 10 mg/kg as compared with those of Δ^8-THC and 11-oxo-Δ^8-THC (fig. 3). On the other hand, the blood level of 11-oxo-Δ^8-THC was lower than those of Δ^8-THC and 11-OH-Δ^8-THC in the same experiment.

Disposition of Δ^8-THC and Its Metabolites in Liver, Blood, and

TABLE 2

Brain/blood ratio of unchanged Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC at different time intervals after administration

Each value represents the mean for four mice.

Cannabinoids	Ratio at Time (Min) After Injection					
	0.5	1	5	15	30	60
Δ^8-THC	0.13	0.33	1.58	2.97	2.78	4.76
11-OH-Δ^8-THC	0.72	1.56	6.99	11.47	20.52	39.80
11-Oxo-Δ^8-THC	0.78	1.76	12.56	24.84	20.75	27.80

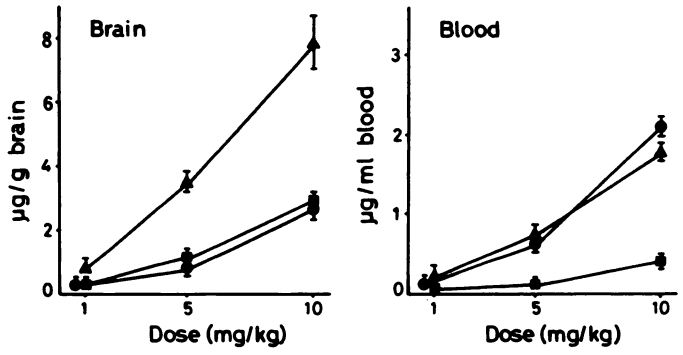

FIG. 3. *Brain and blood levels of unchanged compounds at 5 min after the injection at different doses of Δ^8-THC and its metabolites.*

Each point represents the mean ± SE for four mice. ●, Δ^8-THC; ▲, 11-OH-Δ^8-THC; ■, 11-oxo-Δ^8-THC.

TABLE 1

Brain levels of unchanged Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC

Cannabinoids were injected iv into mice at doses of 10 mg/kg. Each value is expressed as the mean ± SE for four mice.

Cannabinoids	Concentrations at Time (Min) After Injection					
	0.5	1	5	15	30	60
			μg/g			
Δ^8-THC	3.48 ± 0.13	2.86 ± 0.14	3.12 ± 0.16	2.59 ± 0.17	1.65 ± 0.17	1.21 ± 0.05
11-OH-Δ^8-THC	10.64 ± 0.85	8.61 ± 0.51	10.54 ± 1.46	9.46 ± 0.82	3.90 ± 0.19	1.99 ± 0.11
11-Oxo-Δ^8-THC	4.25 ± 0.18	3.93 ± 0.43	3.42 ± 0.16	2.99 ± 0.29	0.83 ± 0.07	0.25 ± 0.03

TABLE 3

Contents of the metabolites of Δ⁸-THC, 11-OH-Δ⁸-THC, and 11-oxo-Δ⁸-THC in the mouse liver, blood, and brain.

Each value represents the mean ± SE for four mice. Animals were killed 15 min after the iv injection (10 mg/kg).

Tissue	Cannabinoids Injected	Δ⁸-THC	11-OH-Δ⁸-THC	11-Oxo-Δ⁸-THC	Δ⁸-THC-11-oic Acid
			μg/g		
Liver	Δ⁸-THC	1.31 ± 0.13	3.62 ± 0.26	0.07 ± 0.01	3.82 ± 0.22
	11-OH-Δ⁸-THC		4.58 ± 1.65	0.14 ± 0.01	6.46 ± 0.56
	11-Oxo-Δ⁸-THC		0.74 ± 0.07	0.46 ± 0.05	12.00 ± 2.22
			μg/ml		
Blood	Δ⁸-THC	1.19 ± 0.10	0.28 ± 0.04	< 0.01	0.68 ± 0.02
	11-OH-Δ⁸-THC		0.87 ± 0.10	0.01 ± 0.00	1.26 ± 0.22
	11-Oxo-Δ⁸-THC		0.29 ± 0.04	0.13 ± 0.02	1.93 ± 0.25
			μg/g		
Brain	Δ⁸-THC	2.95 ± 0.15	0.89 ± 0.06	< 0.01	0.25 ± 0.03
	11-OH-Δ⁸-THC		8.39 ± 0.75	0.03 ± 0.03	0.48 ± 0.04
	11-Oxo-Δ⁸-THC		3.27 ± 0.23	2.99 ± 0.29	0.87 ± 0.09

TABLE 4

Effect of SKF 525-A on the metabolic disposition of Δ⁸-THC, 11-OH-Δ⁸-THC, and 11-oxo-Δ⁸-THC in mouse liver and brain

Animals were killed 15 min after the injection of cannabinoids (10 mg/kg, iv). The results are expressed as means ± SE for four mice. *N.D.*, not detected.

Organ	Cannabinoids Injected	Treatment	Δ⁸-THC	11-OH-Δ⁸-THC	11-Oxo-Δ⁸-THC	Δ⁸-THC-11-oic Acid
				μg/g		
Liver	Δ⁸-THC	Control	0.49 ± 0.13	2.36 ± 0.24	0.09 ± 0.01	3.32 ± 0.40
		SKF 525-A	9.97 ± 1.05**	7.24 ± 0.64**	0.04 ± 0.01**	0.32 ± 0.06**
	11-OH-Δ⁸-THC	Control		5.37 ± 0.44	0.19 ± 0.01	6.50 ± 0.61
		SKF 525-A		18.24 ± 1.15**	0.33 ± 0.06	2.75 ± 0.34**
	11-Oxo-Δ⁸-THC	Control		0.50 ± 0.02	0.67 ± 0.10	13.28 ± 0.68
		SKF 525-A		1.83 ± 0.16*	1.54 ± 0.31*	12.57 ± 1.21
Brain	Δ⁸-THC	Control	3.03 ± 0.10	0.97 ± 0.16	< 0.01	0.32 ± 0.04
		SKF 525-A	5.47 ± 0.28**	1.41 ± 0.24	N.D.	< 0.1**
	11-OH-Δ⁸-THC	Control		7.40 ± 0.76	0.03 ± 0.01	0.48 ± 0.04
		SKF 525-A		12.12 ± 0.86**	0.03 ± 0.00	< 0.1**
	11-Oxo-Δ⁸-THC	Control		2.89 ± 0.22	2.33 ± 0.06	1.20 ± 0.09
		SKF 525-A		3.30 ± 0.27	2.61 ± 0.19	1.29 ± 0.06

* Significantly different ($p < 0.05$) from respective control (Student's *t*-test).

** Significantly different ($p < 0.01$) from respective control (Student's *t*-test).

Brain. As summarized in table 3, 15 min after the iv injection of Δ⁸-THC (10 mg/kg), a higher level of its metabolite, 11-OH-Δ⁸-THC, was found in the liver as compared with the level in the brain and blood. 11-Oxo-Δ⁸-THC was also found as a metabolite of Δ⁸-THC and 11-OH-Δ⁸-THC, but the content was very low in the liver in contrast to a high level of Δ⁸-THC-11-oic acid. Table 3 further shows that 11-oxo-Δ⁸-THC was partially reduced to 11-OH-Δ⁸-THC, although a main metabolic route of 11-oxo-Δ⁸-THC appeared to be oxidation to Δ⁸-THC-11-oic acid in the liver of mice.

As shown above, the elimination of 11-OH- and 11-oxo-Δ⁸-THC is faster than that of Δ⁸-THC. A small amount of 11-oxo-Δ⁸-THC (0.01 μg/ml) was found in the blood of mice 15 min after the iv injection of 11-OH-Δ⁸-THC (table 3). On the other hand, it was barely detectable (< 0.01 μg/ml) as a metabolite of Δ⁸-THC.

A much higher level of 11-OH-Δ⁸-THC was found in the brain after the iv injection of 11-oxo-Δ⁸-THC (10 mg/kg) than those in the liver and blood (table 3). Furthermore, the level of 11-OH-Δ⁸-THC (3.27 μg/g) was significantly higher as compared with that of Δ⁸-THC-11-oic acid (0.87 μg/g) in the brain. On the contrary, Δ⁸-THC-11-oic acid was a predominant metabolite of 11-oxo-Δ⁸-THC in liver and blood.

Effect of SKF 525-A on the Metabolism of Δ⁸-THC, 11-OH-Δ⁸-THC, and 11-Oxo-Δ⁸-THC at the 11-Position. Pretreatment of mice with SKF 525-A (25 mg/kg, ip) resulted in a significant increase of unchanged Δ⁸-THC in the brain and liver at 15 min after the iv injection of Δ⁸-THC (table 4). In addition, the level of 11-OH-Δ⁸-THC in the liver was also increased significantly. Table 4 further shows that SKF 525-A inhibited the conversion of 11-OH-Δ⁸-THC to Δ⁸-THC-11-oic acid, as judged from the lower level of Δ⁸-THC-11-oic acid in the brain and the liver after 11-OH-Δ⁸-THC administration than in controls.

Discussion

After the iv injection into mice of Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC, the blood levels of unchanged cannabinoids declined biphasically. Biological half-lives of Δ^8-THC, 11-OH-Δ^8-THC, and 11-oxo-Δ^8-THC in the slow phase were 32, 12, and 6 min, respectively. In this connection, Lemberger *et al.* (16, 22) reported that the half-lives of Δ^9-THC and 11-OH-Δ^9-THC were very long in man (57 and 22 hr, respectively). Interestingly, 11-OH-Δ^8-THC when administered iv into mice showed three times higher concentration in brain as compared with Δ^8-THC, although the former was eliminated more rapidly from blood than the latter. In addition, 11-OH- and 11-oxo-Δ^8-THC showed 6–7 times higher brain/blood ratios than did Δ^8-THC at 0.5 min after their injections, suggesting that both metabolites of Δ^8-THC can penetrate much more readily into brain of mice than the parent compound. The result is of interest because these metabolites are less lipophilic than Δ^8-THC, and therefore their slower penetration into brain is expected. In fact, Gill *et al.* (23) have reported that octanol/water partition coefficients of Δ^9-THC and 11-OH-Δ^9-THC were 6000 and 3500, respectively.

This interesting penetration rate of Δ^8-THC and 11-OH-Δ^8-THC might be explained by a difference in binding affinities of these cannabinoids to plasma proteins. The binding of drugs with plasma proteins is known to influence greatly the transport of drugs into the tissues. It is recognized that most of Δ^9-THC in plasma binds to lipoproteins *in vivo* (24, 25) as well as *in vitro* (26, 27). 11-OH-Δ^9-THC also binds to plasma proteins, but the affinity seems to be lesser than that of Δ^9-THC (27). Further studies will, however, be necessary to confirm the above explanation.

In connection with the higher distribution of 11-OH-Δ^8-THC in brain of mice than that of Δ^8-THC, Christensen *et al.* reported that 11-OH-Δ^8-THC and 11-OH-Δ^9-THC had twice the pharmacological potency as compared with Δ^8-THC and Δ^9-THC when injected iv into mice (14). More recently, we also found that cataleptogenic, hypothermic, pentobarbital-induced sleep-prolonging, and anticonvulsant effects of 11-OH- and 11-oxo-Δ^8-THC in mice were greater than those of Δ^8-THC, and that the effects of these metabolites appeared more rapidly than those of Δ^8-THC (17, 18). The difference of the pharmacological potency between Δ^8-THC and 11-OH-Δ^8-THC may therefore be attributed in part to the higher levels of 11-OH-Δ^8-THC than of Δ^8-THC in brains of mice.

The elimination of Δ^8-THC from brain, on the other hand, was slower than were those of both metabolites, 11-OH- and 11-oxo-Δ^8-THC. The result suggests that Δ^8-THC has a higher lipophilic property than the metabolites and is not metabolized in brain of mice as reported by Christensen *et al.* (14). The result also coincided with the report of Perez-Reyes *et al.* (15), who showed that Δ^9-THC possessed more long-lasting psychological and physiological effects in man as compared with 11-OH-Δ^9-THC.

In addition, the present study revealed that a considerable amount of 11-OH-Δ^8-THC was found in the brains of mice after the injection of 11-oxo-Δ^8-THC although the levels in the liver and blood were not so high. The result obtained, therefore, suggests that 11-OH-Δ^8-THC may play the important role in the pharmacological effect of 11-oxo-Δ^8-THC.

SKF 525-A, a known inhibitor of microsomal mono-oxygenase, has been shown to inhibit the oxidation of 11-OH-Δ^8-THC to 11-oxo-Δ^8-THC. The result indicates that the oxidation of 11-OH-Δ^8-THC to 11-oxo-Δ^8-THC is also mediated by the microsomal mono-oxygenase system in mice, which was reported previously in rats (28). Contrary to the result of Gill and Jones (29), the present results implied that SKF 525-A seemed also to affect the oxidation of Δ^8-THC to 11-OH-Δ^8-THC, inasmuch as the levels of Δ^8-THC became higher in all cases than those of 11-OH-Δ^8-THC after pretreatment with this inhibitor.

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