the test tone combinations shift in their position along the scale. For instance, if the pitch memory store were laid out in a linear fashion, the peak of errors should appear to move progressively closer to the pitch of the first test tone as the test tone combinations move upward in the scale. However, no such peak shift in either direction is discernible from the data. It would therefore appear that the pitch memory store is logarithmically arranged.

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Δ^9-Tetrahydrocannabinol and Ethyl Alcohol: Evidence for Cross-Tolerance in the Rat

Abstract. *Rats trained in a one-way avoidance situation were made tolerant to the depressant effects of Δ^9-tetrahydrocannabinol. Ethyl alcohol (3.2 grams per kilogram, intraperitoneally) did not greatly affect rats that were tolerant to Δ^9-tetrahydrocannabinol but depressed the behavior of nontolerant rats. Rats made tolerant to ethyl alcohol were less affected by Δ^9-tetrahydrocannabinol.*

Many claims and counterclaims have been made about whether marijuana use leads to abuse of other pharmacological agents. This controversy rages in spite of a paucity of data on cross-tolerance between cannabis derivatives and other drugs of abuse. Two studies that deal with this problem are both concerned with hallucinogenic compounds. These studies indicate a lack of cross-tolerance between (−)-Δ^9-*trans*-tetrahydrocannabinol (Δ^9THC) and D-lysergic acid diethylamide-25 (LSD-25) in man (*1*) and between Δ^9THC and LSD-25 or mescaline in rats (*2*).

Implicit in the conceptualization of these studies is the assumption that cannabis derivatives are hallucinogenic. While it is true that these agents have hallucinogenic properties, there is evidence that the cannabis derivatives have sedative and depressant (*3*) as well as analgesic effects (*4*). It seemed reasonable to look for cross-tolerance to representatives of these classes of drugs. Our results support the hypothesis that there exists a cross-tolerance between Δ^9THC and ethyl alcohol.

Subjects were 40 male Holtzman albino rats that weighed 270 to 440 g at the start of the experiment. They had free access to food and water throughout the experiment. The animals were tested in a one-way shock avoidance apparatus (*5*). The start of a trial was signaled by illumination of a circle of lights. The animal had 5 seconds to jump onto a platform before the onset of 1.0-ma shock administered via the grid floor. The shock remained on for 5 seconds or was terminated when the rat jumped on the platform. The lights also went off at this time. After 30 seconds the animal was automatically pushed from the ledge back onto the grid to await the start of the next trial. The trials were presented on a variable-interval schedule with a 30-second average interval. The subjects were given 50 trials per day and were tested 5 days per week.

The experimental procedures are shown in Table 1. There were ten rats in each group. The criterion of tolerance was 90 percent avoidance or greater 3 out of 5 days. The Δ^9THC (*6*) was suspended in 4 percent Tween-20. (The Tween-20 solution alone is referred to as vehicle.) A 15 percent solution (by volume) of ethyl alcohol in 0.9 percent saline was used. All injections were given 5 minutes before the animals were placed in the avoidance box. The dose of Δ^9THC was 20 mg/kg, and that of ethyl alcohol was 3.2 g/kg. With Δ^9THC the tolerance criterion was met in 13.1 ± 2.7 days. Statistical analyses were performed by orthogonal comparisons with a significance level of $P < .05$.

Administration of saline had no observable effect on avoidance responses (Fig. 1), but ethyl alcohol reduced these responses to 58.7 percent. On the day after alcohol administration the

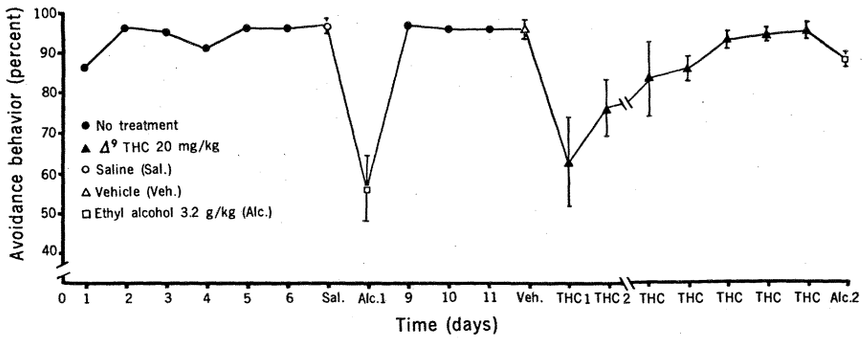

Fig. 1. Effects of ethyl alcohol before and after development of tolerance to Δ^9THC. Ten animals were used. The break in the time scale during Δ^9THC administration is due to the fact that the animals met the tolerance criterion in varying periods of time, with the average time being 13.1 ± 2.7 days.

Table 1. Schedule of experimental procedures for animals in different drug-treatment categories. There were five sets of 50 trials per week at all times. Trial days are numbered consecutively. During the tolerance acquisition period, the indicated treatment was given 7 days per week.

Time	Drug-treatment category			
	Δ^9THC given:		Vehicle given before trials	Ethyl alcohol given before trials
	Before trials	After trials		
Day 1 to 6	Training trials	Training trials	Training trials	Training trials
Day 7	Saline injection 5 minutes before trials	Saline injection 5 minutes before trials	Saline injection 5 minutes before trials	Vehicle injection 5 minutes before trials
Day 8	Ethyl alcohol 5 minutes before trials	Ethyl alcohol 5 minutes before trials	Ethyl alcohol 5 minutes before trials	Δ^9THC 5 minutes before trials
Day 9 to 11	Trials with no drug treatment	Trials with no drug treatment	Trials with no drug treatment	Trials with no drug treatment
Day 12	Vehicle 5 minutes before trials	Vehicle after trials	Vehicle 5 minutes before trials	Saline 5 minutes before trials
Tolerance acquisition	Δ^9THC daily, 5 minutes before trials on trial days, until tolerance is seen	Δ^9THC daily, after trials on trial days, for 21 days	Vehicle daily, 5 minutes before trials on trial days, for 21 days	Ethyl alcohol daily, 5 minutes before trials on trial days, until tolerance is seen
Test	Ethyl alcohol 5 minutes before trials	Ethyl alcohol 5 minutes before trials	Ethyl alcohol 5 minutes before trials	Δ^9THC 5 minutes before trials

animals were back to baseline performance. The initial administration of Δ^9THC produced a depression of avoidance behavior, but this effect became progressively less with continued administration of Δ^9THC. Clearly, the second alcohol administration was without significant effect. That is, tolerance to Δ^9THC seems to confer tolerance to the disruptive effects of alcohol on avoidance behavior.

Two questions require an immediate answer. (i) Could the lessened response to the second administration of ethyl alcohol be due to the extra training during Δ^9THC administration? (ii) Did the animals learn to react while being intoxicated with Δ^9THC—a state-dependent learning—and were thus able to respond while under alcohol intoxication?

Since one subject took 21 days to develop tolerance to Δ^9THC, we used 21 days as the analogous period for control groups. When vehicle was given for 21 days and then alcohol given a second time, the effects of alcohol (percentage of avoidance, 56.0 ± 10.0) were slightly greater than those after the first dose (50.6 ± 7.8), but this difference was not statistically significant ($P > .05$). When we gave Δ^9THC after the daily session for 21 days, and thus did not test animals that were under the influence of just-administered Δ^9THC, we observed a significant improvement in performance after the second alcohol administration (percentage of avoidance, from 48.2 ± 10.3 to 77.6 ± 7.0; $P < .01$). There were no significant differences between the performances of the three groups after alcohol was given the first time. After the second dose of alcohol, both groups that had received the Δ^9THC (either before or after the session) had significantly higher avoidance scores than did the group that had received vehicle alone. There was no significant difference between the two groups that received Δ^9THC. Thus, the observation of a decreased response to ethyl alcohol in rats tolerant to Δ^9THC cannot be explained by either increased training or state-dependent learning.

Other data indicate that the cross-tolerance is symmetrical. The animals that were given Δ^9THC and then made tolerant to the effects of ethyl alcohol showed significantly improved avoidance (40 percent) to the second dose of Δ^9THC. The cross-tolerance is dose related; that is, making animals tolerant to the effects of Δ^9THC shifts the dose-response function for ethyl alcohol to the right.

Support for the existence of cross-tolerance between Δ^9THC and ethyl alcohol comes from Thompson and Proctor (*7*) who demonstrated that pyrahexyl, a synthetic THC derivative, ameliorates the symptoms of patients with postalcoholic syndromes. Jones and Stone (*8*) have shown that heavy marijuana users are resistent to the effects of 120 to 150 ml of 100-proof alcohol and "responded to this substantial dose of alcohol much as a group of chronic alcoholic users might." Their results, along with our data, are evidence for the existence of cross-tolerance between Δ^9THC and ethyl alcohol. This cross-tolerance does not appear to be due to training or state-dependent learning, but rather to the drugs themselves. Of course much more research in a wide variety of species and on different behaviors needs to be done to determine the generality of these findings. Social implications are unwarranted until much more extensive pharmacological and behavioral research has been done. It is hoped that these results will stimulate such needed research.

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