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Comparing the Effects of Scopolamine on Operant and Aggressive Responses in Squirrel Monkeys[1]

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PLOTNIK, R., S. MOLLENAUER, W. GORE AND A. POPOV. *Comparing the effects of scopolamine on operant and aggressive responses in squirrel monkeys.* PHARMAC. BIOCHEM. BEHAV. 3(5) 739–748, 1975.– The anticholinergic drug, scopolamine, causes disinhibition or an increase in responses that an animal normally suppresses. Experiment 1 confirmed this effect in squirrel monkeys. Experiment 2 explored the implications of drug-produced disinhibition on aggressive interactions. In Experiment 1, scopolamine produced increased unreinforced responding on a DRL schedule and increased responding during unreinforced (Time Out) periods. In contrast, the peripheral control drug, methyl scopolamine, caused decreased responding in both situations. In Experiment 2, social rank and drug treatment interacted. When space was restricted so that the opportunity for social interactions was maximized, scopolamine consistently increased aggressiveness in the dominant monkey and decreased aggressiveness in a submissive monkey. When space was increased so that the opportunity for social interactions was minimized, scopolamine caused decreased aggressive responses in all monkeys. Neither the effective dosage nor the drug's effect on the operant task could be easily generalized to aggressive responses.

Scopolamine Aggression Operant responding Social rank Squirrel monkey

COMPARED with normal animals, which stop responding, those treated with anticholinergic drugs may continue to make responses that result in punishment or nonreinforcement [2]. Since normal animals stop responding, scopolamine is said to produce disinhibition or the occurrence of normally inhibited responses. Although this finding is well documented in the rat, there have been very few reports of whether cholinergic mechanisms are involved in the inhibition process in monkesy [5,7]. Experiment 1 studied the effects of the anticholinergic drug, scopolamine, on the squirrel monkey's performance during a task that is sensitive to disinhibition.

The increased responding or disinhibition produced by anticholinergic drugs [2] has important implications for an animal's responses in social interactions. If social responses that an animal normally suppresses are released by anticholinergic drugs, then the animal's social interactions may be disrupted, depending upon its position in the social hierarchy. Previous studies have shown that the social position of an animal may interact with experimental treatments [11]. Thus, we might expect that submissive animals that normally inhibit aggressive responding against more dominant animals might become more aggressive following anticholinergic treatment. It has been found that submissive animals show increased aggressiveness when the dominant animal became less aggressive following a brain lesion [12]. This latter study indicates that submissive monkeys do have aggressive responses in their repertoires and that they are inhibiting these responses when the dominant animal is present. On the other hand, dominant animals, which presumably inhibit little if any aggressive responding, might show little change in aggressive responding or in rank after drug treatment. Experiment 2 of the present study explored the effects of an anticholinergic drug, scopolamine, on the aggressive responses of squirrel monkeys. By comparing the effects of scopolamine on an operant task (Experiment 1) and on aggressive interactions (Experiment 2) we hoped to determine whether drug effects and drug dosages could be generalized across these two very different behavioral situations.

EXPERIMENT 1: EFFECTS OF SCOPOLAMINE ON DRL PERFORMANCE

Since the differential reinforcement of low rates (DRL) schedule requires that an animal wait or suppress responding during a certain time period, this schedule is an appropriate test for drug-induced disinhibition. It has been reported that scopolamine caused rats to increase responding during the waiting period [2], but this effect has not been reported for monkeys. There have been reports that scopolamine caused squirrel monkeys to respond during periods when no reinforcement was avail-

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able [5] and to increase drinking slightly when each lick produced a shock [7]. The purpose of Experiment 1 was to confirm the disinhibition effects of scopolamine in squirrel monkeys and to establish effective doses on an operant schedule, which could later be compared with effective doses on aggressive interactions.

METHOD

Animals

Three naive adult male squirrel monkeys (*Saimiri sciureus*) weighing 940–1200 g, were housed in individual cages and maintained at 90 percent of their ad lib weights. Water was freely available in the monkey's home cage.

Apparatus

An intelligence panel containing a liquid dipper and Plexiglas lever was mounted in the middle of a sound-attenuating experimental chamber (70 cm high, 44 cm deep and 72 cm wide). The dipper was centrally located in the panel and a 5 cm × 1 cm lever was mounted 8 cm to the left of the dipper. The lever protruded 4.5 cm and required 57 grams of force to operate. A light indicating the beginning of the session was placed directly above the lever. Four lights were mounted on the chamber's ceiling; one light was alwasy on and the remaining 3 were illuminated when the session was in progress. A sonalert tone generator was located behind the panel and provided a 1 sec on and 1 sec off beeping tone that signaled the periods during which no reinforcement was available. The monkey was placed in a Plexiglas restraining chair which allowed complete freedom of movement from the waist up. When placed in the experimental chamber in its chair, the monkey was directly in front of the dipper and could operate the lever and drink from the dipper.

Procedure

Animals were first trained for 1 hr periods daily, on a continuous reinforcement schedule (CRF). During the first week of stable CRF performance, several liquid reinforcers were tried: 32 percent dextrose, Hi-C, red Hawaiian Punch, grape Hawaiian Punch, sweetened milk and diluted mashed bananas. Of these, the most consistent response rate was maintained on red Hawaiian Punch, which was used throughout the remainder of the experiment. The dipper dispensed 25 cc for each reinforcement. It was important to use liquid reinforcement when studying anticholinergic drugs since these drugs cause decreased salivation [17] and possible aversion to dry food.

Following stable CRF performance, periods were introduced during which no reinforcement was available (Time Out) but the lever was operative. Five min Time Out periods alternated with 5 min CRF periods throughout the hour long test session. When the monkey was discriminating between the CRF and Time Out periods, DRL training was begun. On the DRL schedule, a monkey has to wait 20 sec after the last response before a new response would result in reinforcement. A response during the 20 sec wait period would reset the 20 sec timer and require a wait of 20 sec before a response would result in reinforcement. The DRL schedule consisted of a 5 min Time Out period, 1 hr of DRL 20; a 5 min Time Out period, 1 hr of DRL 20 and a final 5 min Time Out period. Total session time was 2 hr and 15 min. Monkeys were trained on this schedule 7 days a week.

Drug Injection

Saline injections were begun when monkeys' DRL performance reached the following criteria: (1) no overall increase in percentage of reinforced DRL responses for a period of a week; and, (2) this percentage did not vary more than plus or minus 7.5 percent from the mean of the last consecutive 3 day period. This latter criterion meant that prior to drug injection, a monkey's performance on the DRL schedule never varied more than 15 percent on 3 consecutive days. No criterion was necessary for the Time Out period since by the time monkeys learned the DRL schedule they were showing almost complete response suppression during the Time Out periods. In order to habituate the animals to the injection procedure, they were injected with saline for 3 days. After the 3 saline injections, the drug injections were begun. Monkeys were injected with saline on days they did not receive a drug treatment. A minimum of 5 saline control days elapsed between each drug injection. In addition, the following criterion had to be met for drug injection to take place: the percentage of reinforced DRL responses did not vary more than plus or minus 7.5 percent from the mean of the last consecutive 3 day periods. Thirty min prior to testing, the monkey was placed into a Plexiglas chair. Once in the chair, it was injected and then placed alone in a quiet room for 20 min. At the end of the 20 min period, the monkey was placed into the chamber for testing. The monkey was taken out of the chair and released into its home cage following the 2 hr 15 min testing period.

Drugs

Scopolamine hydrobromide and methyl scopolamine (Penick and Co., 100 Church St., N.Y.) were dissolved in 0.9 percent saline. Injections were given SC and volume was always 1 ml/kg. Initially the order of injection was random until it was apparent that higher doses of scopolamine (0.075 and 0.1 mg/kg) caused a complete cessation of responding. Following this finding, lower doses of the drugs were included to maximize testing of the widest possible dose range. The following doses (mg/kg) were tested with the number of monkeys receiving that dose in parentheses: scopolamine 0.0025 (2), 0.005 (2), 0.015 (3), 0.025 (2), 0.075 (3), 0.1 (3); methyl scopolamine 0.005 (2), 0.015 (2), 0.025 (2), 0.075 (2).

RESULTS

Once a monkey had reached stable performance on the DRL 20 schedule, the monkey tended to maintain that performance across weeks. In their performance on the DRL 20, 2 of the 3 monkeys had a high baseline of 3.0–4.0 responses per min and one had a low baseline of 2.3–2.5 responses per min. Because of this difference in baseline performance between monkeys, the results are reported in terms of gain scores which correct for this difference in baseline. Gain scores were computed by dividing the score on the drug day by mean score of the three immediately preceding control days. Thus, a gain score of 1 would indicate no change from baseline

performance; a gain score greater than 1 would indicate an increase from baseline performance; and a gain score less than 1 would indicate a decrease from baseline performance.

Data were combined for the 2 DRL periods and analyzed in terms of unreinforced responses, that is, those responses which occurred during the 20 sec wait period and did not result in reinforcement; reinforced responses, those occurring after the 20 sec wait period and thus resulting in reinforcement; and those responses occurring during the three combined Time Out periods.

Figure 1 shows that during the Time Out periods, each monkey made significantly more unreinforced responses at a lower dose of scopolamine, 0.015 mg/kg, (t = 4.34, df = 2, $p<0.05$) while higher doses (0.075 and 0.01 mg/kg) produced a significant decrease in unreinforced responses (t = 8.77, df = 2, $p<0.02$). In contrast to the increase produced by the low doses of scopolamine, all doses of methyl scopolamine resulted in a decrease in unreinforced responses; the decrease was significant for the highest dose, 0.075 mg/kg (t = 19.6, df = 1, $p<0.05$).

There was no difference in the number of reinforced responses for the low doses of scopolamine (0.0025–0.025 mg/kg). That is, for these low drug doses, monkeys obtained as many reinforcements as they did during the prior 3 days of saline injections. The two higher doses of scopolamine produced a significant decrease in overall responding and thus a decrease in the number of reinforced responses: for 0.075 mg/kg, t = 8.82 (df = 2, $p<0.02$); and for 0.1 mg/kg, t = 10.32 (df = 2, $p<0.01$). Similar to the higher doses of scopolamine, only the highest dose of methyl scopolamine (0.075 mg/kg) caused a significant decrease in reinforced responses (t = 15.76, df = 1, $p<0.05$).

As shown in Fig. 2, compared with saline the 0.015 mg/kg dose of scopolamine caused a significant increase in unreinforced responding during DRL 20 (t = 5.97, df = 2, $p<0.05$), while higher doses produced a great decrease or complete cessation in responding. The highest dose of methyl scopolamine (0.075 mg/kg) also resulted in a significant decrease in response rate during the Time Out period (t = 12.92, df = 1, $p<0.05$).

There was no difference in the monkey's DRL or Time Out performances between the first and second hours of testing. That is, if drug caused increased responding during the first Time Out and first DRL periods, it produced the same effects on the second DRL and last Time Out periods.

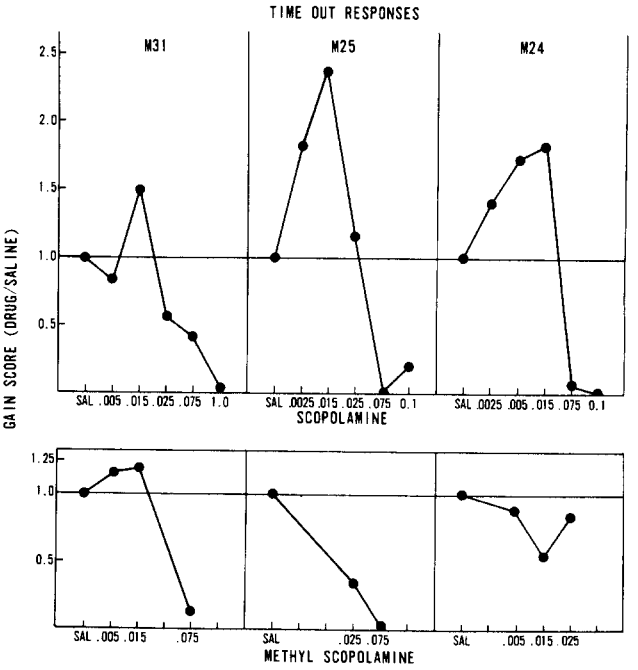

FIG. 1. Responses during Time Out periods of individual monkeys (M31, M25, M24) following treatment with scopolamine (upper graph) or methyl scopolamine (lower graph). Gain scores were used to correct for baseline differences; a gain score of 1 indicates no change from baseline; a score greater than 1 indicates increased responding, and a score less than 1 indicates decreased responding.

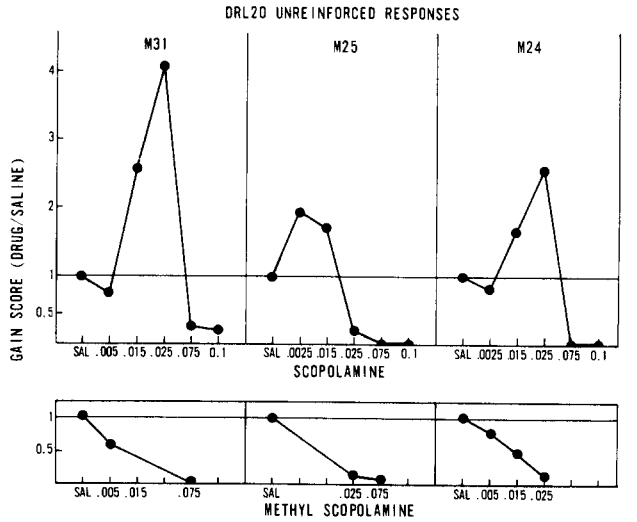

FIG. 2. Unreinforced responses during DRL 20 of individual monkeys (M31, M25, M24) following treatment with scopolamine (upper graph) or methyl scopolamine (lower graph). Gain scores were used to correct for baseline differences. A score of 1 indicates no change from baseline; a score greater than 1 indicates increased responding and a score of less than 1 indicates decreased responding.

DISCUSSION

A lower dose of scopolamine produced a significant increase in unreinforced responding, that is, responding during the 20 sec wait period, and a significant increase in responding during the Time Out periods. Higher doses of scopolamine consistently produced a decrease in response rate on all parts of the schedule. In contrast to the increased responding produced by the lower dose of scopolamine, all doses of methyl scopolamine caused decreases in responding. Since methyl scopolamine, which produces the peripheral but not the central effects of scopolamine, caused only decreases and never increases in responding, it can be assumed that the increase in unreinforced and Time Out responding produced by scopolamine was due to the drug's action on the brain. Decreases in responding produced by methyl scopolamine have been reported elsewhere [7,8]. The increased responding or disinhibition of responding produced by scopolamine is in agreement with previous studies [2,5]. There have been

two reports in which an anticholinergic drug generally failed to produce disinhibition [7,8]. A possible explanation for the discrepant findings is that dry food was used as a reinforcer. It has been suggested that dry food may be aversive following anticholinergic treatment because of decreased salivation [17]. In the present experiment monkeys readily consumed the red Hawiian punch used as reinforcement except at the highest doses of scopolamine. This is in contrast to the reports that rats and monkeys failed to consume dry food rewards following scopolamine injection [8].

There is considerable agreement upon effective dosages of scopolamine for squirrel monkeys between Miczek [7], who reported increased punished responding at 0.02 mg/kg and the present experiment, which reported increased unreinforced and Time Out responding at 0.015 mg/kg. At doses of scopolamine above 0.02 mg/kg, there is general agreement that decreased responding occurs on punished drinking [7]; on responding during establishment of aversive thresholds [6]; on conditioned suppression produced by a stimulus which was formerly paired with a reward [8]; and on responding during a DRL 20 schedule in the present study. Thus, for the squirrel monkey, effective dosage (IM or SC route) for increased responding on a variety of operant tasks would be in the 0.015–0.02 range while doses above 0.075 result in decreased responding. Hanson *et al.* [5] have reported increased responding of squirrel monkeys during Time Out periods, but since their route of administration was by gavage (2 cc/kg), it is somewhat difficult to compare their dosages with those administered by IM or SC.

EXPERIMENT 2: EFFECTS OF SCOPOLAMINE ON AGGRESSIVE RESPONSES

Experiment 1 and previous literature [5,7] indicate that responses normally suppressed by squirrel monkeys were released or disinhibited by scopolamine. On two different operant tasks ([7], Experiment 1) the dosage of scopolamine which produced disinhibition was in the range of 0.015–0.02 mg/kg. This and other doses were used in Experiment 2 to determine whether the drug dosage effective on operant tasks is the same dosage that would be effective on social interactions.

Social interactions were studied in 2 situations, the shuttle box and group cage. In the shuttle box, the opportunity for social interactions was maximized by greatly restricting the space available to each monkey. In the group cage, which was three times as large as one shuttle box compartment, the opportunity for social interactions was minimized by increasing the space available to each monkey for avoiding or maintaining distance from other animals. When tested in either the shuttle box or group cage, monkeys were on the same food deprivation schedule and received the same number of reinforcements.

METHOD

Animals

Four wild-born adult male squirrel monkeys (*Saimiri sciureus*), weighing from 805–1010 g, were maintained at 90 percent of their ad lib weight and housed individually between experimental sessions. Each monkey was identified by a collar of different colored beads. These animals had been used in a previous pilot study which determined that the handling and restraint necessary for drug injection did not disrupt the social interactions. Two months elapsed between the pilot project and start of Experiment 2.

Apparatus

Shuttle-box. The shuttle box was composed of two 61 × 61 × 61 cm Plexiglas compartments connected by a tunnel that was only wide enough to permit one monkey to cross at a time (10 cm wide by 17 cm high by 12 cm long). Guillotine doors, manually operated by the observer, were placed on each end of the tunnel. A buzzer was mounted over one of the compartments.

In each compartment was a Plexiglas cup which was filled with banana juice from a liquid dispenser remotely operated by the experimenter.

Group cage. The group cage's dimensions were 91 × 91 × 91 cm and it was constructed of 2 cm wire screen. The area available to the monkeys in the group cage was well over 3 times the area available to the monkeys in each compartment of the shuttle box. A wooden perch 20 cm wide was mounted 30 cm up from the bottom of the back wall of the group cage.

Procedure

Shuttle-box training. After habituation, monkeys were individually trained to shuttle between compartments. The start of a trial was signaled by buzzer onset for 5 sec, followed by the tunnel door raising allowing access to the opposite compartment and baited food cup. The reinforcement (0.06 ml) was a mixture of fresh bananas, water and sugar. Following an intertrial interval of 30 sec, the trial was repeated for 20 trials per day. Individual training continued until all monkeys were shuttling on 18/20 trials in less than 5 sec. The experimenter sat about two meters from the front of the shuttle box.

After reaching criterion on the individual shuttle trials, group testing in the shuttle box began. On each group training day, monkeys were given 5 individual shuttle responses. These baseline trials would assess possible drug effects on speed, coordination and drinking responses. After each monkey has completed its 5 individual trials, the 4 monkeys were placed together in one compartment of the shuttle box and given 15 trials for which the shuttle procedure was similar except that all 4 monkeys were present. There were 2 min between trials and total time was 30 min.

Group cage observations. Immediately after group testing in the shuttle box, the monkeys were observed in the group cage. The group cage was moved into the testing room that housed the shuttle box, monkeys were transferred to the cage, and the experimenter sat about 1/2 meter from the cage. Once every 2 min for a 30 min period the experimenter placed a grape in a tube suspended over the cage and the grape would roll down the tube and land on top of and about in the middle of the cage.

Testing Procedures. The order of testing was always the same: (a) 5 individual trials in the shuttle box, (b) group testing in the shuttle box, (c) group testing in the group cage, (d) animals separated and returned to their individual home cages and fed.

The above order of testing was continued until a stable social hierarchy developed and was maintained, that is, no

reversals occurred for 10 successive sessions. Then monkeys were habituated to the injection procedure. Next came a week of testing during which saline was given on the day that drug injections would normally occur. This comprised the first saline test sessions. Next the drug injections were begun. Finally, the last test session was a final saline session.

Measures. During the individual shuttle trials, running speeds were taken to assess possible drug effects on speed and coordination.

In group shuttle testing, the order through the tunnel and the recipient of banana juice was recorded. Additionally, between trials, numerous social interactions occurred and these were recorded by the observer on a tape recorder. Aggressive responses were the same as those used previously [12]: genital display, grabbing, pushing, chasing and biting. The social rank of each monkey was defined by the number and direction of aggressive responses initiated. As previously reported [12], adult male squirrel monkeys, under competitive conditions, exhibit a stable social dominance hierarchy as measured by direction of aggressive interactions.

In the group cage, the experimenter recorded which monkey received the grape and all aggressive interactions as described above.

Drug treatments. Monkeys were habituated to injection procedures by putting each one into a restraining chair, injecting it SC with 1 ml/kg of 0.9 percent saline solution and then 20 min later testing them together in the shuttle box and group cage. This procedure was repeated 3 times, on every other day, with no observable effect on social interactions.

There were 4 doses of scopolamine hydrobromide (Penick and Co.): 0.005, 0.015, 0.025, and 0.05 mg/kg; one dose of methyl scopolamine (0.05 mg/kg) was administered to the most dominant monkey only.

All drugs were dissolved in 0.9 percent saline and administered SC in a volume of 1 ml/kg. Time from injection of the first monkey to completion of all daily testing was 100 min. It was established in Experiment 1 that the drug continued to be effective for this length of time.

Each monkey received all 4 doses of scopolamine and only one monkey was drugged per week. For each week, the schedule was as follows: Monday, no injection; Tuesday, all monkeys injected with saline; Wednesday, 3 monkeys injected with saline, one with scopolamine; Thursday, no injection; Friday, no injection. Assignment of drug treatment was random with the following restrictions: (a) only one monkey per week would receive a dose of scopolamine, (b) all monkeys would receive all dose levels, (c) there would be a minimum of 2 weeks between drugging of the same monkey with scopolamine. All drug injections and data collection were conducted with the experimenter blind to which monkey received which drug treatment.

After all 4 monkeys had received all four drugs, several additional drug tests were conducted. To determine whether the effects of 0.05 mg/kg scopolamine were attributable to central or peripheral actions of the drug, an equimolar dose of methyl scopolamine, which has only peripheral actions, was administered to the most dominant animal. One week later the most dominant monkey was retested with the 0.05 mg/kg dose of scopolamine to assess the reliability of this treatment. Next, the most dominant monkey (M1) was removed from the group and the remaining 3 monkeys (M2, M3, M4) were studied. They were observed for 2 days for any changes in social interactions; and then following the regular drug injection schedule, the monkey most dominant in this group, M2, was given 0.05 mg/kg scopolamine. Finally, all 4 animals were put together for one day and then observed for one week with saline injected on the regular drug day (Wednesday); this was the final saline period shown in the figures.

RESULTS

As shown in Fig. 3, the four monkeys had a clearly defined social dominance hierarchy in which the dominant monkey (M1) aggressed on all other monkeys, the next monkey (M2) aggressed on 2 animals but not on M1, the next monkey (M3) aggressed on one monkey and not on the 2 monkeys above it, and the last monkey (M4) was aggressed on by all but rarely showed any aggression against the other three monkeys. The individual measures of aggression (biting, chasing, pushing, pulling and penile display) were summed in a total aggressive score for each monkey. Since M4 had few aggressive responses, it was not included in the figures showing changes in aggressive responses. From the first to the 21st week of testing, the social interactions were always in the same direction; that is, there were no reversals in social rank, although the total number of aggressive responses increased. In the shuttle box, the total number of aggressive responses for 4 monkeys was 103 for Week 1 and 362 for Week 21. This change represented a gradual increase in the number of aggressions in the shuttle box during the last half of the study. In contrast, the total number of aggressive responses in the group cage was 626 for Week 1 and 725 for Week 21, showing relatively little increase across the 21 weeks of testing. Although number of aggressive responses increased across weeks, the number of aggressive responses was generally stable within a week. Therefore, any change in aggressive responses on the drug injection day (Wednesday) was always compared to the preinjection saline day (Tuesday) and the postinjection control days (Thursday and Friday) of that particular week.

Figure 4 shows that in the group cage, scopolamine produced a consistent decrease in aggressive responses at all doses for the three higher-ranking monkeys. Since M4 had an extremely low aggressive response rat (0–4 per session), it was not possible to evaluate a further drug-induced decrease. The decrease in aggressive responses produced by scopolamine was observed only on the drug day and not on the 2 postinjection days. In the group cage under the drug, monkeys typically spent most of the time moving about the sides and floor of the cage with less frequent periods of sitting on the perch. Thus, the decrease in aggressive responses was not caused by a decrease in locomotor activity or general depression in behavior. Although testing in the group cage always followed the shuttle box, the decrease in aggression in the group cage can hardly be attributed to a decrease in drug action. In Experiment 1 the drug was shown to be active during the entire two hours in the operant task.

The number of aggressive responses an animal received did not change with drug treatment. Since squirrel monkeys do not display any obvious submissive gestures, submissive responses can only be analyzed in terms of numbers of aggressive responses received.

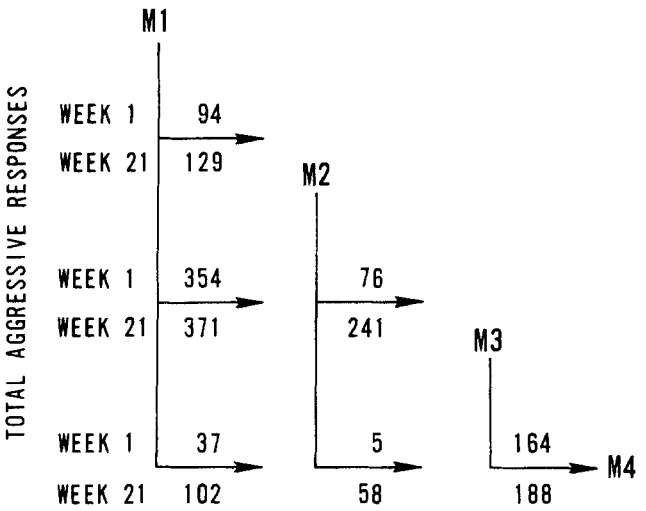

FIG. 3. Comparison of total aggressive responses for individual monkeys during Week 1 (5 test days) immediately preceding and Week 21 (5 test days) immediately following last drug injection. The direction of aggressive responses is indicated by the arrow and the frequency of aggressive responses in indicated by the number on the arrow. For example, M1, the dominant monkey, aggressed against M2 94 times during Week 1 and aggressed against M3 354 times during Week 1.

Higher doses of scopolamine produced a decrease in the number of grapes obtained provided the baseline was sufficiently high to permit a decrease (Fig. 5). Although drugged monkeys received fewer grapes, they did compete normally for the grapes. The lowest dose of scopolamine, 0.005 mg/kg, did not decrease grape-getting but did cause a great decrease in aggressive responses in the group cage (Fig. 4). If a drugged monkey did obtain a grape, the animal would often drop it, have it stolen by another animal or spend up to 2 min licking the skin and finally eating it. Normally, a monkey would consume a grape in ten sounds and guard against its being stolen.

For the highest ranking monkey, M1, the effects of scopolamine on aggressive responses in the shuttle box (Fig. 6) was dramatically different from its effect in the group cage. In contrast to the decrease in aggressive responses in the group cage, M1 showed a marked increase in aggressive responses in the shuttle box at the highest dose of scopolamine, 0.05 mg/kg. Although the lower doses produced no observable change in aggression in the shuttle box, the increase in aggression at the highest dose was reliable; as Fig. 6 shows, the second test with this dose of scopolamine also produced a substantial increase in M1's aggressive responses. The equimolar dose of methyl scopolamine produced no change in M1's behavior. The second-ranking monkey, M2, did not show an increase in aggressive responses in the shuttle box;

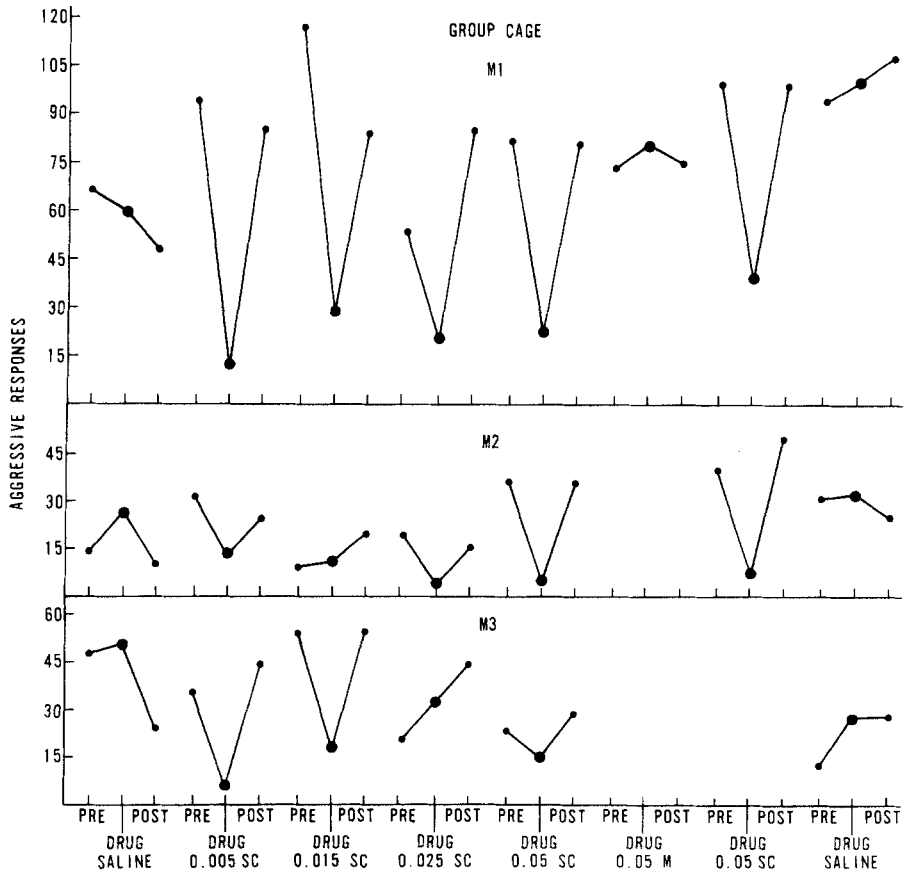

FIG. 4. Aggressive responses of monkeys (M1, M2, M3) tested together in the group cage after injection with saline, scopolamine (SC) or methyl scopolamine (M). PRE indicates the day immediately preceding the treatment day; DRUG indicates the treatment day, and POST indicates the mean of two days immediately following the treatment day. When the 0.05 SC dose was repeated for M2, the most dominant monkey, M1, had been removed from the group.

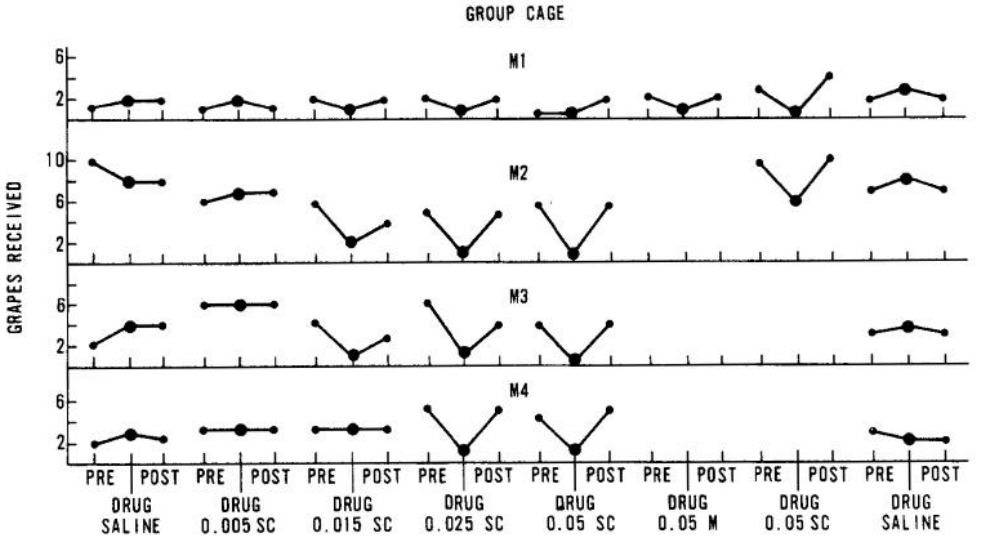

FIG. 5. Grapes received by individual monkeys (M1, M2, M3, M4) tested together in the group cage after injection with saline, scopolamine (SC) or methyl scopolamine (M). PRE indicates the day immediately preceding the treatment day; DRUG indicates the treatment day, and POST indicates the mean of two days immediately following treatment day. When the 0.05 SC dose was repeated for M2, themost dominant monkey, M1, had been removed from the group.

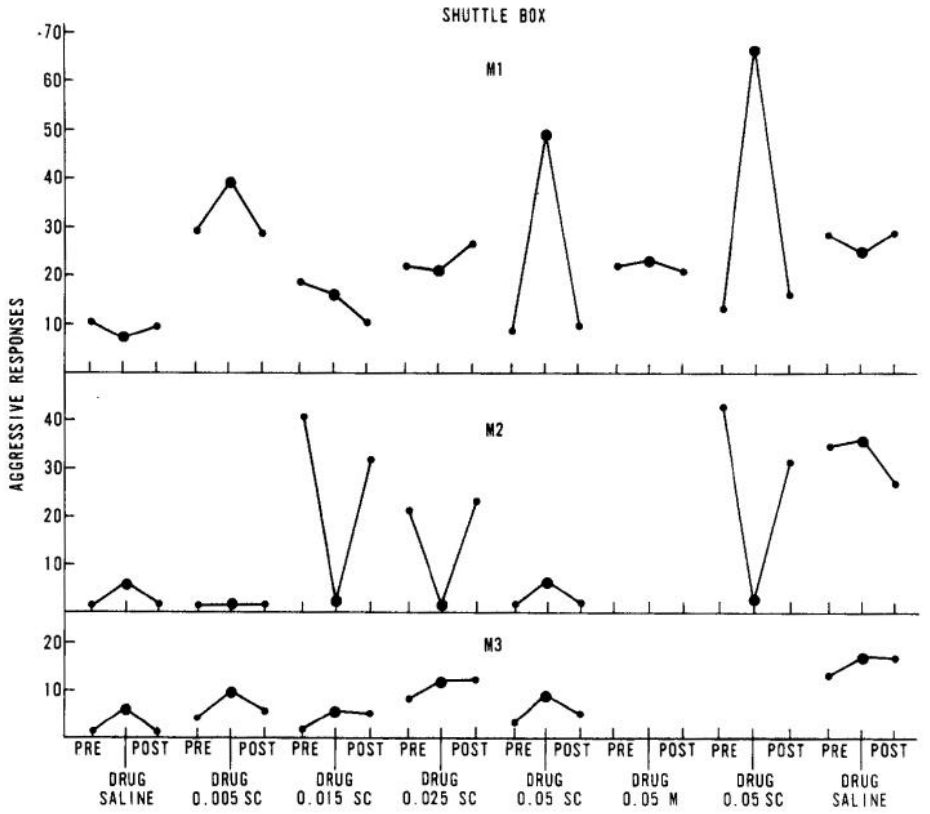

FIG. 6. Aggressive responses of monkeys, M1, M2, and M3, tested together in the shuttle box after injection with saline, scopolamine (SC) or methyl scopolamine (M). PRE indicates the day immediately preceding the treatment day; DRUG indicates the treatment day, and POST indicates the mean of two days immediately following treatment day. When the 0.05 SC dose was repeated for M2, the most dominant monkey, M1, had been removed from the group.

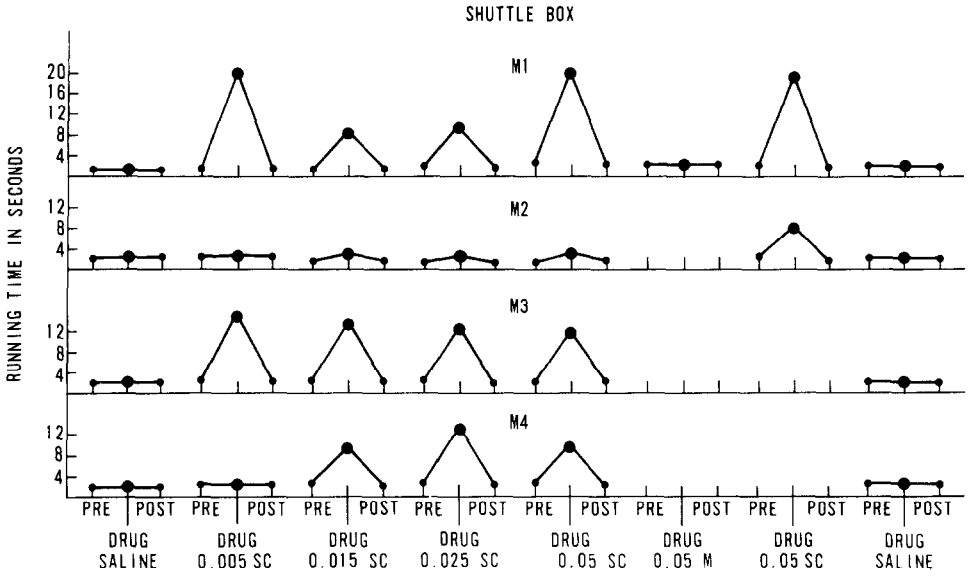

FIG. 7. Time to shuttle for monkeys tested individually in the shuttle box after injection with saline, scopolamine (SC) or methyl scopolamine (M). PRE indicates the day immediately preceding the treatment day; DRUG indicates the treatment day, and POST indicates the mean of two days immediately following the treatment day.

rather it showed a reliable decrease, provided the baseline was high enough to allow a decrease. When retested with the highest dose of scopolamine after the dominant monkey, M1, had been removed, M2 once again showed the clear decrease in aggressive responses. The lower-ranking monkey, M3, showed no change in shuttle-box aggressive responses under the drug. However, the extremely low baseline of this animal precluded observation of a decrease; the same was true for M4.

Although drug treatment changed the frequency of aggressive responses, it did not change the direction of aggressive responses or the target perference. Each monkey aggressed more frequently against one particular monkey. Both M1 and M2 aggressed most frequently against M3; M3 aggressed most frequently against M4. Under the drug, M1 showed an increase in aggression only against its preferred target. Thus, under the 0.05 mg/kg dose of scopolamine, M1 showed a dramatic increase in aggression against M3 and a normal number of aggressive responses against the other two monkeys.

Figure 7 shows that three of the monkeys showed consistent increases in time to shuttle on the individual shuttle trials and this increase occurred for all doses. One monkey, M2, showed little change in running time under the drug regardless of dosage. The increases in running times were not caused by depression or ataxia. Apparently, they resulted from increased startle responses to the buzzer and door opening which interfered with the shuttle response. Methyl scopolamine, 0.05 mg/kg, produced no change in running time for M1; this was in contrast to the marked increase produced by 0.05 mg/kg scopolamine.

All 4 of the monkeys showed little interest in the food cup under the drug, regardless of dosage. Often, on the individual shuttle trials, a monkey would take no more than a lick or would not even approach the food cup. On the group shuttle trials, the monkey that crossed first and received the reinforcement was not the dominant animal as defined by aggressive interactions, but rather the third-ranking monkey, M3. When M3 was drugged, the number of times this monkey crossed first decreased from the usual 15 to 3, 9, 4, 9 for the four drug doses, 0.005–0.05 mg/kg, respectively.

Normal activity patterns in the shuttle box were characterized by long periods of inactivity in which the animals were huddled side by side, and short bursts of aggressive activity. Under thd drug, M1 and, to a lesser degree, the other 3 monkeys spent less time huddling and showed increased activity, visual scanning, and startleability. This increased activity was present for all drug doses. The drugged monkey appeared more responsive to any noises in the corridor and when it did huddle, its head was constantly moving as if scanning its environment.

In the shuttle box, as in the group cage, analysis of the number of aggressive responses received by the drugged monkey did not reveal any pattern or even any observable effect of drug dosage. This suggests that the drugged monkey appeared relatively normal to the other monkeys.

GENERAL DISCUSSION

In Experiment 2, scopolamine had different effects on aggressive responses depending on the environment and the social rank of the animal. In the group cage, the 3 higher-ranking monkeys showed a consistent decrease in aggressive responses under scopolamine. The fourth monkey rarely showed any aggressive responses, regardless of treatment. The normal activity pattern in the cage was not grossly disrupted by the drug, since the observer reported a normal amount of exploratory and locomotor responses. In light of the animal's behavior in the shuttle box, the drug-induced decrease in aggressive responses in the group cage was probably due to the animal's increased distractability, and was not caused by decreased activity

or general depression. Provided the baseline for grape-getting behavior was sufficiently high, the monkeys appeared to compete normally for grapes under the drug. However, they obtained fewer grapes, and the grapes they did obtain were either dropped, stolen or were eaten abnormally slowly over a period of minutes. Aggressive behaviors were more sensitive to scopolamine than grape-getting since the lowest dose of scopolamine caused a decrease in aggressive behavior, but only moderate and higher doses affected grape-getting.

In the shuttle box, the dominant monkey reliably displayed a dramatic increase in aggressive behavior under scopolamine, and this increase was directed specifically against the monkey that M1 had most often aggressed upon. Thus, the drug-induced increase in aggression was not indiscriminate; the drugged dominant monkey would often seek out the preferred monkey to attack. In contrast, the second-ranking monkey reliably showed a decrease in aggressive behaviors. The third and fourth-ranking monkeys, whose baselines in the shuttle box were too low to show a decrease in aggression, showed no change under the drug. Three monkeys showed a consistent increase in running times (decreased speed), while one monkey showed little change. Increased running times from one compartment to the other were due primarily to the increased distractability observed in the drugged monkeys. Under the drug, stimuli (noises, door opening, buzzer sounding, movement of Observer), which previously elicited no responses, would cause a drugged monkey to cease what it was doing and apparently attend to those stimuli. In the shuttle box, the observer was often able to correctly identify the drugged animal from its increased exploring, locomoting and visual scanning. Monkeys were neither depressed in overall behavior nor ataxic. The fact that the monkeys were more responsive to distracting stimuli is consistent with previous literature showing that anticholinergic drugs cause animals to behave as though they had not been habituated to the environment [2].

In the shuttle box, increased exploring and locomoting does not entirely account for the increased aggression shown by the dominant monkey under scopolamine, since the other higher doses of scopolamine produced similar increases in locomoting but no increase in aggression. In a study with rhesus monkeys, when the monkey of a triad was given amphetamine the result was more social interactions and in one case less agonistic behavior [9]. In squirrel monkeys, amphetamine caused increased bar pressing to avoid shock without affecting the animal's aggressive response when handled with a glove [16]. Thus, increases in activity or operant responding alone do not necessarily result in increased aggression.

The changes in aggressive responses were presumably due to the central action of scopolamine, since methyl scopolamine, which acts peripherally rather than centrally, had no effect on aggressive behavior or activity. Also, of the unnumerable reports using anticholinergic drugs, virtually all of the evidence indicates that the behavioral effects of these drugs are due to actions on the central nervous system.

In Experiment 1, monkeys treated with a moderate dose of scopolamine failed to withhold responses on DRL 20 and showed an increase in responding during the Time Out periods. This finding is consistent with numerous reports that anticholinergic drugs cause animals to show a disinhibition of unreinforced or punished responses [2,7]. Experiment 2 had been addressed to the possibility that this disinhibition of responses seen in many operant situations could be generalized to social situations. The only effect in the present results that approximated disinhibition was the increase in aggressive responses in the dominant monkey, and this occurred at a different dosage from that causing overresponding on the DRL 20 schedule. Experiments 1 and 2 indicate the difficulty in predicting drug effects on social behavior from drug effects on operant behavior. Also, these experiments show that the effective dosage in an operant task does not necessarily generalize to a social situation.

The present experiment indicates the difficulty in predicting drug changes in a social setting from changes that occurred in a learning task. For example, chlorpromazine has been shown in squirrel monkeys to increase lever pressing preceding shock but decrease bites following shock [4]. These results would appear to have significance for social interactions, but what that would be is not clear. There are several reports that chlordiazepoxide (Librium) caused an animal to expose itself to, or be less responsive to an aversive stimulus [7,16]. Based on the latter, one might expect that submissive monkeys given this drug would receive more attacks since they would be less responsive to, or show less avoidance of the dominant monkey's attacks or threats. When one dose of this drug was given to a submissive rhesus monkey in a group, it caused a general depression in most behaviors [1], so a wider dose range would have to be explored to test the above prediction. On evidence from operant behavior [7], one might predict that d-amphetamine might increase punished responding in a social situation. However, when d-amphetamine was given to one rhesus monkey in a triad, there was an increase in social activity and a decrease in agonistic behavior [9]. Thus, it is difficult to predict effects on social behavior from drug-induced changes in operant situations. It may well be that drugs that reliably produce disinhibition on operant schedules will have dramatically different effects on social behaviors.

Experiment 2 lends only weak support for the the involvement of a cholinergic system in emotional behavior [14,15]. This support comes from the dominant monkey's reliable increase in aggressive responses under scopolamine in the shuttle box. Since the other doses of scopolamine resulted in similar increases in activity, scanning and distractability, these changes alone cannot account for the increased aggression following the highest dose of scopolamine.

Experiment 2 is in agreement with previous reports of electrical stimulation [13] and drug treatments [10] having different effects depending upon the social rank or pretreatment level of emotionality of the animals. In Experiment 2, scopolamine caused an increase in aggression in a dominant monkey and a decrease in aggression in a submissive monkey. This factor of pretreatment emotionality or social rank remains one of the most important variables in the study of social-emotional responses.

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