THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 197, No. 3

Printed in U.S.A.

TOLERANCE AND LIMITED CROSS-TOLERANCE TO THE EFFECTS OF N,N-DIMETHYLTRYPTAMINE (DMT) AND LYSERGIC ACID DIETHYLAMIDE-25 (LSD) ON FOOD-REWARDED BAR PRESSING IN THE RAT[1, 2]

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Accepted for publication January 20, 1976

KOVACIC, BEVERLY AND EDWARD F. DOMINO: Tolerance and limited cross-tolerance to the effects of N,N-dimethyltryptamine (DMT) and lysergic acid diethylamide-25 (LSD) on food-rewarded bar pressing in the rat. J. Pharmacol. Exp. Ther. **197:** 495–502, 1976.

Lysergic acid diethylamide-25 (LSD) and N,N-dimethyltryptamine (DMT) abolish food-rewarded, fixed-ratio bar pressing by rats in a dose-related fashion. Adult male Holtzman rats trained to press a bar (respond) for milk reward on a 4-response fixed-ratio schedule were given i.p. injections of 3.2 or 10 mg/kg of DMT every 2 hours for 21 days. Every 24 hours the animals were placed in operant chambers for 30 minutes before a scheduled injection and were left in the chambers for 30 to 80 minutes after. During the first week of chronic treatment, daily bar pressing worsened progressively until the 6th day of the series, at which time rats in the 10 mg/kg group did not bar press at all. As the chronic injections continued, rates of bar pressing gradually increased until responding was not disrupted at all by an injection of DMT. Rats in the 3.2 mg/kg group showed cross-tolerance to an injection of LSD (0.1 mg/kg). Another group of rats was made partially tolerant to the disruptive effects of LSD (0.1 mg/kg i.p.) on bar pressing with a series of injections given once per day for 21 days and then three times per day for the next 4 days. Cross-tolerance was not demonstrated to a challenge injection of 10 mg/kg of DMT. The LSD injections were continued for another 3 to 5 days until the animals were completely tolerant to the LSD. They then displayed cross-tolerance to 3.2 mg/kg of DMT.

N,N-Dimethyltryptamine (DMT) is structurally similar to a portion of the lysergic acid diethylamide-25 (LSD) molecule and in humans produces acute psychic and autonomic effects similar to those of LSD, although of quicker onset and shorter duration (Szára, 1956; Sai-Halász *et al.*, 1958). In several animal species, the two drugs have similar effects on a variety of responses.

Tolerance to mental and physical effects of LSD in man (Isbell *et al.*, 1956, 1961) and behavioral effects of LSD in rats (Appel and Freedman, 1968; Rech *et al.*, 1974; Tilson and

Received for publication February 4, 1975.
[1] This study was supported by a grant from the State of Michigan for schizophrenia research.
[2] A preliminary abstract of this work was presented at the April 1974 FASEB Meetings in Atlantic City (Kovacic and Domino, 1974).

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Sparber, 1973; Winter, 1971) has been demonstrated. Humans display a mild degree of cross-tolerance to the mental but not physical effects of DMT (Rosenberg *et al.*, 1964). Attempts to demonstrate tolerance to DMT have so far yielded negative results (Cole and Pieper, 1973; Gillin *et al.*, 1973; Kaplan *et al.*, 1974; Rech *et al.*, 1974). DMT appears to be rapidly biotransformed (Szára, 1956) and, considering injection schedules employed in the cited DMT tolerance studies, failure to demonstrate tolerance may have been due to failure to maintain sufficiently high tissue levels of the drug for an adequate period of chronic treatment.

The present study demonstrates that if injections are given frequently for an extended period of time, tolerance develops to the disruptive effects of DMT on food-rewarded bar pressing in rats. Further, DMT-tolerant rats display some cross-tolerance to LSD. Rats made tolerant to LSD display some cross-tolerance to DMT.

Methods

Male Holtzman rats at least 90 days old were housed individually in a room with constant temperature and humidity. Experiments were conducted in an isolated, darkened room using operant chambers obtained from Lehigh Valley Electronics, Fogelsville, Pa. (rodent test cages, model 143-21). Each box had a single bar which was located 5 cm above the floor of the box and required an operating force of approximately 24 g. A solenoid driven dipper with a cup size of 0.01 ml, when activated, dipped into a reservoir and returned immediately to a position accessible from the animal working space. Walls were of Plexiglas. Each box was equipped with a light and masking noise and was enclosed in an insulated, ventilated outer cubicle. Doors of the cubicle were fitted with viewing mirrors but, in the darkened experiment room, the doors could be opened or closed cautiously without disturbing bar pressing. They were left open during observation periods to facilitate viewing several animals simultaneously.

Rats were given Purina chow pellets daily in amounts estimated to maintain their weights at 70% of expected free-feeding weights. Estimates took into consideration amounts of food consumed during experimental sessions. The rats were trained to bar press for an hour a day for sweetened milk which was prepared by combining 400 ml of Carnation evaporated milk, 400 ml of tap water and 60 g of table sugar. The bar pressing schedule was fixed-ratio four (FR_4), *i.e.*, every fourth press activated the milk dipper. Bar presses and reinforcements were recorded automatically on cumulative recorders. After the FR_4 behavior of each rat had stabilized, it was exposed to the schedule for an hour a day for at least 5 days before any injections were given. After each experimental session, rats were given a food pellet in individual transport cages to accustom them to eating at that time and place.

Some of the rats used in the present study (groups II, III, IV and V, described below) had been used in earlier drug experiments (Kovacic and Domino, 1973) but had not received any long-acting compounds. They were drug-free for at least 10 days before the start of the present investigation.

Acute effects of DMT were examined by injecting 26 rats (group I) i.p. with 0, 1, 3.2, 10 or 32 mg/kg, and placing them immediately in operant chambers. They were observed continuously while bar pressing was disrupted or for 1 hour, whichever period was shorter. A checklist of the gross behavior of the animals while under the influence of DMT was developed. After each rat recovered from DMT, as judged by commencement of steady bar pressing, it was left in the chamber for another 60 minutes. If a rat was not bar pressing at 1 hour after injection, which occurred only after 32 mg/kg of DMT, it was removed from the chamber and placed on a table top for about 3 minutes while its posture, gait, exploratory behavior and awareness of table edges were observed. The rat was then placed in a transport cage to determine whether it would accept or ignore a food pellet and then was returned to the chamber. The table-top, food-offer routine was repeated at 30 minute intervals until the rat began bar pressing steadily. Animals in group I were not used again in the present study.

The procedure for examining drug effects in the remaining experiments was as follows. A rat was placed in an operant chamber and 30 minutes later was injected i.p. with the drug under study. The rat was observed continuously while bar pressing was disrupted or for 1 hour after the injection, whichever period was shorter, and was removed from the chamber 30 to 90 minutes after the injection. The rat was not handled during the session except when it was given the injection.

Acute LSD effects were examined in four rats (group II) injected with 0.1 mg/kg. This dose was selected because in pilot experiments its effect on bar pressing was similar to that of 10 mg/kg of DMT.

Tolerance to DMT was examined in 18 rats. They were divided into three groups and all were injected every 2 hours for 21 days. One group (group III, six rats) was always injected with 0.9% NaCl (saline), another (group IV, five rats) with DMT, 3.2 mg/kg, and the last (group V, seven rats) with DMT, 10 mg/kg. Every 24 hours each rat was placed in an operant chamber 30 minutes before a scheduled injection. The initial injection of the series was given during an experimental session.

Cross-tolerance to LSD was examined on the day after the last experimental session of the DMT series.

During the intervening 24 hours, serial injections (one every 2 hours) were continued to groups III (saline), IV (DMT, 3.2 mg/kg) and V (DMT, 10 mg/kg). Ninety minutes after the last serial injection, the rats were placed in chambers and 30 minutes later were injected with LSD (0.1 mg/kg). One rat in group V did not receive LSD because of a problem with equipment.

Direct tolerance to LSD and cross-tolerance to DMT was examined in six rats (group VI). Their reaction to a control injection of 10 mg/kg of DMT was obtained 1 week before a series of LSD injections. The series began with administration of LSD (0.1 mg/kg) i.p. once a day. This schedule of injection was selected because there are reports that, using a dose slightly below (Winter, 1971) or above (Freedman *et al.*, 1964) 0.1 mg/kg, daily administration of LSD produced in less than 8 days tolerance to the disruptive effect of the drug on food-rewarded fixed-ratio bar pressing in rats. In the present study however, tolerance was not produced by the daily injection of 0.1 mg/kg of LSD for 21 days. The frequency of injection was then increased to three times per day. Beginning on day 22 of the LSD series, an injection of 0.1 mg/kg of LSD was administered at 7:00 A.M., 3:00 P.M. and 11:00 P.M.

At 7:00 A.M. on the 4th day of the more intensive treatment (day 25 of the entire LSD series) most animals were fairly tolerant to the drug. Serial injections were continued at 3:00 and 11:00 P.M. of day 25 and on day 26 a challenge injection of DMT (10 mg/kg) was substituted for the 7:00 A.M. LSD injection in all six rats of group VI. The animals were not tolerant to this dose of DMT. The serial injections of LSD were again continued once every 8 hours until the animals showed good tolerance to the LSD. For three rats (subgroup VI-A), good LSD tolerance was demonstrated on day 28 (7:00 A.M.). LSD was administered to these three rats again at 3:00 and 11:00 P.M. on day 28; at 7:00 A.M. on day 29 they were tested for cross-tolerance to 3.2 mg/kg of DMT. For the other three rats in group VI (subgroup VI-B), complete LSD tolerance was not demonstrated until day 30 of the series (7:00 A.M.]. They received LSD injections again at 3:00 and 11:00 P.M. of day 30 and on day 31 (7:00 A.M.) they were tested for cross-tolerance to 3.2 mg/kg of DMT. Bar pressing data on the effect of the challenge injection of 3.2 mg/kg of DMT were combined for subgroups VI-A and VI-B.

A control group of four rats (group VII) was treated exactly like subgroup VI-A except that saline rather than LSD was administered.

To quantitate data for the various groups, cumulative records were divided into successive 15-minute intervals and the mean number of bar presses for each interval was calculated. Two tailed Student's t tests were calculated according to Snedecor (1956) using a value of $P < .05$ as significant. Paired comparisons were used where appropriate.

Durations of disruption of bar pressing were specified only when they were reasonably simple to quantitate by visual inspection of cumulative records. This occurred when bar pressing was abolished completely (or nearly so), resumed abruptly, and, once resumed, continued at a steady uninterrupted pace. "Duration of disruption" is defined as the period between cessation and resumption of steady bar pressing, even if slopes on the cumulative record are lower after resumption than before cessation of pressing.

DMT doses refer to the free base; solutions were prepared by dissolving the free base in an equivalent amount of HCl and adding saline with a pH adjustment with 0.1 N NaOH such that the final volume had a pH of 5 to 7.4. Doses of LSD refer to LSD-25 substance. DMT base was obtained from Aldrich Chemical Company, Inc. (Milwaukee, Wisc.) and/or Sigma Chemical Company (St. Louis, Mo.). LSD (Delysid) substance was obtained from NIDA courtesy of Dr. M. Braude.

Results

Well-trained rats began bar pressing almost immediately after being placed in an operant chamber. Typical cumulative records of normal, undrugged animals are shown in the left column of figure 1. Individual rates of pressing varied but each rat continued at a steady pace for an entire 60-minute session.

Acute DMT effects. The right column of figure 1 shows typical records obtained after various doses of DMT. A dose of 1 mg/kg i.p. caused little or no disruption of bar pressing. After receiving a dose of 3.2 mg/kg, the rats spent about 25 minutes lying still, often in a characteristic slightly flattened position, with eyes open, occasionally crawling about. Bar pressing began rather abruptly and from that point on, cumulative records were much like controls. A dose of 10 mg/kg abolished bar pressing for approximately 50 minutes. This dose produced marked motor symptoms including twitching, trembling, flattening of the hindquarters, extension of the hindlimbs perpendicular to the trunk of the body, dangling hindlimbs through bars of the floor of the operant chamber, Straub tail, rigidity, jerkiness of movement, circling and walking backwards. All motor symptoms disappeared well before bar pressing began. After a dose of 32 mg/kg, motor symptoms including convulsions were more pronounced and longer lasting. At about 90 minutes after this dose, the animals appeared normal; they explored, groomed and, if given the opportunity, gnawed on a food pellet, but bar pressing did not begin until about 2 hours or

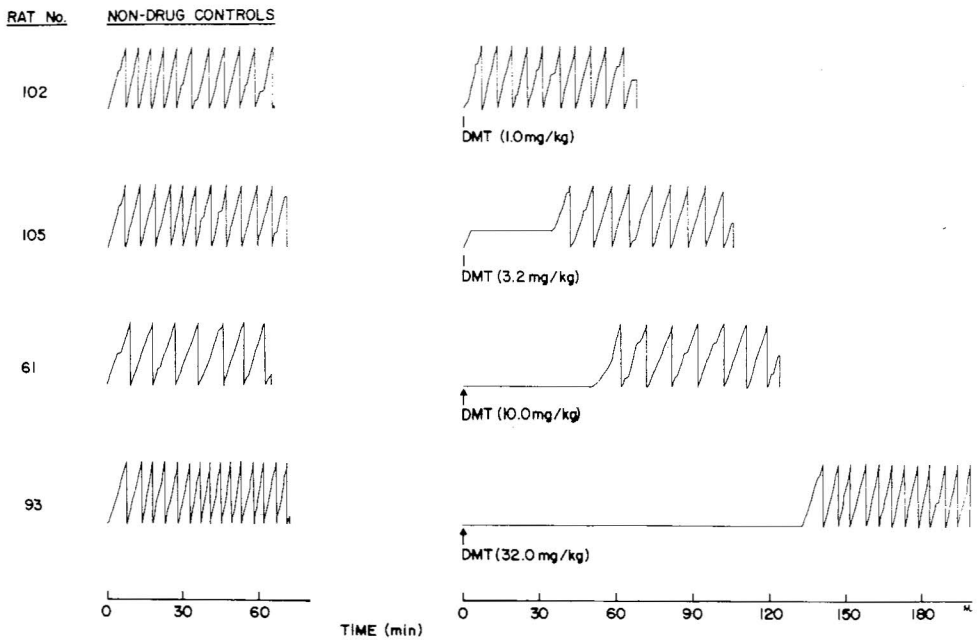

FIG. 1. Cumulative records showing the effects of DMT on rats bar pressing for milk reinforcement on a FR_4 schedule. Records in the right column were obtained on the day after those in the left column. All injections were given i.p. Each peak represents 550 bar presses.

longer after the injection. The mean number of minutes ± S.E. of abolition of bar pressing behavior after DMT was 27 ± 3 for eight rats given 3.2 mg/kg, 47 ± 4 for eight rats given 10 mg/kg, and 127 for two rats given 32 mg/kg i.p. Sparber and Tilson (1971) have emphasized the role of handling and replacement of rats into the operant chamber in altering the duration of bar pressing disruption. Hence the dose-effect data given are only valid where conditions were kept constant, *i.e.*, below 32 mg/kg. No obvious differences were observed in the reaction to DMT when the same doses of the drug were administered to the same animals on 3 consecutive days.

Acute LSD effects. A single injection of LSD (0.1 mg/kg) to four rats (group II) abolished bar pressing for 47 ± 7 minutes (mean ± S.E.). The animals spent most of this time lying quietly in a flattened position, occasionally crawling about. Bar pressing resumed abruptly and continued for the next 30 minutes although not at as steady a pace as during the preinjection control period.

DMT tolerance. Figure 2 shows typical results obtained on various days of the 21-day DMT tolerance study. The initial injections of the series produced effects (top row) similar to those described for acute DMT, that is, saline had no effect; 3.2 mg/kg of DMT abolished bar pressing for 19 ± 2 minutes and 10 mg/kg of DMT abolished pressing for 46 ± 2 minutes.

As the experiment progressed, bar pressing of the saline group (group III) was little affected by the chronic 2-hour injections. In the DMT groups, bar pressing gradually deteriorated as the study progressed. Of the seven rats in the 10 mg/kg group (group V) all had at least 1 day on which there was no bar pressing at all. The most severely affected rat had 11 such days and the mean for the group was 4.8 non-bar-pressing days. For the group as a whole, the day of the series on which bar pressing was most severely affected was day 6. On that day, six of the seven rats had flat cumulative records. In the 3.2 mg/kg group (group IV), no rat ever had a totally flat cumulative record; the poorest records were obtained on days 2 through 8.

In general, bar pressing in the DMT groups began to increase after day 6 and toward the end of the series three out of five of the rats in group IV (DMT 3.2 mg/kg) and five out of seven of those in group V (DMT 10 mg/kg) displayed complete tolerance (no disruption of bar press-

ing) on at least 1, and in some cases, on several days. Toward the end of the series, however, most of these rats on some days showed mild DMT effects after an injection. Other rats in groups IV and V showed partial tolerance in that more bar pressing occurred during the last week of the series than during the first week. Mean rates of bar pressing for groups III, IV and V on various days of the DMT tolerance study are shown in figure 3.

During the course of chronic treatment, body weights of rats in group V showed a downward trend from day 3 to day 15, then a slight upward trend until the end of the series. Mean weights ± S.E. on days 3, 15 and 21 were 383 ± 10, 333 ± 9 and 346 ± 11, respectively. On days 11 to 14, some of the rats in group V did not always consume their entire ration of Purina chow pellets. Therefore, at the time of the low body weight, the continuing improvement in bar pressing cannot be interpreted as a function of an increase in degree of food deprivation. A comparison of daily cumulative records of individual rats with their daily changes in body

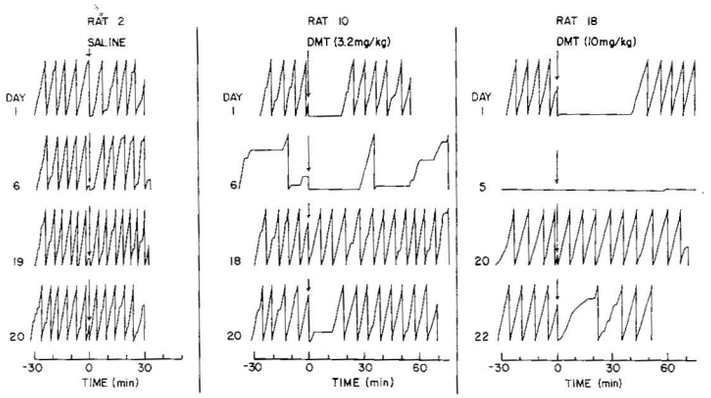

FIG. 2. Cumulative records showing sensitization followed by tolerance to the disruptive effect of DMT on food-rewarded bar pressing (FR_4) in the rat. Rats were injected (i.p.) every 2 hours with either saline (rat 2), 3.2 mg/kg of DMT (rat 10) or 10 mg/kg of DMT (rat 18). Every 24 hours they were placed in operant chambers 30 minutes before a scheduled injection. The top row shows the effect of the first injection of the series. After each injection, the pen of the cumulative recorder was manually returned to the base line. Each peak represents 550 bar presses.

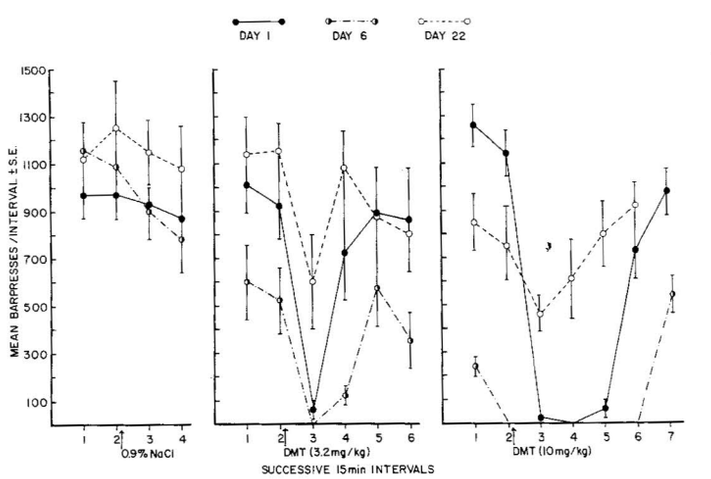

FIG. 3. Sensitization followed by tolerance to the effects of chronic DMT on food-rewarded bar pressing (FR_4) in the rat. Rats were injected (i.p.) every 2 hours for 21 days with either saline (six rats, group III), 3.2 mg/kg of DMT (five rats, group IV) or 10 mg/kg of DMT (seven rats, group V). Every 24 hours they were placed in a Skinner box 30 minutes before a scheduled injection.

weight did not reveal any consistent relationship between weight gain or loss and disappearance or reappearance of tolerance.

Although bar-pressing behavior was the most severely affected on day 6 of chronic DMT, the gross neurologic effects (splayed legs, twitching, Straub tail, etc.) were diminished at that time. Gross neurologic effects in the 10 mg/kg group were most intense after the initial injection in the series. Gross effects in the 3.2 mg/kg group were mildly enhanced on the 2nd and 3rd day.

Test for cross-tolerance to LSD. Results are shown in figure 4. Most of the animals that had been chronically treated with a dose of 3.2 mg/kg of DMT (group IV) displayed cross-tolerance to LSD (0.1 mg/kg). Comparison of the cumulative records of group V (chronic 10 mg/kg DMT) and group III (chronic saline) reveals that during the first 1/2 hour after the LSD injection, the group V animals were less disrupted than those in group III; during the second 1/2 hour the opposite was true. It should be noted that there appears to be a qualitative change in effect. The chronic saline animals showed abrupt cessation of bar pressing with return at about pre-LSD rates, whereas after chronic DMT there was not a return at similar rates but more of a slope change along with break-and-run cumulative records.

LSD tolerance. The initial injection of LSD to the six rats in group VI disrupted bar pressing in five of the rats for 21 ± 3 minutes. Inexplicably, bar pressing of the sixth rat in the group was not disrupted. The animal was clearly affected, however, for it kept shaking its head in an atypical manner (like a wet dog) for more than 1/2 hour after the injection. For the remainder of the series, results obtained with this animal were in line with those of the rest of the group. It should be noted that group VI showed a much shorter duration of suppression of bar pressing than did group II. No explanation is apparent.

During the first 2 weeks of the LSD series, most rats were increasingly sensitive to the drug. Bar pressing was abolished for longer periods and, once resumed, was often irregular. When the frequency of injections was stepped up to three times per day, bar pressing improved considerably. Good tolerance was obtained at the end of the series (fig. 5).

Test for DMT cross-tolerance. The reaction to 10 mg/kg of DMT of rats partially tolerant to LSD (group VI) was not significantly different from that of the same rats before they were tolerant or from that of a control group that had been chronically treated with saline (group VII). The duration of DMT-induced cessation of bar pressing in the three instances was 41 ± 5, 57 ± 5 and 42 ± 1 minutes, respectively. When the same animals that had been partially tolerant to LSD were made almost completely tolerant

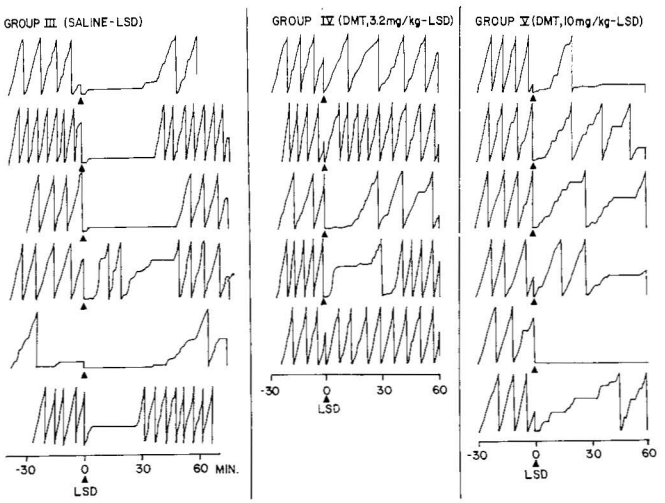

FIG. 4. Cumulative records showing the effect of LSD (0.1 mg/kg, i.p.) on rats pretreated chronically with saline (group III), 3.2 mg/kg of DMT (group IV), or 10 mg/kg of DMT (group V). Rats were pretreated with an injection (i.p.) every 2 hours for 21 days. LSD was administered 2 hours after the last chronic pretreatment injection. After each injection, the pen of the cumulative recorder was manually returned to the base line. Each peak represents 550 bar presses.

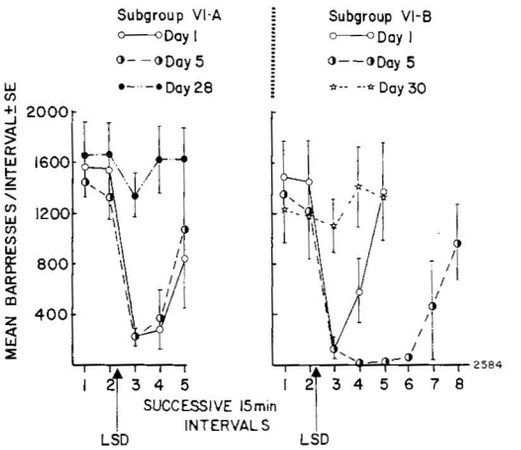

FIG. 5. Effects of chronic LSD on food-rewarded bar pressing. Rats were injected with LSD (0.1 mg/kg i.p.) once a day for 21 days, followed by three times a day for the next 7 days (subgroup VI-A, three rats) or 9 days (subgroup VI-B, three rats). On day 26, a challenge injection of DMT (10 mg/kg i.p.) was substituted for one of the serial LSD injections (results not shown in figure, see text).

to the drug, they displayed cross-tolerance to 3.2 mg/kg of DMT. A challenge injection of 3.2 mg/kg of DMT abolished bar pressing for 4 ± 2 minutes (combining the data for subgroups VI-A and VI-B). This value is significantly lower ($P < .05$) than the corresponding value of 18 ± 3 minutes for the control group that had been pretreated with chronic saline (group VII). It must be emphasized that when a challenge injection of 10 mg/kg of DMT was tested, the level of LSD tolerance was lower than when a challenge of 3.2 mg/kg of DMT was tested.

Discussion

Tolerance can develop to the disruptive effect of DMT on food-rewarded, fixed-ratio bar pressing in the rat. Approximately 3 weeks of i.p. injections of doses of 3.2 or 10 mg/kg every 2 hours around the clock were required to induce tolerance. Attempts by others (Cole and Pieper, 1973; Gillin *et al.*, 1973; Kaplan *et al.*, 1974; Rech *et al.*, 1974) to produce tolerance to various effects of DMT in fewer days or with less frequent injections per day in rats and other species have not been successful.

In the present study, during the 1st week of chronic treatment, sensitivity to effects of the drug on bar pressing increased dramatically and was most severe on about day 6. By that time, however, gross motor abnormalities were greatly reduced, suggesting differential tolerance development.

After complete tolerance to bar pressing effects was obtained, it did not persist in spite of continued chronic treatment. Instead, the rats on some days of the 3rd week of chronic treatment displayed mild DMT effects after an injection. No pattern to the disappearance and reappearance of tolerance was discernible but the study was not carried out long enough to determine whether tolerance fluctuated in a cyclic manner such as that reported by Koella, *et al.* (1964) for the effect of LSD on ambulation in goats.

Rats tolerant to 3.2 mg/kg of DMT (Group IV) displayed cross-tolerance to LSD, but another group of rats (Group V) tolerant to 10 mg/kg of DMT displayed very slight cross-tolerance to LSD and only during the first 1/2 hour after the injection. During the next 1/2 hour, they exhibited increased sensitivity rather than cross-tolerance to LSD (see fig. 4).

Effects of less numerous chronic DMT injections on food-rewarded, fixed-ratio bar pressing have been reported by Rech *et al.* (1974) who injected rats with a dose of 3 mg/kg once a day for 10 days and by Cole and Pieper (1973) who injected squirrel monkeys with a dose of 10.8 μmol/kg (approximately 2 mg/kg) for 36 to 38 days. These investigators employed higher fixed-ratios than that used in the present study and it could be argued that they did not obtain tolerance because the higher ratios are better able to detect disruptive effects of the drug. However, one would expect that they could easily detect an increase in sensitivity to a drug. Rech *et al.* and Cole and Pieper did not report increased sensitivity such as was seen during the 1st week of chronic treatment in the present study. It seems unlikely, therefore, that the different results are due to different ratios.

Sterotyped behavior seen immediately after administration of DMT disappeared completely before bar pressing began. After the highest dose of DMT (32 mg/kg) there was a lengthy interval between complete disappearance of motor symptoms and commencement of bar pressing. During this interval, rats would gnaw on a food pellet if offered one. This suggests that disruption of bar pressing is not mediated through interference with appetite and involves mechanisms different from or in addition to those producing the motor effects. LSD (0.1

mg/kg) affected bar pressing in a manner comparable to that seen after 10 mg/kg of DMT but did not produce the motor effects seen after that dose of DMT. This suggests that, at the doses indicated, the drugs act *via* a common mechanism, or on a final common pathway, and that DMT, in addition, acts on another mechanism which is unaffected by LSD.

A relatively long period of chronic treatment was required to induce tolerance to 0.1 mg/kg of LSD (once per day for 21 days followed by three times per day for another 7–9 days). This is to be contrasted with the results of Freedman *et al.* (1964) and Winter (1971), who, using doses near 0.1 mg/kg, obtained tolerance in 8 or less days to the disruptive effect of LSD on fixed ratio, food-rewarded bar pressing in rats. The reason for the late appearance of tolerance in the present study is not understood.

Cross-tolerance to DMT was seen after a dose of 3.2 but not 10 mg/kg perhaps because the level of LSD tolerance obtained was lower when a 10 mg/kg dose of DMT was tested than when 3.2 mg/kg of DMT was tested.

Acknowledgments. The authors wish to thank Ms. Diane Ruffing for excellent technical assistance, Dr. Robert H. Moore and Ms. Ruth Johnson for aiding with the chronic injections.

Added in proof: Freedman, D. X. and Boggan, W. also have observed tolerance to DMT given every 2 hours in the rat on a FR schedule (Personal communication, 1976).

References

Appel, J. B. and Freedman, D. X.: Tolerance and cross-tolerance among psychotomimetic drugs. Psychopharmacologia **13:** 267–274, 1968.

Cole, J. M. and Pieper, W. A.: The effects of N,N-dimethyltryptamine on operant behavior in squirrel monkeys. Psychopharmacologia **29:** 107–112, 1973.

Freedman, D. X., Appel, J. B., Hartman, F. R. and Molliver, M. E.: Tolerance to behavioral effects of LSD-25 in rat. J. Pharmacol. Exp. Ther. **143:** 309–313, 1964.

Gillin, J. C., Cannon, E., Magyar, R., Schwartz, M. and Wyatt, R. J.: Failure of N,N-dimethyltryptamine to evoke tolerance in cats. Biol. Psychiat. **7:** 213–220, 1973.

Isbell, H., Belleville, R. E., Fraser, H. F. Wikler, A. and Logan, C. R.: Studies on lysergic acid diethylamide (LSD-25). 1. Effects in former morphine addicts and development of tolerance during chronic intoxication. A.M.A. Arch. Neurol. Psychiat. **76:** 468–478, 1956.

Isbell, H., Wolbach, A. B., Wikler, A. and Miner, E. J.: Cross tolerance between LSD and psilocybin. Psychopharmacologia **2:** 147–159, 1961.

Kaplan, J., Stillman, R. C., Gillin, J. C. and Wyatt, R. J.: Attempts to evoke tolerance to DMT in man. Presented at the American Psychiatric Association Annual Meeting, New Research—Abstracts, Detroit, May 1974.

Koella, W. P., Beaulieu, R. F. and Bergen, J. R.: Stereotyped behavior and cyclic changes in response produced by LSD in goats. Int. J. Neuropharmacol. **3:** 397–403, 1964.

Kovacic, B. and Domino, E. F.: Effect of various drugs on DMT-induced disruption of rat barpressing behavior. Pharmacologist **15:** 218, 1973.

Rech, R. H., Tilson, H. A. and Marquis, W. J.: Adaptive changes in behavior after repeated administration of various psychoactive drugs. *In* Neurobiological Mechanisms of Adaptation and Behavior, ed. by A. J. Mandell, pp. 263–286. Raven Press, New York, 1975.

Rosenberg, D. E., Isbell, H., Miner, E. J. and Logan, C. R.: The effect of N,N-dimethyltryptamine in human subjects tolerant to lysergic acid diethylamide. Psychopharmacologia **5:** 217–227, 1964.

Sai-Halász, A., Brunecker, G. and Szára, S.: Dimethyltryptamin: Ein neues Psychoticum. Psychiat. Neurol. (Basel) **135:** 285–301, 1958.

Snedecor, G. W.: Statistical Methods 5th ed., Iowa State College Press, Ames, 1956.

Sparber, S. B. and Tilson, H. A.: Environmental influences upon drug-induced suppression of operant behavior. J. Pharmacol. Exp. Ther. **179:** 1–9, 1971.

Szára, S.: Dimethyltryptamin: Its metabolism in man: the relation of its psychotic effect to the serotonin metabolism. Experimenta (Basel) **12:** 441–442, 1956.

Tilson, H. A. and Sparber, S. R.: Similarities and differences between mescaline, lysergic acid diethylamide-25 (LSD) and *d*-amphetamine on various components of fixed interval responding in the rat. J. Pharmacol. Exp. Ther. **184:** 376–384, 1973.

Winter, J. C.: Tolerance to a behavioral effect of lysergic acid diethylamide and cross-tolerance to mescaline in the rat: absence of a metabolic component. J. Pharmacol. Exp. Ther. **178:** 625–630, 1971.