Psychopharmacologia (Berl.) 39, 193—198 (1974)

Original Investigations

Effect of Δ^8-THC on Alcohol-induced Sleeping Time in the Rat

E. Friedman and S. Gershon

Neuropsychopharmacology Research Unit, Department of Psychiatry
New York University Medical Center, New York, New York

Received January 15, 1974; Final Version May 27, 1974

Abstract. The effect of acute and repeated Δ^8-THC administration on alcohol-induced sleeping time was studied in male albino rats. We have observed that acute pretreatment with Δ^8-THC markedly potentiates alcohol-induced sleeping time in a dose-related manner. This potentiation of the alcohol sleeping time is shortened significantly after repeated prior treatment with Δ^8-THC and can be observed 72 hrs post-chronic treatment. The effect of Δ^8-THC on alcohol-induced sleeping time is not associated with an altered alcohol metabolism rate.

Key words: Acute and Chronic Δ^8-THC — Alcohol — Sleeping Time.

Introduction

In its social use, *Cannabis sativa* often interacts with ethyl alcohol. The results are reported to be the enhancement of the cannabis effects. In man, marihuana and alcohol impair motor and mental performance (Manno, Kiplinger, Scholz, and Forney, 1971; Hollister and Gillespie, 1970; Jones and Stone, 1970); in rats, Jaffe and Baum (1971) found that both alcohol and marihuana increased the number of trials required to reach an extinction criterion. Moreover, loss in short-term memory has been reported for both alcohol and marihuana (Ames, 1958; Melges, Tinklenberg, Hollister, and Gillespie, 1970; Tamiren, Weiner, Popper, Steinglass, and Mendelson, 1971). Newman, Lutz, Gould, and Domino (1972) have found that rats that were tolerant to the depressant effect of Δ^9-tetrahydrocannabinol (Δ^9-THC) in a one-way avoidance situation were not affected by alcohol, while in nontolerant rats alcohol depressed this behavior. Alcohol sleeping time in rats has been shown to be potentiated by prior treatment with Δ^9-THC (Forney and Kiplinger, 1971). In this report, we describe the effects of acute and repeated pretreatment with Δ^8-tetrahydrocannabinol (Δ^8-THC) on alcohol-induced sleeping time in rats. We also explore the possible effect of Δ^8-THC on the disposition of alcohol in blood and brain.

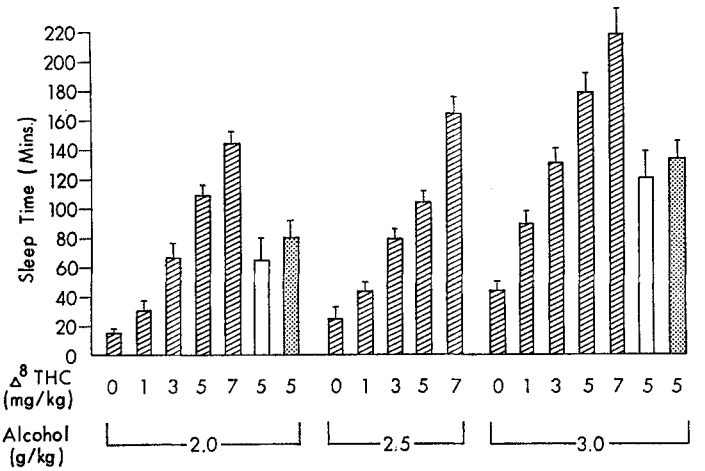

Fig. 1. The effect of prior treatment with Δ^8-THC on alcohol-induced sleeping time. Rats were pretreated with single (lined bars) and repeated (clear bars) injections of Δ^8-THC, followed by a single dose of ethyl alcohol 15 min later; sleeping time was subsequently measured. Dotted bars represent the sleeping time of group of animals which were treated with Δ^8-THC for 8 days, allowed 3 days off drug, and then injected with Δ^8-THC, 5 mg/kg i.p., followed by ethanol 15 min later. Each bar represents the mean $\pm$ S.E.M. of 12 rats

Methods

The experiments were conducted on male Sprague-Dawley rats weighing 200—250 g, housed in a 12-hrs light/12-hrs darkness lighting cycle, with lab chow and water *ad lib*. Synthetic Δ^8-THC (received from Professor Mechoulam, Jerusalem, Israel) was injected intraperitoneally (i.p.) as a suspension in propylene glycol-saline-1% Tween 80, as described by Kubena and Barry (1970). The control injection consisted of the suspension vehicle. Repeated treatment consisted of eight single daily injections of either THC singly or its vehicle. Ethanol (20%, v/v) was administered i.p. 15 min following the last injection of Δ^8-THC. Sleeping time was measured as the period between the loss of the righting reflex and the first spontaneous movement of the animal after regaining its righting reflex. Tail blood and brain alcohol levels were determined by a gas chromatographic procedure (Wallace and Daohl, 1966).

The data were analyzed by means of Student's *t* test.

Results

The Effects of Acute and Chronic Δ^8-THC Treatments on Alcohol Sleeping Time. The effect of Δ^8-THC on alcohol sleeping time is shown in Fig. 1. A dose-related increase of alcohol sleeping time was observed at the 3 doses of alcohol employed. The percentage increase in alcohol-induced sleeping time diminished, however, as the dose of alcohol was increased while maintaining the Δ^8-THC dose constant. This phenomenon

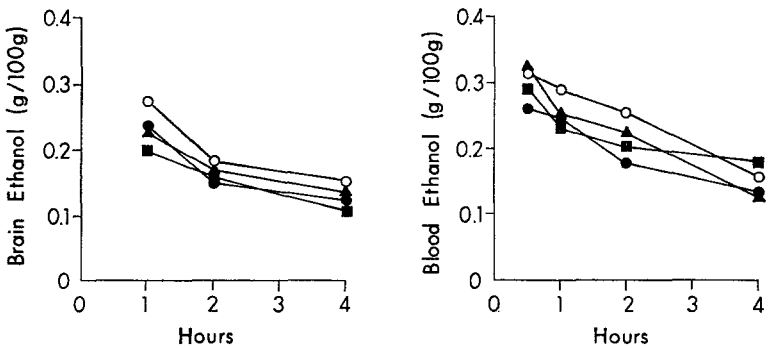

Fig. 2. Blood and brain ethanol levels in rats pretreated with various doses of Δ^8-THC, followed by ethanol (2 g/kg) 15 min later. Each point is the mean level obtained from 8 rats. Control vehicle pretreated (o——o); THC, 3 mg/kg (▲——▲); THC, 5 mg/kg (■——■); and THC, 10 mg/kg (■)

was especially noted with the higher (5 and 7 mg/kg) doses of THC. Enhancement of alcohol sleeping time of the order of 2 to 4 times control values was obtained with the 1 and 3 mg/kg doses of Δ^8-THC, and 4 to 10 times control values with the 5 and 7 mg/kg doses of Δ^8-THC.

Partial tolerance to the Δ^8-THC-induced increase in alcohol sleeping time was observed after repeated treatment with the cannabinol. Following a chronic pretreatment with eight single daily doses of Δ^8-THC 5 mg/kg, significant ($P < 0.01$) reductions in alcohol sleeping times (Fig. 1, clear bars) were observed when compared with a single pretreatment does of Δ^8-THC 5 mg/kg. This partial tolerance development to the effect of THC following prolonged treatment lasted at least 72 hrs. Rats pretreated with eight successive daily doses of THC were allowed 72 hrs off the drug and on the third day received Δ^8-THC 5 mg/kg followed by alcohol 15 min later. Alcohol sleeping time was not altered by the 3-day interruption of treatment with Δ^8-THC, and remained significantly ($P < 0.01$) reduced from the effect observed after a single injection of Δ^8-THC.

The Effects of Prior Treatment with Δ^8-THC on Blood and Brain Ethyl Alcohol Levels. Groups of animals were pretreated with various acute doses of Δ^8-THC. They were administered ethyl alcohol; brain and blood ethyl alcohol levels were measured at $^1/_2$, 1, 2, and 4 hrs thereafter. Brain and blood alcohol concentrations were not significantly altered by previous treatment with Δ^8-THC (Fig. 2). Likewise, repeated prior treatment with Δ^8-THC for 8 consecutive days did not alter the metabolism of blood alcohol (Fig. 3). Statistical significance was determined by the t test between pairs of conditions at the various time intervals.

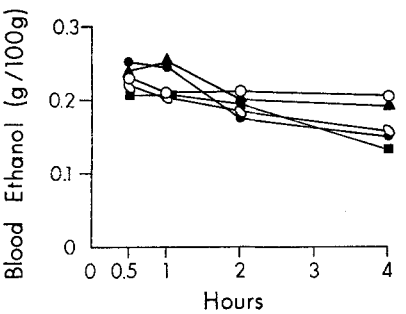

Fig. 3. Blood ethanol levels in rats injected with ethanol (2 g/kg) following pretreatment with various repeated doses of Δ^8-THC. The points represent the mean alcohol levels of 8 rats: chronic vehicle (▲); chronic vehicle followed by acute THC, 5 mg/kg and ethanol 15 min later (●); chronic THC, 3 mg/kg (○); chronic Δ^8-THC, 5 mg/kg (■); chronic THC, 10 mg/kg (□)

Discussion

The enhancement of alcohol sleeping time by Δ^8-THC is in agreement with the previous data by Forney and Kiplinger (1971) on Δ^9-THC. These observations are in general accord with the prevailing view of the qualitative similarities between the two active isomers of THC.

Alcohol and the tetrahydrocannabinols are similar in some aspects of their pharmacology. Both drugs have been described as central nervous system depressants at some doses and environmental settings. Hollister and his coworkers (1970) have compared the drugs in man and have found them alike in decreasing motor activity and in impairing performance on psychometric tests. Similarly, alcohol and Δ^9-THC impaired psychomotor performance on reaction time (Hollister *et al.*, 1970). Additive effects of alcohol on the THC effects in man were also observed by Manno *et al.* (1971). The possibility of cross-tolerance between alcohol and marihuana in man was raised in a study by Jones and Stone (1970). These authors reported tolerance to the effects of both marihuana and alcohol in heavy users of marihuana. Cross-tolerance between Δ^9-THC and alcohol was also shown to occur in rats trained in a one-way avoidance situation by Newman *et al.* (1972).

The diminished effect of alcohol after protracted treatment with Δ^8-THC, as compared with a single acute pretreatment dose of the drug, may suggest an induction of drug-metabolizing enzymes by THC that affects the metabolism of alcohol. This mechanism, however, is not supported by the present study. Prior injection of Δ^8-THC (singly or repeatedly) did not significantly alter the disposition of blood ethanol. In brain, acute pretreatment with various doses of Δ^8-THC resulted in a

trend toward lower ethanol levels, but these did not attain significance when compared with levels in vehicle-pretreated rats. Similarly, Dewey, Kennedy, and Howes (1970) have found that 5 injections of Δ^9-THC in cats did not alter microsomal drug-metabolizing activity. This conclusion is also supported by studies by Dewey, McMillan, Harris, and Turk (1973) in pigeons and by Lawrence and Pertwee (1973) in rats, in which no differences in the metabolism and distribution of THC and its metabolites occurred after repeated administrations of THC.

The long-lasting (72 hrs) effects observed following repeated treatment with Δ^8-THC may be associated with its long half-life in man and rat (Agurell, Nilsson, Ohlsson, and Sandberg, 1970; Klausner and Dingel, 1971; Lemberger, Silberstein, Axelrod, and Kopin, 1970).

In conclusion, we have observed that acute pretreatment with Δ^8-THC markedly potentiates alcohol-induced sleeping time in a dose-related manner. This potentiation of the alcohol sleeping time is shortened significantly after repeated prior treatment with Δ^8-THC and can be observed 72 hrs post-chronic treatment. The effects of Δ^8-THC on alcohol-induced sleeping time do not involve altered metabolic rates of alcohol, and may be due to action on the central nervous system.

Acknowledgment. The authors wish to thank Diane Forde for her excellent assistance.

References

Agurell, S., Nilsson, I. M., Ohlsson, A., Sandberg, F.: On the metabolism of tritium-labeled Δ^1-tetrahydrocannabinol in the rabbit. Biochem. Pharmacol. **19**, 1333—1339 (1970)

Ames, F.: A clinical and metabolic study of acute intoxication with cannabis sativa and its role in model psychosis. J. ment. Sci. **104**, 972—999 (1958)

Dewey, W. L., Kennedy, J. S., Howes, J. F.: Some autonomic, gastrointestinal and metabolic effects of two constituents of marihuana. Fed. Proc. **29**, 650 (1970)

Dewey, W. L., McMillan, D. E., Harris, L. S., Turk, R. F.: Distribution of radioactivity in brain of tolerant and non-tolerant pigeons treated with ^{3}H-Δ^9-tetrahydrocannabinol. Biochem. Pharmacol. **22**, 399—405 (1973)

Forney, R. B., Kiplinger, G. F.: Toxicology and pharmacology of marihuana. Ann. N.Y. Acad. Sci. **191**, 74—79 (1971)

Hollister, L. E., Gillespie, H. K.: Marihuana, ethanol and dextroamphetamine: mood and mental function alterations. Arch. gen. Psychiat. **23**, 199—203 (1970)

Jaffe, P. G., Baum, M.: Increased resistance to extinction of an avoidance response in rats following the administration of hashish resin. Psychopharmacologia (Berl.) **20**, 97—102 (1971)

Jones, R., Stone, G.: Psychological studies of marijuana and alcohol in man. Psychopharmacologia (Berl.) **18**, 108—117 (1970)

Klausner, H. A., Dingell, J. V.: The metabolism and excretion of Δ^9-tetrahydrocannabinol in the rat. Life Sci. **10**, 49—59 (1971)

Kubena, R. K., Barry, H.: Interactions of Δ^1-tetrahydrocannabinol with barbiturates and methamphetamine. J. Pharmacol. exp. Ther. **173**, 94—100 (1970)

Lawrence, D. K., Pertwee, R. G.: Brain levels of Δ^1-tetrahydrocannabinol and its metabolites in mice tolerant to the hypothermic effect of Δ^1-tetrahydrocannabinol. Brit. J. Pharmacol. **49**, 373—375 (1973)

Lemberger, L., Silberstein, S. D., Axelrod, J., Kopin, I. J.: Marihuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. Science **170**, 1320—1322 (1970)

Manno, J. E., Kiplinger, G. F., Scholz, N., Forney, R. B.: The influence of alcohol and marihuana on motor and mental performance. Clin. Pharmacol. Ther. **12**, 202—211 (1971)

Melges, F. T., Tinklenberg, J. R., Hollister, L. E., Gillespie, H. K.: Marihuana and temporal disintegration. Science **168**, 1118—1120 (1970)

Newman, L. M., Lutz, M. P., Gould, M. H., Domino, E. F.: Δ^9-Tetrahydrocannabinol and ethyl alcohol: evidence for cross-tolerance in the rat. Science **175**, 1022—1023 (1972)

Tamiren, J. S., Weiner, S., Popper, R., Steinglass, P., Mendelson, J. H.: Alcohol and memory: Amnesia and short-term memory function during experimentally induced intoxication. Amer. J. Psychiat. **127**, 95—100 (1971)

Wallace, J. E., Dahl, E. V.: Rapid vapor phase method for determining ethanol in blood and urine by gas chromatography. Amer. J. clin. Path. **46**, 152—154 (1966)

Dr. E. Friedman
Neuropsychopharmacology Research Unit
Department of Psychiatry
New York University Medical Center
550 First Avenue
New York 10016, U.S.A.