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Ethanol and Delta-9-Tetrahydrocannabinol: Mechanism for Cross-Tolerance in Mice[1]

GARY L. SPRAGUE[2] AND ARTHUR L. CRAIGMILL

College of Pharmacy, Washington State University, Pullman, WA 99163

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SPRAGUE, G. L. AND A. L. CRAIGMILL. *Ethanol and delta-9-tetrahydrocannabinol: mechanism for cross-tolerance in mice.* PHARMAC. BIOCHEM. BEHAV. 5(4) 409–415, 1976. – The pharmacological interaction between equipotent doses of ethanol (1.35 g/kg) and delta-9-tetrahydrocannabinol (THC, 17 mg/kg) was evaluated in mice using rotarod performance as a measure of drug action. Tolerance to the effects of ethanol and THC as well as a symmetrical cross-tolerance between these two drugs was demonstrated. Ethanol elimination was not altered by previous treatment with either ethanol or THC as determined by measuring blood ethanol concentrations with an enzymatic assay. THC metabolite ratios in blood, brain and liver tissues determined after a dose of ^{3}H-THC demonstrated that THC treatment had no effect upon THC metabolism or disposition. Ethanol treatment altered the distribution of THC and also altered hepatic THC metabolism as evidenced by the occurrence of increased proportions of polar THC metabolites. No treatment regimens produced lower whole brain levels of subsequent ethanol or THC suggesting that tolerance to ethanol or THC and cross-tolerance between these two drugs does not develop due to lower brain concentrations. A vehicle effect was shown when treatment with a mixture of propylene glycol and Tween-80 altered the metabolic and behavioral effects of subsequently administered THC.

Ethanol Delta-9-tetrahydrocannabinol Cross-tolerance Rotarod-performance Delta-9-tetrahydrocannabinol metabolism

RECENT reports have been inconclusive in determining whether or not symmetrical cross-tolerance develops between ethanol and delta-9-tetrahydrocannabinol (THC). Newman and coworkers [22] first reported evidence for cross-tolerance to ethanol in THC pretreated rats using a shock-avoidance paradigm. Further evidence followed in support of cross-tolerance development using an operant paradigm [21]. Kalant and LeBlanc [10] reported that treatment with low doses of THC in rats trained to walk on a moving belt produced tolerance to the disruptive effects of THC but not to those of ethanol. No studies have been reported concerning the mechanism of cross-tolerance development between ethanol and THC, if it does indeed occur.

The objectives of this study were (1) to determine if symmetrical cross-tolerance develops between equipotent doses of ethanol and THC in mice performing an unlearned behavior and (2) to evaluate the contributions of disposition and metabolism of ethanol and THC to development of the observed cross-tolerance.

METHOD

Animals and Drugs

Male, Swiss-Webster mice (Hilltop Lab Animals, Chatsworth, Ca.) weighing 23–33 g were used throughout the study. The animals were housed in groups of 5 in 17 × 27 × 11 cm plastic cages with a regulated 12-hr light-dark lighting schedule. Purina lab chow and tap water were available *ad libitum*. Body weights of all animals were recorded daily.

In most cases, THC (95% THC obtained from the National Institute of Mental Health) was administered as a suspension in 10% propylene glycol and 1% Tween-80 [26] which was prepared as follows. THC in ethanol was added to an appropriate volume of propylene glycol and Tween-80 and the ethanol was evaporated using N_2. Isotonic saline was then added and the suspension was mixed using sonication. THC was administered as a suspension in 1% Pluronic F-68 (poloxalene) in another part of the study. This suspension was prepared by adding THC in ethanol to an appropriate amount of Pluronic F-68. Following the evaporation of ethanol with N_2 and the addition of isotonic saline, the suspension was mixed using sonication. Suspensions containing ^{3}H-THC (obtained from the National Institute of Drug Abuse) were prepared in 10% propylene glycol:1% Tween-80 in isotonic saline to provide a specific activity of 10 μc/mg THC. Ethanol was administered either in 10% propylene glycol:1% Tween-80 (prepared in isotonic saline) or in isotonic saline. The 11-OH-THC used as a standard in thin-layer chromatography (TLC) was obtained

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[2] American Foundation for Pharmaceutical Education Graduate Fellow. Present address, Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri, 64110.

from the National Institute of Drug Abuse. All drugs were administered intraperitoneally in a volume of 10 ml/kg.

Experimental Procedure

Performance on a rotarod apparatus [5] was used as a behavioral measure of drug action. The ability of each mouse to maintain equilibrium on a 1-1/4 in. dia. rotating rod turning at 4 rpm was scored by assigning mice which maintained their balance for 1 min a score of 1 and those that fell a score of 0. Group performance scores were recorded as the number of animals given scores of 0 and 1 and differences between group performance scores were evaluated using a Chi-squared statistical analysis.

The time of maximum impairment of rotarod performance by ethanol and THC was determined and dose-response curves for each drug were obtained at that time. The ED50 doses of ethanol and THC were determined by the method of Litchfield and Wilcoxon [16] and used thereafter throughout the study. The time required for tolerance to develop to ethanol or THC was determined in groups of animals treated with either drug. Rotarod performance in each group was measured after each treatment and compared to the baseline performance level prior to any drug treatment. The criterion for tolerance development in this study was met when the group performance score after drug treatment did not significantly differ from the group baseline performance. The observed treatment schedules necessary for ethanol and THC tolerance development were then repeated in groups in which only the baseline performance level and that following the last drug treatment were measured in order to determine whether the tolerance observed was or was not behaviorally mediated.

Twelve groups of mice were initially used to determine if cross-tolerance developed between ethanol and THC. Four treatment schedules were used with 3 groups of animals given each treatment. Three groups were given single daily injections of THC (17 mg/kg) for 6 days and 3 groups were given 2 daily injections of ethanol (1.35 g/kg) for 11 days. Since both THC and ehtanol were administered in 10% propylene glycol: 1% Tween-80 in isotonic saline, the control groups consisted of 3 groups given single daily injections of this solvent (10 ml/kg) for 6 days and 3 groups given 2 daily injections for 11 days. Twenty-four hr after the termination of each of the 4 treatments, a single injection of a second compound was given. The second compound consisted of THC (17 mg/THC), ethanol (1.35 g/kg) or 10% propylene glycol:1% Tween-80 in isotonic saline (10 ml/kg). Rotarod performance of each group measured 20 min after the administration of the second compound was compared to the baseline rotarod performance measured prior to any drug treatment. The criterion for cross-tolerance was met if the rotarod performance in the etanol-treated group after THC administration was not significantly different from its baseline control level and the cross-tolerance was symmetrical if the performance of the THC-treated group after ethanol did not significantly differ from its baseline level.

Four groups of mice were used to further evaluate the action of THC in mice previously treated with THC or ethanol. The 4 treatments consisted of THC (17 mg/kg) in 1% Pluronic F-68 (in isotonic saline) once daily for 6 days, 1% pluronic F-68 in isotonic saline (10 ml/kg) once daily for 6 days, ethanol (1.35 g/kg) in isotonic saline twice daily for 11 days or isotonic saline (10 ml/kg) twice daily for 11 days. Twenty-four hr after the termination of each of the 4 treatments, a single injection of THC (17 mg/kg) in 1% Pluronic F-68 was given. Rotarod performance of each group measured 20 min after the single THC injection was compared to the baseline rotarod performance.

The change in rotarod performance with time after single injections of ethanol or THC was measured in mice previously treated with ethanol, THC or isotonic saline. Four treatment schedules were used with 2 groups of mice given each treatment. The schedules consisted of single daily injections of THC (17 mg/kg) in 1% Pluronic F-68 for 6 days, single daily injections of isotonic saline (10 ml/kg) for 6 days, ethanol (1.35 g/kg) in isotonic saline twice daily for 11 days or isotonic saline (10 ml/kg) twice daily for 11 days. Twenty-four hr after the termination of each treatment, a single injection of either ethanol (1.35 g/kg) or THC (17 mg/kg) was given and rotarod performance was measured at 10 min intervals for a period of 100 min.

Assays

Another group of mice was used to study the effect of prior treatment upon drug distribution and metabolism. Blood ethanol levels in treatment groups given ethanol (1.35 g/kg) were determined 20 min after ethanol administration. Blood was removed by cardiac puncture in animals killed with CO_2 and the ethanol concentration was determined using a modified enzymatic technique [17].

THC metabolite ratios in blood, brain and liver tissues in 4 treatment groups and in an untreated group given no prior drug treatments were determined 20 min after the administration of ^{3}H-THC (17 mg THC/kg, 10 μc/mg THC). The 4 drug treatments given prior to the single injection of ^{3}H-THC consisted of THC (17 mg/ml) in 10% propylene glycol: 1% Tween-80 in isotonic saline once daily for 6 days, 10% propylene glycol:1% Tween-80 once daily for 6 days, ethanol (1.35 g/kg) in 10% propylene glycol: 1% Tween-80 twice daily for 11 days or 10% propylene glycol: 1% Tween-80 twice daily for 11 days. Blood was removed by cardiac puncture in animals killed with CO_2 and immediately diluted in 3 volumes of distilled water and frozen. Whole brains and portions of liver tissue were quickly removed, weighed, homogenized in cold distilled water and then frozen.

THC and its metabolites in each tissue were extracted from each homogenate 3 times with 3 volumes of ethyl acetate. The 3 aliquots from each sample were pooled and evaporated to dryness using a Buchler rotary evaporator and the residue was redissolved in 1 ml of ethyl acetate which was then equally applied to 2 Brinkman precoated TLC plates (SIL G-25). The plates were developed 15 cm in either Solvent A (hexane:diethyl ether:acetone, 4:2:3) or Solvent B (4% methanol in chloroform). Radioactivity was separated into 4 areas with R_f values of 0, 0.20, 0.50 (11-OH-THC) and 0.80 (THC) using Solvent A and 0, 0.10, 0.23 (11-OH-THC) and 0.70 (THC) using Solvent B. Each area was scraped into a scintillation vial and 10 ml of toluene:PPO:POPOP cocktail was added. Radioactivity is expressed as the % found in each of the 4 TLC zones and data from Solvents A and B were combined. The tissue homogenate remaining after ethyl acetate extraction was dried using a Virtis freeze dry apparatus, the residue dissolved in 1 ml Protosol Tissue Solubilizer (New England Nuclear, Boston, MA) and 10 ml of the toluene:PPO:POPOP scintillation cocktail was added. Radioactivity was

determined with a Packard Model 3320 Tri-carb Scintillation Spectrometer. Total tissue readioactivity was determined as the sum of the radioactivity on the 2 TLC plates and that found in the freeze dried residue for each tissue sample. The extent of extraction of radioactivity from blood was 93.1 ± 1.1% (mean ± S.E.M.) and that from brain and liver tissues was 69.5 ± 1.6%. All samples were corrected for quenching using an internal standard consisting of ^{3}H-toluene. The data obtained were evaluated using Chi-squared and Students t statistics.

RESULTS

Rotarod Performance

Ethanol and THC both impaired rotarod performance in a dose-related manner as shown in Fig. 1. ED50 values for ethanol and THC were 1.35 g/kg and 17 mg/kg respectively and the potency ratio of the 2 drugs was 79.4. The peak effect of both ethanol and THC on rotarod performance was evident 20 min after IP administration.

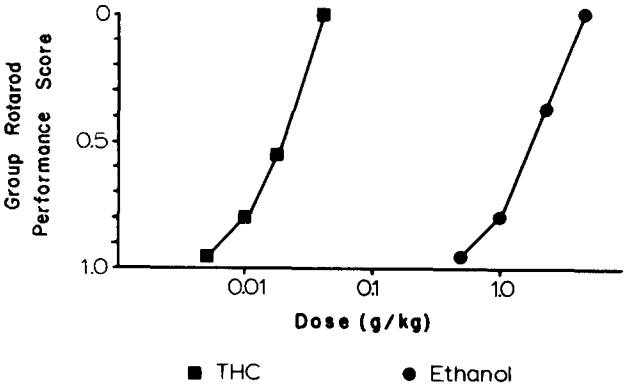

FIG. 1. Dose-response curve for ethanol and THC in mice using rotarod performance measured 20 min after an IP dose of either drug. Group rotarod performance score is determined as the sum of the individual scores divided by the number of animals in the group. Each point consists of at least 10 animals.

Tolerance to THC developed in 7 days with 1 injection/day whereas tolerance to ethanol developed in 12 days with 2 injections/day. Tolerance to ethanol or THC was observed either when performance was measured after each treatment or when rotarod performance was measured only after the final drug treatment.The daily body weights of mice in all treatment groups did not significantly differ from normal animals given no drug treatment.

Table 1 shows the impairment of rotarod performance induced by THC (17 mg/kg), ethanol (1,35 g/kg) and 10% propylene glycol: 1% Tween-80 is isotonic saline (10 ml/kg) in each of the drug treatment groups. Performance was not impaired in any group after the administration of the propylene glycol:Tween 80 mixture. Tolerance to ethanol and THC and cross-tolerance between these 2 drugs was observed in that performance of the ethanol- and THC-treated groups was not significantly impaired by either ethanol or THC. Performance of the groups previously treated for 6 or 11 days with propylene glycol:Tween-80 was significantly imparied by ethanol but was not significantly affected by THC. Thus, treatment with the propylene glycol:Tween-80 mixture for either 6 or 11 days appeared to produce tolerance to THC. An additional study was performed to further evaluate the action of THC (17 mg/kg) in treated groups and to determine if the tolerance to THC and cross-tolerance to THC was induced by the administration of the propylene glycol:Tween-80 mixture. Animals treated with THC in 1% Pluronic F-68 exhibited tolerance to the effects of THC and those treated with ethanol in isotonic saline exhibited cross-tolerance to THC. Neither saline nor Pluronic F-68 treatment had any effect on THC-induced impairment of rotarod performance.

The change in rotarod performance with time after ethanol or THC administration in mice previously treated with ethanol, THC or isotonic saline is shown in Fig. 2. In the animals treated with isotonic saline for 6 or 11 days, the subsequent administration of ethanol or THC produced an initial, significant impariment of rotarod performance. Since the results obtained with either 6 or 11 day isotonic saline treatment did not significantly differ, the results for these 2 groups were pooled and used in Fig. 2. The

TABLE 1

IMPAIRMENT OF ROTAROD PERFORMANCE RESULTING FROM THC, ETHANOL OR PROPYLENE GLYCOL:TWEEN 80 ADMINISTRATION

First Drug Treatment	Second Drug Treatment		
	THC (17 mg/kg)	Ethanol (1.35 g/kg)	10% propylene glycol: 1% Tween 80 (10 ml/kg)
17 mg THC/kg (6 days)	−10.0 (20)	−16.7 (30)	10.0 (20)
10% propylene glycol: 1% Tween 80 (6 days)	−20.0 (20)	−40.0* (40)	5.0 (20)
1.35 g ethanol/kg (11 days)	−10.0 (40)	−15.0 (40)	0.0 (38)
10% propylene glycol: 1%Tween 80 (11 days)	0.0 (20)	−30.0* (20)	5.0 (20)

The first drug was repeatedly administered for the duration indicated in parentheses as described in METHOD. Both ethanol and THC were administered in 10% propylene glycol:1% Tween 80 (in isotonic saline). Values are expressed as the % change in each groups performance from its baseline level and values in parentheses indicate the sizes of the groups used. Rotarod performance after second drug which was significantly different from the baseline level is indicated by *($p<0.05$).

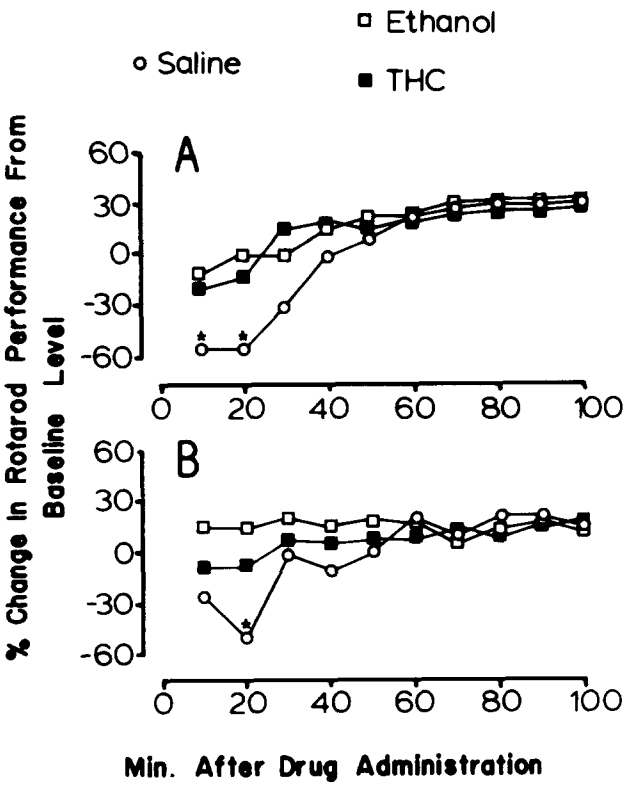

FIG. 2. Change in rotarod performance with time in mice given an IP injection of 1.35 g ethanol/kg (A) or 17 mg THC/kg (B). Prior to ethanol or THC administration, mice were treated with isotonic saline, ethanol or THC as described in METHOD. Ethanol was administered in isotonic saline and THC was administered as a suspension in 1% Pluronic F-68 in isotonic saline. Rotarod performance for each group was compared to its baseline performance level determined prior to any drug treatment in order to evaluate the extent of drug-induced changes in performance. Each group consisted of at least 20 mice and * indicates a significant change in performance from baseline ($p<0.05$).

performance of the ethanol- or THC-treated groups was not significantly impaired at any time within 100 minutes after ethanol or THC administration. A change in the performance to levels greater than baseline was noted in several groups, especially 40–50 min after ethanol or THC administration. Approximately 15–20% of the animals in each group were unable to maintain their balance on the rotarod when the baseline performance level was determined. The improvement in group performance apparently resulted from practice by those animals previously unable to maintain their equilibrium.

Disposition and Metabolism

The blood ethanol concentration determined 20 min after the IP administration of 1.35 g/kg ethanol to normal animals given no treatment was 1.28 ± 0.02 (mean ± S.E.M.) mg/ml and ethanol or THC treatment did not significantly alter this value. When the same dose of ethanol was administered to mice previously treated for 6 or 11 days with 10% propylene glycol:1% Tween-80 in isotonic saline, the blood ethanol concentrations obtained were 1.10 ± 0.02 mg/ml and 1.46 ± 0.02 mg/ml respectively. Both of these values were significantly different from the value obtained for untreated mice.

Table 2 shows the total tissue radioactivity 20 min after the IP administration of ^{3}H-THC (17 mg/kg) to mice given no treatment and mice in each treatment group. Neither THC nor propylene glycol:Tween-80 treatment altered total blood, brain or liver radioactivities. All 3 total tissue radioactivities were significantly higher than control values in the ethanol- treated group.

Figure 3 shows the distribution of extractable radioactivity 20 min after ^{3}H-THC in blood, brain and liver tissues in control animals given no drug treatment and in mice in the treatment groups. Groups treated with ethanol for 11 days or with propylene glycol:Tween-80 for 6 or 11 days showed blood THC metabolite patterns which did not significantly differ from those seen in the control group. The blood of mice treated with THC (17 mg/kg) for 6 days had a significantly higher percentage of radioactivity in Zone 3 (corresponding to 11-OH-THC) than did that of

TABLE 2

TOTAL TISSUE RADIOACTIVITY FOLLOWING ADMINISTRATION OF ^{3}H-THC

First Drug Treatment	Tissue		
	Blood	Brain	Liver
Untreated	5.5 ± 1.1	7.7 ± 1.9	132.6 ± 18.4
17 mg THC/kg (6 days)	5.9 ± 0.7	11.7 ± 3.6	171.6 ± 34.6
10% propylene glycol: 1% Tween 80 (6 days)	5.0 ± 0.9	10.0 ± 1.7	144.6 ± 26.8
1.35 g ethanol/kg (11 days)	8.5 ± 0.6*	14.6 ± 2.6*	198.9 ± 15.8*
10% Propylene glycol: 1% Tween 80 (11 days)	5.9 ± 1.2	9.5 ± 2.5	193.8 ± 38.2

The first drug was repeatedly administered for the duration indicated in parentheses as described in METHODS. The specific activity of the ^{3}H-THC administered following the termination of treatment with the first drug is also described in METHODS. Ethanol, THC and ^{3}H-THC were administered in 10% propylene glycol:1% Tween 80 (in isotonic saline). Values are expressed as mean ± S.D. x 10^3 dpm/ml or g of wet tissue. Each group consisted of 6 mice and * signifies values which are significantly different from those for the untreated group ($p<0.05$).

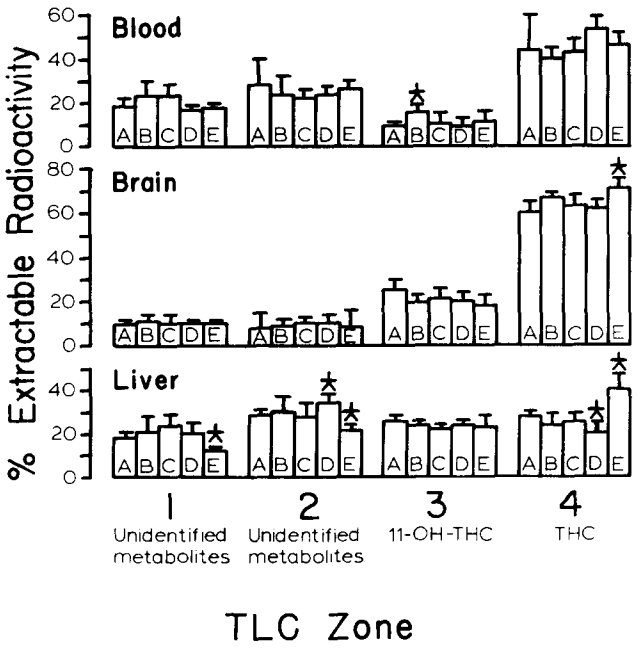

FIG. 3. Distribution of extractable radioactivity in blood, brains and livers of mice 20 min after the administration of ^{3}H-THC. Animals were previously treated with 17 mg THC/kg for 6 days, 1.35 g ethanol/kg for 11 days or 10% propylene glycol: 1% Tween 80 in isotonic saline for 6 or 11 days. Both THC and ethanol were administered in 10% propylene glycol:1% Tween 80 (in isotonic saline). Values are expressed as means of % extractable radioactivity in each TLC zone and standard deviations are indicated by brackets. Each group consisted of 6 mice and * indicates values which are significantly different from those obtained from untreated animals ($p<0.05$). (A) Untreated; (B) THC-treated (6 days); (C) Propylene glycol: Tween 80-treated (6 days); (D) Ethanol-treated (11 days); (E) Propylene glycol: Tween 80-treated (11 days).

control animals. The brain THC metabolite ratio was altered only in the group treated for 11 days with the propylene glycol:Tween-80 mixture where a significantly higher percentage of radioactivity was observed in Zone 4 (corresponding to THC) than in control animals. Mice treated for 6 days with either THC or the propylene glycol:Tween-80 mixture showed a higher percentage of radioactivity in Zone 2 and a lower percentage in Zone 4 compared to control values. The THC liver metabolite ratios were also altered in the group treated for 11 days with propylene glycol:Tween-80, with a higher percentage of radioactivity found in Zone 4 and lower levels in Zones 1 and 2 compared to controls.

Figure 3 also shows that the distribution of radioactivity differed in the 3 tissues used. The percentage of radioactivity in the blood which appeared in Zone 4 (THC) was about 4 times that in Zone 3 (11-OH-THC). Almost one-half of the radioactivity in blood was found in Zones 1 and 2 corresponding to highly polar THC metabolites. In the brain, however, less than 15% of the radioactivity was found in Zones 1 and 2, approximately 29% was in Zone 3, and Zone 4, corresponding to the parent THC, contained more than 69% of the radioactivity. In liver tissue, it was found that the radioactivity was approximately equally distributed between the 4 TLC zones.

DISCUSSION

Tolerance to the effects of both ethanol and THC in mice was observed in the present study using rotarod performance as a measure of drug action. Treatment with ethanol had no effect upon the elimination of subsequently administered ethanol, suggesting that tolerance to this drug did not develop through a pharmacokinetic alteration. Pharmacokinetic processes include the absorption, distribution and elimination of a drug. The present study also showed no indication for a behaviorally augmented tolerance to ethanol since the frequency of measurement of rotarod performance in ethanol treated animals had no effect upon the rate of tolerance development. These results support those from other studies which indicate that tolerance to ethanol develops through a process of tissue adaptation at the site of drug action [12, 13, 20].

Tolerance to THC has been demonstrated in several species, including mice, using several measures of drug action [19] and the present study confirms this. The mechanism for this tolerance has not been clearly established, however. The results of some experimental studies suggest that THC tolerance develops due to an increased rate of THC metabolism following chronic administration of this drug [3,7]. Other studies show that tolerance to THC may involve tissue adaptation [11,19] with no change in the rate of THC metabolism. Results from this study using mice, showed that behaviorally augmented tolerance to THC did not develop and also that tolerance to THC did not result because of stimulated hepatic metabolism or changes in whole brain levels of this drug. THC distribution was not altered from control values after a dose of THC in animals treated with THC since whole tissue radioactivities were similar in THC-treated and untreated control groups. Blood THC metabolite ratios were altered in the THC-treated group but the distribution of THC or its metabolites in the brain was not affected by this change. This observed alteration of blood THC metabolite ratios was not affected by a change in hepatic THC metabolism and it may reflect either altered metabolism in another tissue or a change in blood proteins which bind THC and its metabolites. The latter possibility may explain this observed change since THC and its metabolites in blood have been shown to be largely protein bound with different proteins responsible for transporting the parent THC and its metabolites [27,30].

A symmetrical cross-tolerance was demonstrated in the mouse between equipotent doses of ethanol and THC using rotarod performance as a measure of drug action. This confirms the observed cross-tolerance to ethanol in the rat after THC pretreatment found in other studies [21,22] and further indicates that the cross-tolerance is symmetrical and can be demonstrated using an unlearned motor task and relatively low doses of the 2 drugs. The contradiction in the literature regarding development of cross-tolerance between ethanol and THC may result from differences in dosages of the 2 drugs and the vehicles used to administer THC. All studies, including the present one, which demonstrated cross-tolerance between ethanol and THC used equipotent doses of the 2 drugs [21,22] and this was not the case in the study failing to demonstrate cross-tolerance [10]. Ethanol and THC were given via the same route in studies demonstrating cross-tolerance and the absorption of THC given in the propylene glycol vehicle used in the present study was clearly demonstrated using tissue levels of THC

and its metabolites determined after a dose of ^{3}H-THC. In the study which found no evidence for cross-tolerance between ethanol and THC, THC was given intravenously in a protein-containing vehicle. Because of the high degree of protein binding of THC [27], the usefulness of this vehicle to administer THC is questionable.

The observed cross-tolerance to ethanol may involve tissue adaptation since ethanol or THC treatment had no effect on blood levels of subsequently administered ethanol. The mechanism for cross-tolerance to THC appears to be more complex. Ethanol treatment significantly altered the distribution of a subsequent dose of THC. An effect similar to this has been demonstrated using rats in another study in which the oral absorption of diazepam was enhanced following oral ethanol treatment [29]. Gross peritoneal damage was not observed in animals treated with ethanol in the present study, but ethanol may have produced functional alterations in biomembranes leading to enhanced drug abosrption. This appears to be an area in which further study is needed. Ethanol also apparently stimulated the hepatic metabolism of THC as evidenced by higher proportions of polar THC metabolites observed in those animals treated with ethanol. This may be related to the altered THC distribution due to ethanol since the extent of hepatic THC metabolism in rats has been shown to be related to the dose of THC absorbed [24]. The blood and brain THC metabolite ratios were unaltered from control values in ethanol-treated animals. This confirms results from another study which demonstrated that levels of THC and its metabolites in the brain are less affected by changes in hepatic THC metabolism than are liver and bile levels [24].

It appears then, that the development of cross-tolerance to THC following ethanol adminstration involves some changes in the metabolism and disposition of a subsequently administered dose of THC but these changes tend to produce higher brain levels of THC due to its altered distribution. The mechanism involved in the development of cross-tolerance to THC is apparently that of tissue adaptation at the site of drug action. This is identical to that hypothesized for the development of tolerance to ethanol or THC and also for development of cross-tolerance to ethanol.

In other studies dealing with the effect of THC, this drug is frequently administered in a vehicle containing propylene glycol. Two significant vehicle effects were observed in the present study. It was shown that (1) treatment of mice twice daily for 11 days with 10% propylene glycol:1% Tween-80 in isotonic saline impaired the elimination of a subsequently administered dose of either ethanol or THC. Since the primary route of metabolism of propylene glycol, the major component of this vehicle, involves the action of several oxidative enzymes to form lactic acid, these enzymes may be similar to those suggested to metabolize ethanol [2,14] and THC [4,28]. The mechanism for the observed effect of the propylene glycol vehicle upon ethanol and THC elimination remains to be resolved. It was also found that (2) either 6 or 11 day treatment with the propylene glycol:Tween-80 mixture diminished the observed behavioral effect resulting from THC administration. The metabolic effect produced by 11 day treatment with this mixture could not be responsible for the effect since higher, rather than lower, brain levels of the active compounds were evident. No metabolic effect was shown in the group treated for 6 days with the propylene glycol:Tween-80 mixture but tolerance to THC was still evident. Propylene glycol, the main component of the solvent used, has been shown to produce behavioral effects similar to those produced by ethanol [9]. The cross-tolerance to THC produced by administration of the propylene glycol:Tween-80 mixture observed here may be similar to that produced by ethanol. These results indicate, that in future studies involving repeated administration of THC, the use of another vehicle may be advisable.

Studies have been done in humans which show many similar actions of ethanol and THC [1, 8, 18]. Studies using experimental animals to compare the actions of ethanol and THC have also shown evidence for similar actions of the 2 drugs and in some cases these effects were found to be additive [6, 15, 23, 15]. The results of this study further suggest that ethanol and THC may have similar modes of action. Both of these agents produce a similar type of behavioral impairment in mice measured using performance on a rotarod apparatus (Fig. 1). Further evidence for a similar mechanism of action of ethanol and THC is presented by the development of symmetrical cross-tolerance between these 2 drugs. The mechanism for development of tolerance to ethanol or THC and cross-tolerance between these drugs is also similar and apparently may involve a process of tissue adaptation at the site of drug action rather than changes in their absorption, distribution and elimination.

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