IN VIVO EFFECTS OF TETRAHYDROCANNABINOLS AND THEIR EIGHT MONOOXYGENATED METABOLITES ON THE HEPATIC MICROSOMAL DRUG-METABOLIZING ENZYME SYSTEMS OF MICE

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In vivo effects of tetrahydrocannabinols (THCs) and their eight monooxygenated metabolites on the hepatic microsomal drug-metabolizing enzymes in mice were studied. Δ^8 -THC and its metabolites (7 α -hydroxy-, 7 β -hydroxy- and 7-oxo- Δ^8 -THC, and 8 α , 9 α - and 8 β , 9 β -epoxyhexahydrocannabinol) tended to increase the enzyme contents or activities except for 7 β -hydroxy- Δ^8 -THC which affected the microsomal enzymes in a different manner between the single and subchronic treatments. Single administration (5 mg/kg, i.v.) of 7-oxo- Δ^8 -THC, 8 α , 9 α - and 8 β , 9 β -epoxyhexahydrocannabinol led to a significant increase in hepatic microsomal *p*-nitroanisole O-demethylase and aniline hydroxylase activities accompanying a significant increase in cytochrome P-450 content in hepatic microsomes. The same results were obtained with subchronic treatment of mice with these metabolites (5 mg/kg/d, i.v. for 7 d), although the effect of 8 β , 9 β -epoxyhexahydrocannabinol on cytochrome P-450 was not statistically significant. 7 β -Hydroxy- Δ^8 -THC significantly increased nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome c reductase and aniline hydroxylase activities by single administration, while the metabolite significantly decreased the contents of cytochrome b₅ and P-450 and *p*-nitrophenol uridine diphosphate-glucuronyltransferase activity by the subchronic treatment. In contrast, Δ^9 -THC and its metabolites (8 α -hydroxy-, 8 β -hydroxy- and 8-oxo- Δ^9 -THC) did not significantly affect the microsomal enzymes by both treatments except that the single administration of 8 α -hydroxy- Δ^9 -THC and the subchronic treatment of Δ^9 -THC significantly decreased NADPH-cytochrome c reductase activity. These results indicated that monooxygenated metabolites of Δ^8 - and Δ^9 -THC affect the hepatic microsomal drug-metabolizing enzyme systems of mice differently.

Keywords — Δ^8 -tetrahydrocannabinol; Δ^9 -tetrahydrocannabinol; monooxygenated metabolite; cytochrome P-450; NADPH-cytochrome c reductase; aniline hydroxylase; *p*-nitroanisole O-demethylase; *p*-nitrophenol uridine diphosphate-glucuronyltransferase; single administration; subchronic administration

INTRODUCTION

Δ^8 - and Δ^9 -Tetrahydrocannabinol (THC), which are psychoactive principles of marijuana, are highly lipophilic and known to affect the hepatic microsomal drug-metabolizing enzyme system *in vitro* and *in vivo*.¹⁻⁹⁾ Δ^8 - and Δ^9 -THC are also good substrates for the above enzyme system and transform a number of metabolites,^{10,11)} some of which are known to be pharmacologically active.¹²⁾ It is, therefore, considered that more attention should be directed toward greater understanding of the biological effects of THC metabolites. An inhibitory effect of 11-hydroxy- Δ^9 -THC (11-OH- Δ^9 -THC) on rat hepatic microsomal aniline hydroxylase and N-de-

methylases of aminopyrine and ethylmorphine was reported by Leighty,¹³⁾ although benzo[*a*]pyrene hydroxylase activity was enhanced by this metabolite. We also reported *in vitro* and *in vivo* inhibitory effects of 11-OH- Δ^8 -THC and 11-oxo- Δ^8 -THC on the hepatic microsomal drug-metabolizing enzymes in mice.⁸⁾ Contrary to these reports, we recently found that the activity of mouse hepatic microsomal drug-metabolizing enzymes was enhanced by repeated administration of 11-OH- Δ^8 -THC.¹⁴⁾ These conflicting findings indicate that the effect of THC and its metabolites on hepatic microsomal drug-metabolizing enzymes is affected by experimental conditions. The present study thus,

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FIG. 1. Structures of Cannabinoids Used

investigates effects of single and subchronic (7 daily) administrations of Δ^8 - and Δ^9 -THC and their eight monooxygenated metabolites (Fig. 1) on the hepatic microsomal drug-metabolizing enzyme system of mice.

MATERIALS AND METHODS

Chemicals — Δ^8 -THC,¹⁵⁾ 7α -OH- Δ^8 -THC,¹⁶⁾ 7β -OH- Δ^8 -THC,¹⁶⁾ 7 -oxo- Δ^8 -THC,¹⁶⁾ $8\alpha,9\alpha$ -epoxyhexahydrocannabinol ($8\alpha,9\alpha$ -EHHC),¹⁷⁾ $8\beta,9\beta$ -EHHC,¹⁷⁾ 8α -OH- Δ^9 -

THC,¹⁸⁾ 8β -OH- Δ^9 -THC,¹⁸⁾ and 8 -oxo- Δ^9 -THC¹⁸⁾ were prepared by the methods described previously. Nicotinamide adenine dinucleotide phosphate (NADP) and glucose-6-phosphate were purchased from Boehringer Mannheim GmbH. Reduced nicotinamide adenine dinucleotide phosphate (NADPH), cytochrome c (type III), uridine diphosphate glucuronic acid (UDPGA) and glucose-6-phosphate dehydrogenase (type V) were obtained from Sigma Chemical Co. All other chemicals used were of

TABLE I. Change in Relative Liver Weight in Mice Following Administration of THC_s and Their Metabolites

Days of treatment	Control Relative liver weight (g/kg body weight)	% of control $\pm$ S.E.					
		Δ^8 -THC	7α -OH- Δ^8 -THC	7β -OH- Δ^8 -THC	7 -Oxo- Δ^8 -THC	$8\alpha,9\alpha$ -EHHC	$8\beta,9\beta$ -EHHC
1 d	66 $\pm$ 1	91 $\pm$ 3	100 $\pm$ 3	99 $\pm$ 3	86 $\pm$ 1 ^{b)}	87 $\pm$ 5 ^{a)}	82 $\pm$ 5 ^{b)}
7 d	62 $\pm$ 1	87 $\pm$ 7	95 $\pm$ 0 ^{a)}	93 $\pm$ 0 ^{a)}	90 $\pm$ 0 ^{a)}	83 $\pm$ 3 ^{b)}	82 $\pm$ 1 ^{b)}

Days of treatment	Control Relative liver weight (g/kg body weight)	% of control $\pm$ S.E.			
		Δ^9 -THC	8α -OH- Δ^9 -THC	8β -OH- Δ^9 -THC	8 -Oxo- Δ^9 -THC
1 d	68 $\pm$ 1	94 $\pm$ 1	93 $\pm$ 1 ^{a)}	90 $\pm$ 3 ^{a)}	84 $\pm$ 2 ^{b)}
7 d	64 $\pm$ 2	85 $\pm$ 2 ^{b)}	90 $\pm$ 1 ^{b)}	91 $\pm$ 1 ^{b)}	95 $\pm$ 1 ^{b)}

The value represents the mean $\pm$ S.E. of four pairs from eight mice. a) Significantly different from the control ($p < 0.05$). b) Significantly different from the control ($p < 0.01$).

the best quality commercially available.

Animals and Treatments — Male ddN mice weighing 20 to 25 g were used in this study and were given food and water *ad lib.* Cannabinoids were suspended in isotonic saline containing 1% (v/v) Tween 80 and injected intravenously (i.v.) at a dose of 5 mg/kg/d. The control group was

given an equivalent volume (10 ml/kg body weight) of the vehicle. Mice were killed by cervical dislocation 24 h after a single or 7 daily (sub-chronic) administrations of THC or metabolites. Microsomes were prepared by a differential centrifugation method described previously.¹⁹⁾

Enzyme Assays — Aniline hydroxylase and

TABLE II. *Effects of Single Administration of THC's and Their Metabolites on the Hepatic Microsomal Drug-Metabolizing Enzyme Systems of Mice*

Cannabinoids treatment	% of control $\pm$ S.E.			
	Cytochrome P-450	Cytochrome b_5	NADPH-cytochrome c reductase	<i>p</i> -Nitroanisole O-demethylase
Δ^8 -THC	102 $\pm$ 4	100 $\pm$ 6	98 $\pm$ 3	100 $\pm$ 3
7 α -OH- Δ^8 -THC	115 $\pm$ 10	123 $\pm$ 10	125 $\pm$ 4 ^{b)}	115 $\pm$ 5
7 β -OH- Δ^8 -THC	120 $\pm$ 8	120 $\pm$ 10	136 $\pm$ 3 ^{b)}	138 $\pm$ 10 ^{b)}
7-Oxo- Δ^8 -THC	132 $\pm$ 6 ^{a)}	105 $\pm$ 3	95 $\pm$ 3	139 $\pm$ 3 ^{b)}
8 α ,9 α -EHHHC	152 $\pm$ 12 ^{a)}	112 $\pm$ 12	98 $\pm$ 9	144 $\pm$ 12 ^{a)}
8 β ,9 β -EHHHC	140 $\pm$ 9 ^{a)}	102 $\pm$ 8	102 $\pm$ 8	193 $\pm$ 20 ^{b)}
Δ^9 -THC	101 $\pm$ 15	95 $\pm$ 18	97 $\pm$ 5	96 $\pm$ 5
8 α -OH- Δ^9 -THC	96 $\pm$ 24	87 $\pm$ 10	91 $\pm$ 2 ^{a)}	88 $\pm$ 10
8 β -OH- Δ^9 -THC	89 $\pm$ 6	100 $\pm$ 8	93 $\pm$ 5	94 $\pm$ 5
8-Oxo- Δ^9 -THC	96 $\pm$ 8	95 $\pm$ 8	91 $\pm$ 5	96 $\pm$ 11

Cannabinoids treatment	% of control $\pm$ S.E.		
	Aniline hydroxylase	UDPGT (– Triton X-100)	UDPGT (+ Triton X-100)
Δ^8 -THC	106 $\pm$ 3	—	—
7 α -OH- Δ^8 -THC	115 $\pm$ 10	126 $\pm$ 27	109 $\pm$ 8
7 β -OH- Δ^8 -THC	121 $\pm$ 13	88 $\pm$ 9	93 $\pm$ 8
7-Oxo- Δ^8 -THC	127 $\pm$ 8 ^{a)}	88 $\pm$ 10	93 $\pm$ 8
8 α ,9 α -EHHHC	142 $\pm$ 12 ^{a)}	126 $\pm$ 27	109 $\pm$ 8
8 β ,9 β -EHHHC	150 $\pm$ 1 ^{b)}	103 $\pm$ 4	109 $\pm$ 6
Δ^9 -THC	83 $\pm$ 11	111 $\pm$ 11	103 $\pm$ 5
8 α -OH- Δ^9 -THC	76 $\pm$ 11	90 $\pm$ 15	108 $\pm$ 8
8 β -OH- Δ^9 -THC	89 $\pm$ 2	87 $\pm$ 12	108 $\pm$ 7
8-Oxo- Δ^9 -THC	96 $\pm$ 6	85 $\pm$ 18	91 $\pm$ 4

Each value represents the mean (expressed as percent of control) $\pm$ S.E. of four experiments from eight mice. The mean values of enzyme contents or activities of controls are as follows: (control for Δ^8 -THC and its metabolites), cytochrome P-450 content, 0.70 $\pm$ 0.05 nmol/mg protein; cytochrome b_5 content, 0.30 $\pm$ 0.02 nmol/mg protein; NADPH-cytochrome c reductase, 198 $\pm$ 7 nmol/min/mg protein; *p*-nitroanisole O-demethylase, 0.59 $\pm$ 0.06 nmol *p*-nitrophenol formed/min/mg protein; aniline hydroxylase, 0.78 $\pm$ 0.06 nmol *p*-aminophenol formed/min/mg protein; *p*-nitrophenol glucuronidation (– Triton X-100), 1.08 $\pm$ 0.12 nmol *p*-nitrophenol conjugated/min/mg protein; *p*-nitrophenol glucuronidation (+ Triton X-100), 8.95 $\pm$ 0.25 nmol *p*-nitrophenol conjugated/min/mg protein; (control for Δ^9 -THC and its metabolites), cytochrome P-450 content, 0.72 $\pm$ 0.06 nmol/mg protein; cytochrome b_5 content, 0.39 $\pm$ 0.03 nmol/mg protein; NADPH-cytochrome c reductase, 229 $\pm$ 5 nmol/min/mg protein; *p*-nitroanisole O-demethylase, 0.83 $\pm$ 0.03 nmol *p*-nitrophenol formed/min/mg protein; aniline hydroxylase, 0.54 $\pm$ 0.02 nmol *p*-aminophenol formed/min/mg protein; *p*-nitrophenol glucuronidation (– Triton X-100), 1.31 $\pm$ 0.07 nmol *p*-nitrophenol conjugated/min/mg protein; *p*-nitrophenol glucuronidation (+ Triton X-100), 5.32 nmol *p*-nitrophenol conjugated/min/mg protein. a) Significantly different from the control ($p < 0.05$). b) Significantly different from the control ($p < 0.01$).

p-nitroanisole O-demethylase were determined by methods previously described.¹⁴⁾ The determinations were based on the measurement of *p*-aminophenol or *p*-nitrophenol formed. Cytochrome *b*₅ and P-450 contents were determined by the methods of Omura and Sato²⁰⁾ using extinction coefficients of 185 and 91 mM⁻¹, respectively. NADPH-cytochrome *c* reductase activity was assayed by the method of Phillips and Langdon²¹⁾ which measure absorbance at 557 nm. For assaying *p*-nitrophenol UDP-glucuronyltransferase (UDPGT) activity, *p*-nitrophenol (0.25 mM) was incubated with hepatic microsomes (0.2 g liver equivalent), 5 mM MgCl₂, 3 mM UDPGA, 100 mM Tris-HCl buffer (pH 7.4) in a final volume of 1 ml. The reaction was terminated by the addition of 1 ml of 1 M trichloroacetic acid and the *p*-nitrophenol remaining in the reaction mixture was determined by the method of Bock *et al.*²²⁾

RESULTS

The effects of single and subchronic treatments of mice with THC and their metabolites on liver weight are shown in Table I. A significant decrease in relative liver weight was noted by a single administration of 7-oxo- Δ^8 -THC, 8 α , 9 α - and 8 β , 9 β -EHHHC, 8 α -OH- Δ^9 -THC, 8 β -OH- Δ^9 -THC and 8-oxo- Δ^9 -THC. In the subchronic treatment (7 daily administration), all cannabinoids tested except for Δ^8 -THC significantly decreased the relative liver weight compared with the control. Table II summarizes the effects of single administration of cannabinoids on the hepatic microsomal enzymes. The treatments with Δ^8 -THC and its metabolites tended to increase the contents of cytochrome *b*₅ and P-450 or enzyme activities. 7 β -OH- Δ^8 -THC, 7-oxo- Δ^8 -THC, 8 α , 9 α - and 8 β , 9 β -EHHHC significantly increased *p*-nitroanisole O-demethylase activity. 7-Oxo- Δ^8 -THC, 8 α , 9 α - and 8 β , 9 β -EHHHC also significantly increased aniline hydroxylase activity by 27, 42 and 50%, respectively, accompanied by a significant increase in cytochrome P-450 content in hepatic microsomes. 7 α -OH- Δ^8 -THC and 7 β -OH- Δ^8 -THC significantly increased NADPH-cytochrome *c* reductase activity by 25 and 36%, respectively. On the other hand, Δ^9 -THC and its metabolites tended to decrease the contents or activities of the enzymes. A significant effect was observed on NADPH-cytochrome *c* reductase activity in

hepatic microsomes of mice treated with 8 α -OH- Δ^9 -THC. None of the cannabinoids tested significantly affected *p*-nitrophenol UDPGT activity with or without Triton X-100.

Table III summarizes the subchronic effects of THC and their metabolites on the hepatic microsomal enzymes. In the treatments with Δ^8 -THC and its metabolites, 7 α -OH- Δ^8 -THC, 7-oxo- Δ^8 -THC, 8 α , 9 α - and 8 β , 9 β -EHHHC significantly increased *p*-nitroanisole O-demethylase activity by 21, 22, 28 and 19%, respectively. The latter three cannabinoids also significantly increased aniline hydroxylase activity, and 7-oxo- Δ^8 -THC and 8 α , 9 α -EHHHC increased cytochrome P-450 content by 23 and 39%, respectively. Epoxy metabolites of Δ^8 -THC significantly increased NADPH-cytochrome *c* reductase activity by the subchronic treatment. In contrast, the subchronic treatment with 7 β -OH- Δ^8 -THC led to a decrease in microsomal hemoproteins, cytochrome *b*₅ and P-450 contents. *p*-Nitrophenol UDPGT activity was significantly decreased by 7 β -OH- Δ^8 -THC treatment, although this significant effect was not observed in the presence of Triton X-100. In the subchronic treatments with Δ^9 -THC and its metabolites, a significant effect was observed only on NADPH-cytochrome *c* reductase activity in hepatic microsomes treated with Δ^9 -THC. Other microsomal enzymes were not significantly affected by the subchronic treatments with Δ^9 -THC and its metabolites as well as by the single treatments.

DISCUSSION

The present study demonstrated that single and subchronic treatments with THC and their metabolites led to a decrease in the relative liver weight of mice. The decrease in the relative liver weight tended to be greater in mice treated with THC metabolites than in mice treated with THC. The greater effect of 11-OH- Δ^8 -THC on the relative liver weight than that of Δ^8 -THC has been reported in mice.¹⁴⁾ The decrease in liver weight by Δ^9 -THC has been reported in rabbits,^{23,24)} whereas an opposite effect of Δ^9 -THC has been reported in rats and monkeys.^{23,25,26)} The different effect of Δ^9 -THC may be due to difference in the conditions used, such as animal species, dose, route and period of administration.

The single administration of 7-oxo- Δ^8 -THC,

TABLE III. *Effects of Subchronic Administration of THC's and Their Metabolites on the Hepatic Microsomal Drug-Metabolizing Enzyme Systems of Mice*

Cannabinoids treatment	% of control $\pm$ S.E.			
	Cytochrome P-450	Cytochrome b_5	NADPH-cytochrome c reductase	<i>p</i> -Nitroanisole O-demethylase
Δ^8 -THC	104 $\pm$ 4	97 $\pm$ 4	91 $\pm$ 2	98 $\pm$ 6
7 α -OH- Δ^8 -THC	100 $\pm$ 13	98 $\pm$ 10	111 $\pm$ 3	121 $\pm$ 2 ^{a)}
7 β -OH- Δ^8 -THC	75 $\pm$ 7 ^{a)}	66 $\pm$ 7 ^{a)}	87 $\pm$ 11	112 $\pm$ 5
7-Oxo- Δ^8 -THC	123 $\pm$ 1 ^{b)}	112 $\pm$ 3	120 $\pm$ 2	122 $\pm$ 5 ^{a)}
8 α ,9 α -EHHHC	139 $\pm$ 11 ^{a)}	116 $\pm$ 5	127 $\pm$ 7 ^{a)}	128 $\pm$ 4 ^{b)}
8 β ,9 β -EHHHC	122 $\pm$ 12	105 $\pm$ 5	141 $\pm$ 5 ^{b)}	119 $\pm$ 8 ^{a)}
Δ^9 -THC	107 $\pm$ 8	100 $\pm$ 9	79 $\pm$ 3 ^{a)}	115 $\pm$ 18
8 α -OH- Δ^9 -THC	97 $\pm$ 3	93 $\pm$ 7	83 $\pm$ 2	79 $\pm$ 4
8 β -OH- Δ^9 -THC	101 $\pm$ 4	91 $\pm$ 5	83 $\pm$ 2	80 $\pm$ 4
8-Oxo- Δ^9 -THC	103 $\pm$ 1	102 $\pm$ 5	85 $\pm$ 4	79 $\pm$ 4

Cannabinoids treatment	% of control $\pm$ S.E.		
	Aniline hydroxylase	UDPGT (–Triton X-100)	UDPGT (+Triton X-100)
Δ^8 -THC	131 $\pm$ 6 ^{a)}	—	—
7 α -OH- Δ^8 -THC	104 $\pm$ 8	84 $\pm$ 7	95 $\pm$ 6
7 β -OH- Δ^8 -THC	98 $\pm$ 6	54 $\pm$ 18 ^{a)}	89 $\pm$ 11
7-Oxo- Δ^8 -THC	126 $\pm$ 9 ^{a)}	89 $\pm$ 7	110 $\pm$ 1
8 α ,9 α -EHHHC	145 $\pm$ 12 ^{a)}	99 $\pm$ 7	113 $\pm$ 1
8 β ,9 β -EHHHC	131 $\pm$ 7 ^{a)}	91 $\pm$ 6	108 $\pm$ 3
Δ^9 -THC	103 $\pm$ 1	87 $\pm$ 3	112 $\pm$ 4
8 α -OH- Δ^9 -THC	88 $\pm$ 5	87 $\pm$ 5	113 $\pm$ 2
8 β -OH- Δ^9 -THC	88 $\pm$ 4	89 $\pm$ 6	113 $\pm$ 7
8-Oxo- Δ^9 -THC	86 $\pm$ 4	86 $\pm$ 5	113 $\pm$ 4

Each value represents the mean (expressed as percent of control) $\pm$ S.E. of four experiments from eight mice. The mean values of enzyme contents or activities of controls are as follows: (control for Δ^8 -THC and its metabolites), cytochrome P-450 content, 0.61 $\pm$ 0.10 nmol/mg protein; cytochrome b_5 content, 0.41 $\pm$ 0.03 nmol/mg protein; NADPH-cytochrome c reductase, 181 $\pm$ 22 nmol/min/mg protein; *p*-nitroanisole O-demethylase, 0.78 $\pm$ 0.04 nmol *p*-nitrophenol formed/min/mg protein; aniline hydroxylase, 0.58 $\pm$ 0.03 nmol *p*-aminophenol formed/min/mg protein; *p*-nitrophenol glucuronidation (–Triton X-100), 1.35 $\pm$ 0.04 nmol *p*-nitrophenol conjugated/min/mg protein; *p*-nitrophenol glucuronidation (+Triton X-100), 7.70 $\pm$ 0.29 nmol *p*-nitrophenol conjugated/min/mg protein; (control for Δ^9 -THC and its metabolites), cytochrome P-450 content, 0.74 $\pm$ 0.03 nmol/mg protein; cytochrome b_5 content, 0.43 $\pm$ 0.02 nmol/mg protein; NADPH-cytochrome c reductase, 253 $\pm$ 19 nmol/min/mg protein; *p*-nitroanisole O-demethylase, 0.60 $\pm$ 0.05 nmol *p*-nitrophenol formed/min/mg protein; aniline hydroxylase, 0.57 $\pm$ 0.06 nmol *p*-aminophenol formed/min/mg protein; *p*-nitrophenol glucuronidation (–Triton X-100), 1.87 $\pm$ 0.22 nmol *p*-nitrophenol conjugated/min/mg protein; *p*-nitrophenol glucuronidation (+Triton X-100), 6.06 $\pm$ 0.29 nmol *p*-nitrophenol conjugated/min/mg protein. a) Significantly different from the control ($p < 0.05$). b) Significantly different from the control ($p < 0.01$).

8 α ,9 α - and 8 β ,9 β -EHHHC significantly increased hepatic microsomal *p*-nitroanisole O-demethylase and aniline hydroxylase activities. The increase in cytochrome P-450 content by these cannabinoids appears to be part of a mechanism for increased activities. Both enzyme activities per cytochrome P-450 in microsomes of mice

treated with these metabolites were almost equal to those of the control. Whether or not these metabolites induce the hepatic microsomal cytochrome P-450 remains to be evaluated with caution since the relative liver weight of mice was significantly decreased by the metabolites. On the other hand, 7 β -OH- Δ^8 -THC increased

p-nitroanisole O-demethylase without a significant effect of cytochrome p-450. The increase in NADPH-cytochrome c reductase activity by 7β -OH- Δ^8 -THC may be associated with the enhancement of the enzyme activity. The subchronic treatments with Δ^8 -THC and its metabolites affected the microsomal drug-metabolizing enzymes in manner similar to the single administration except that 7β -OH- Δ^8 -THC significantly decreased cytochrome b₅ and P-450 contents and *p*-nitrophenol UDPGT activity. *p*-Nitrophenol glucuronidation was, however, returned to the control level by the addition of Triton X-100, which activates latent enzymes in the microsomal membrane. 7β -OH- Δ^8 -THC, therefore, may not affect the enzyme itself but affects the environment of the enzyme such as microsomal lipid components or their conformation. Δ^8 - and Δ^9 -THC could also affect the microsomal lipid components or conformation of microsomal membrane.²⁷⁾ However, the different effect of 7β -OH- Δ^8 -THC on the hepatic microsomal cytochromes by the single and subchronic treatments is somewhat difficult to interpret at present.

In contrast to the tendency of Δ^8 -THC and its metabolites to increase the hepatic microsomal drug-metabolizing enzymes, Δ^9 -THC and its metabolites tended to decrease the enzyme activities. A significant effect was noted in NADPH-cytochrome c reductase activity by the single treatment with 8α -OH- Δ^9 -THC and by the subchronic treatment with Δ^9 -THC. The difference in the effect of Δ^8 - and Δ^9 -THC metabolites on the microsomal enzymes can not be explained at present. We have reported that Δ^8 -THC metabolites tested in the present study exhibited some pharmacological effects in mice,^{28,29)} whereas Δ^9 -THC metabolites tested showed little effect.³⁰⁾ THC is suggested to exert some of its effects through a nonspecific interaction with lipid components of biological membrane.³¹⁾ These findings and the present results suggest that Δ^8 - and Δ^9 -THC metabolites may interact differently with biological membranes.

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