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Evaluation of Response Perseveration of Rats in the Radial Arm Maze Following Reinforcing and Nonreinforcing Drugs

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LOH, E. A., A. M. SMITH AND D. C. S. ROBERTS. *Evaluation of the response perseveration of rats in the radial arm maze following reinforcing and nonreinforcing drugs.* PHARMACOL BIOCHEM BEHAV **44**(3) 735–740, 1993.– The behavioral effects of three drugs with high abuse potential (amphetamine, heroin, and nicotine) and two substances with low abuse potential (haloperidol and scopolamine) were evaluated in an eight-arm radial maze. Rats were trained to explore the maze for the food reward. Unlike most radial arm maze paradigms, a food pellet was made available every time the rat entered an arm; thus, no external restrictions were placed upon rats' exploratory pattern. Following 3 days of drug-free training, rats were injected prior to testing with one of the five drugs. Analysis of the sequences of arm entries demonstrated that the variability of the search strategy was significantly decreased by amphetamine, heroin, and nicotine. In contrast, scopolamine and haloperidol either decreased or had no effect on perseveration. These data, along with previous data on ethanol and diazepam, lead to the speculation that drugs of abuse may share the common property of reducing behavioral variability.

Radial arm maze Amphetamine Heroin Nicotine Haloperidol Scopolamine Perseveration Reinforcement Addiction

STEREOTYPED behavior is a prominent feature of a number of neurological disorders including autism, schizophrenia, and obsessive compulsive disorder (19,23). Perseverative behavior patterns are also produced by psychomotor stimulant drugs, which has prompted the speculation that amphetamine-induced stereotypy might be a useful animal model for investigating psychotic behavior (19). Depending upon the dose, amphetamine elicits a variety of species-typical behaviors; at high dosages, the pattern of activity breaks down into short sequences that are emitted at high frequency (15). A vast literature has explored the topography and neural substrates of behaviors elicited by high doses of amphetamine (12,26). At lower dosages, however, the behavioral repertoire of animals is affected in more subtle ways and it has been suggested that the changes brought about by the lower doses of stimulant drugs may actually provide a better model for neurological disorders (21).

High dosages of amphetamines tend to elicit behaviors, such as licking, chewing, and gnawing, in the rat (20); however, lower dosages also seem to modify naturally occurring behaviors. For example, Ellinwood and colleagues chronicled the effects of amphetamines on the behavior of a number of species. This work elegantly established that amphetamine will promote perseverative behaviors that are largely determined by the behavior being displayed at the time of drug onset. This idea has been confirmed in a number of experimental situations (3,19,26). Thus, perseveration of ongoing behaviors appears to be a primary consequence of psychostimulant administration. Descriptions of the effects of low doses of amphetamine appear to offer important insights into how one class of reinforcing drug might affect ongoing behavior.

The usefulness of the concept of perseveration hinges largely on whether the more subtle drug-induced changes in behavior can be quantified. Amphetamine-induced stereotypy has been measured using categorical scales (11) or through the use of detailed choreographic observations (26). The present article details a method to quantify perseverative response patterns elicited by lower dosages of amphetamine and other psychomotor compounds. The behavior of interest was the foraging pattern of rats in an eight-arm radial maze. Our procedure, however, was different from the more common use of this apparatus. Unlike paradigms used to examine learning and memory in the radial arm maze (18), in the present experiments the goal box was rebaited each time the animal left the arm (8). In this situation, food was available in every arm and the animal was simply required to explore the maze and collect the food. All animals received identical amounts of food irrespective of their exploratory pattern. Pre-

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treatment with the various drugs could not influence the number of food pellets received.

In the present article, we show that amphetamine increases the perseverative nature of the exploratory pattern of rats foraging in the maze. We also examined whether this effect is specific to psychomotor stimulant drugs or whether other reinforcing (nicotine, heroin) and nonreinforcing drugs (scopolamine, haloperidol) might also influence the pattern of the foraging response.

METHOD

Animals

Male Wistar rats (Woodlyn Farms, Ontario, and Charles River Farms, Quebec), weighing 250–300 g at the start of the experiment, served as subjects. Upon arrival from the supplier, rats were housed individually and maintained on a reverse 12D : 12L schedule (lights on at 9:00 p.m.). Following at least 1 week with ad lib access to food and water, food was restricted to 15 g/day. This reduced the average daily weight gain to 1–2g.

Apparatus

Two eight-arm radial mazes were used for these studies. The floor of the first maze was constructed from plywood with an arborite surface. The arms (80 × 9 cm) extended from a central octagonal hub measuring 25 cm in diameter. The sides of the arms (25 cm) and the top of the maze were made of 2.5-cm^2 wire mesh. A second maze had Plexiglas sides and a stainless steel bottom. In both mazes, a small food cup connected to an electronic pellet dispenser was positioned at the end of each arm. The first maze required that an experimenter be present in the maze room while testing. The experimenter activated the pellet dispensers and recorded the arm entries. Arm entries into the second maze were detected by weight sensors located in each arm and in the center of the maze. This information was automatically recorded by a computer. Both mazes were positioned on the floor in the center of a testing room illuminated by a single 15-W bulb located on one wall. Large objects positioned near or on the walls could presumably be used by the animal as spatial cues.

Procedure

Habituation. Rats were permitted to explore the radial maze for a daily 30-min period for 3 consecutive days. During these habituation sessions, rats quickly discovered the food pellets (45-mg Noyse pellet), which were located in the food receptacles at the end of each arm. All food receptacles were frequently replenished during each 30-min habituation session. This procedure allowed rats the opportunity to learn that returning to a once-visited arm would lead to additional food reinforcement.

Baseline testing. During the three baseline testing sessions, each rat was injected with saline (1.0 ml/kg) and returned to its home cage. After a period of time that corresponded to the drug pretreatment interval (see below), rats were placed within a large cardboard cylinder in the central hub of the maze. After a moment, the cylinder was lifted and the rat was allowed to search the maze for food. A rat was permitted to explore until it had completed 25 arm entries, defined as the placement of all four paws within the arm. Once a rat obtained the food reward from a particular arm and had reentered the central hub of the maze, the food pellet was replenished. This testing procedure placed no restrictions on the route of exploration the rat selected.

Drug Testing

Amphetamine and heroin. These drug testing days immediately followed baseline training. For the next 3 days, each group of rats (N = 8) was injected IP with one of the following doses of amphetamine HCl—vehicle, 0.25, 0.5, 1.0, or 2.0 mg/kg or heroin HBr—vehicle, 0.25, 0.5, 1.0, or 2.0 mg/kg 30 min prior to testing. Dosages are expressed as the salt. These drugs were dissolved in 0.9% saline and injected in a volume of 1.0 ml/kg.

Nicotine, haloperidol, and scopolamine. For the trials using nicotine, haloperidol, and scopolamine, rats were tested for 1 day with the appropriate dose of drug. The results were replicated in several separate experiments, each using a control group and various doses of drug. The data have been collapsed into a single analysis. Rats were injected with nicotine SC at doses of vehicle, 0.1, 0.2, and 0.4 mg/kg 30 min prior to testing (N = 23, 9, 23, and 13, respectively). Four doses of haloperidol (vehicle, 12.5, 25, and 50 μg/kg; 2 h prior to testing, IP; N = 23, 6, 6, and 17, respectively) and scopolamine (vehicle, 0.1, 0.2, and 0.4 mg/kg; 20 min prior to testing, IP; N = 21, 11, 10, and 10, respectively) were also tested. Rats receiving vehicle injections had been exposed to the maze for the same number of days as groups receiving drug.

Data Analyses

Two summary measures were developed to evaluate biases: a) the distribution of arm entries into specific arms and b) distribution of directions of turn when leaving an arm. The sequence of arm entries made in each trial was used to determine these measures.

Arm bias. A summary score of arm bias was calculated as

$$\sqrt{\Sigma \left[\frac{\text{arm}_n}{25} \right]^2},$$

where arm_n is the number of entries into a particular arm.

A higher arm bias score indicates a higher frequency of entries into a fewer number of arms. The minimum value that can be obtained is 0.356, reflecting a uniform distribution of arm entries, whereas a maximum score of 1.00 would indicate perseverative reentry into a single arm.

Directional bias. When leaving an arm, a rat has the option to either reenter that arm (360° turn) or enter any of the remaining seven arms, each of which represents a different direction of turn (45, 90, 135, 180, 225, 270, or 325° turns). A summary score indicating a specific bias in the direction of turn made by a rat when exiting one arm and entering the next was calculated as follows:

$$\sqrt{\Sigma \left[\frac{\text{turn}_n}{24} \right]^2},$$

where turn_n is the number of turns made at a particular angle.

Scores based upon 25 arm entries (24 turns) range from 0.354–1.0. Increases in preferential turning bias are indicated by higher scores.

To illustrate how the scores reflect biases in the data, Fig. 1 shows three histograms that represent possible distributions of arm entries or turns displayed during 25 trials along with the calculated bias scores. Note that when the choices are

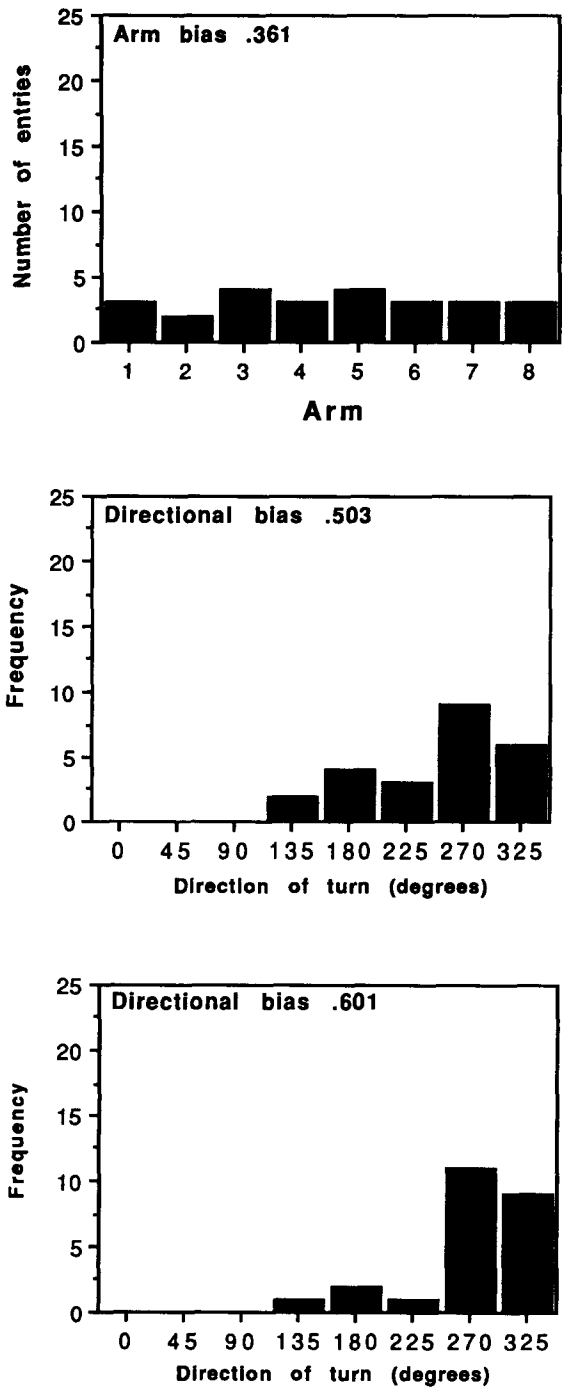

FIG. 1. Representative distributions of directional and arm bias scores. Top: Typical baseline distribution of arm entries. Middle: Typical baseline distribution of direction of turn. Bottom: Typical distribution of direction of turn following an injection of 1.0 mg/kg amphetamine. Numbers represent calculated directional and arm bias scores.

evenly distributed the bias score is low, whereas an uneven distribution is reflected in a higher score. It should also be noted that the bias measures are not orthogonal because a strong arm bias could lead to a high directional bias score.

RESULTS

Directional bias and arm bias scores were analyzed by separate repeated-measures analyses of variance (ANOVAs). In cases where rats received amphetamine or heroin, bias scores obtained on the 3 days when rats were tested with drug were compared with the 3 previous baseline days. In cases where rats were pretreated with a drug on only 1 day (nicotine, haloperidol, and scopolamine), the last day of baseline testing was compared with bias scores obtained on the following day when the animal was tested with drug. Note that "drug" refers to the comparison between baseline days and drug days. Therefore, "dose" was a between-subject variable followed up by Newman-Keuls tests, while drug was a within-subjects variable further evaluated by paired *t*-tests. For the amphetamine and heroin groups, the mean of the directional and arm bias scores obtained on the 3 days of testing with drug pretreatment was used in the Newman-Keuls analysis. For posthoc analyses, statistically significant values are reported at the 0.05 level.

Amphetamine Pretreatment

Repeated-measures analysis of the directional bias measure indicted a significant drug × dose interaction, $F(4, 35) = 6.23$, $p \leq 0.01$, and a significant interaction between drug and day of testing, $F(2, 70) = 4.77$, $p < 0.05$. Subsequent Newman-Keuls analyses indicated that groups of rats that received 0.25, 0.50, 1.0, or 2.0 mg/kg amphetamine perseverated significantly more than groups that received the vehicle injection (Fig. 2). Pair-wise *t*-tests demonstrated that groups receiving 0.25, 0.50, or 1.0 mg/kg amphetamine perseverated significantly more than during baseline testing.

Analysis of the arm bias measure demonstrated a significant drug × day interaction, $F(2, 70) = 6.79$, $p \leq 0.01$, and drug × dose interaction, $F(4, 35) = 3.67$, $p \leq 0.05$. Subsequent Newman-Keuls analysis did not indicate any significant

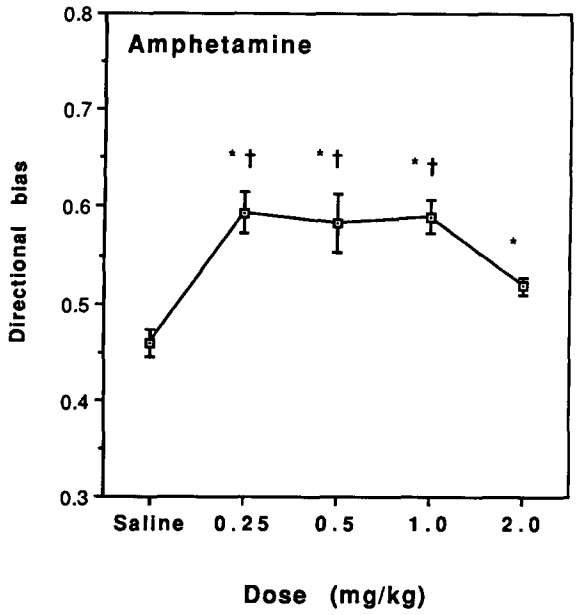

FIG. 2. Effect of amphetamine on directional bias in the radial arm maze. Points represent means (±SEM) for rats pretreated with amphetamine 30 min prior to testing. *Significant difference from the vehicle group. †Significant difference from baseline testing.

differences between the different doses of drug tested, while pair-wise *t*-tests indicated a slight but statistically significant increase in arm bias in the vehicle ($\bar{X}$ = 0.371 vs. 0.376) and 2.0 mg/kg ($\bar{X}$ = 0.364 vs. 0.377) groups when the baseline testing data was compared with drug pretreatment data.

Heroin Pretreatment

Repeated-measures analysis of the directional bias measure indicated a significant drug × dose interaction condition, $F(4, 35) = 6.64$, $p \leq 0.01$, and a significant day effect, $F(2, 70) = 7.52$, $p \leq 0.01$. Subsequent Newman-Keuls analyses indicated that groups of rats that received the 0.25-, 1.0-, and 2.0-mg/kg doses of heroin perseverated significantly more than the group that received the vehicle injection (Fig. 3). Pair-wise *t*-tests indicated an increase in directional bias at the 1.0- and 2.0-mg/kg doses (Fig. 3).

No significant effects were found in the repeated-measures analysis of the arm bias measures.

Nicotine

Repeated-measures analysis of the directional bias data demonstrated a significant drug × dose interaction, $F(3, 64) = 7.81$, $p \leq 0.01$. Newman-Keuls analysis indicated that the group that received 2.0 mg/kg perseverated significantly more than the group that received saline. Pair-wise *t*-tests indicated that groups that received 2.0 and 4.0 mg/kg perseverated significantly more on the day they received drug (Fig. 4).

A significant effect of dose was found in the analysis of the arm bias data, $F(3, 64) = 3.33$, $p \leq 0.05$. Newman-Keuls analysis indicated that groups that received the 0.2- and 0.4-mg/kg doses of nicotine demonstrated a lower arm bias (0.380 and 0.375, respectively) than the group that received the vehicle injection (0.409).

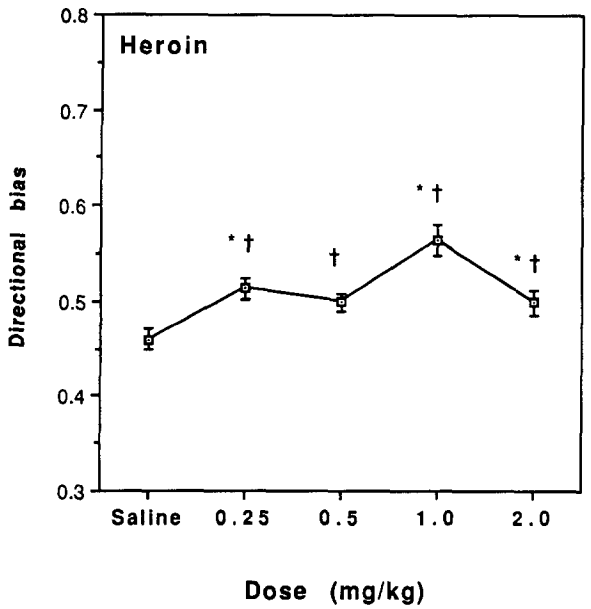

FIG. 3. Effect of heroin on directional bias in the radial arm maze. Points represent means (±SEM) for rats pretreated with heroin 30 min prior to testing. *Significant difference from the vehicle group. †Significant difference from baseline testing.

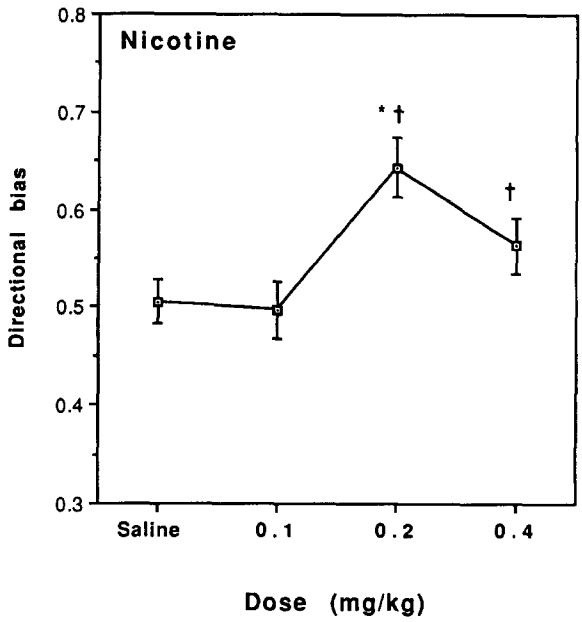

FIG. 4. Effect of nicotine on directional bias in the radial arm maze. Points represent means (±SEM) for rats pretreated with nicotine (0.0, 0.1, 0.2, and 0.4 mg/kg) 30 min prior to testing. *Significant difference from the vehicle group. †Significant difference from baseline testing.

Haloperidol

No significant differences were found in the analysis of the directional or arm bias data (Fig. 5).

Scopolamine

Repeated-measures analysis of the directional bias measure demonstrated a significant dose × drug interaction, $F(3, 48) = 2.79$, $p \leq 0.05$. Newman-Keuls and pair-wise *t*-tests indicated that, when compared with baseline or the saline control group, rats receiving all doses of scopolamine showed significantly less perseveration (Fig. 6).

DISCUSSION

The present experiments show that the exploratory pattern of animals foraging for food in an eight-arm radial maze is altered by a variety of centrally acting drugs. Two dependent variables were developed to quantify the perseverative nature of the exploratory pattern. One measure examined the distribution of arm entries to assess whether individual arms were preferred. The second measure examined whether the pattern of exploration (i.e., direction of turn) was repeated.

The results show that there was little tendency for animals to develop a bias to one particular arm. The minimum arm bias score is 0.356 and the average arm bias scores in the present experiments were remarkably close to this value. Significant effects were noted but the percentage change was not consistent across drug treatments. This is in accord with the statement by Olton et al. that "animals appear to have a strong predisposition to randomly alternate responses among spatially distinct choices even though there is no differential reinforcement contingent on this behavior" [(17), p. 300].

On the other hand, even during baseline testing animals

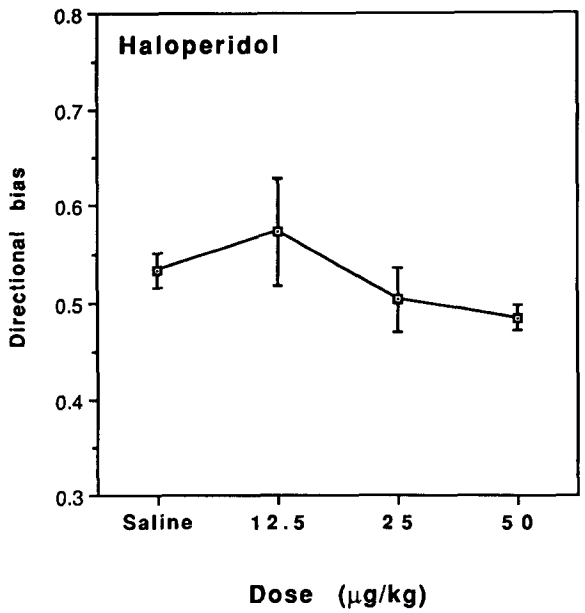

FIG. 5. Effect of haloperidol on directional bias in the radial arm maze. Points represent means (±SEM) for rats pretreated with haloperidol 2 h prior to testing. *Significant difference from the vehicle group. †Significant difference from baseline testing.

displayed a slight bias in the way they explored the maze. Each animal was likely to repeat certain angles of turn over the course of the session, reflected in average directional bias scores significantly greater than the theoretical random score.

Amphetamine pretreatment significantly increased the directional bias scores; the lower doses of amphetamine appeared to have a greater effect than the highest dose (2.0 mg/kg). Animals showed an increased frequency in a decreased number of possible angles of turn. Thus, for this behavioral measure animals showed increased perseveration. These data extend the observation that psychomotor stimulant drugs decrease the variability of behavior, whether it be locomotor activity (15,24,25) or higher-order processing (21,22).

The present results indicate that the behavior of animals following heroin pretreatment also becomes less variable and more perseverative. It is well known that low doses of opiates can produce locomotor stimulation (1,2,10,16), and a number of other investigators previously described opiate-induced stereotyped behaviors (1,7,10). Just as stimulants produce higher rates of activity in more limited response categories (14), we demonstrated that opiates, under appropriate circumstances, also cause a similar perseveration. Similarly, nicotine was also found to increase perseverative patterns in the radial arm maze. This appears to be the first report of nicotine-induced repetitive behavior.

It should be emphasized that the arms of the maze were continually rebaited; therefore, all animals received identical amounts of food irrespective of their exploratory pattern. Consequently, the systematic change in the exploratory pattern cannot be accounted for by a change in food reinforcement.

Whereas amphetamine, heroin, and nicotine were found to increase perseveration, neither haloperidol nor scopolamine significantly increased the directional bias. In fact, scopolamine reduced the bias significantly. These data suggest that not all centrally acting drugs produce the same effect on exploratory behavior. If all drugs tested produced perseveration, it might be concluded that the effect was simply a nonspecific disruption of normal behavior.

Ethanol and diazepam have previously been shown to decrease variability of exploratory patterns in the radial arm maze (i.e., increase perseveration) (13), and the present data extend the list to include amphetamine, heroin, and nicotine. All these are drugs of abuse, which prompts us to speculate that the observed drug-induced increase in perseveration might be related to reinforcement. Reinforcing stimuli have by tradition been defined by their ability to increase the probability of a particular response. Of course, an increase in the response rate of one behavioral category, such as lever pressing, would be at the expense of other behavioral categories, such as exploration. Clearly, reinforcing stimuli usually cause a focusing of the behavioral repertoire, sometimes to the point that one particular response prevails over all others. Such is the case in most operant conditioning paradigms. Conversely, withholding reinforcement (extinction) usually causes behavior to become more variable and diversified (4).

We suggest that the behavioral repertoire might be described along a continuum. At one end, an organism perseverates in a single response category (highly reinforced responding), while at the other extreme the behavior would be more variable. Whether behavior is perseverative or variable depends upon the state of reinforcement. If this formulation is correct, one might predict that the behavioral repertoire might be shifted in the perseverative direction by reinforcing drugs.

We hypothesize that reinforcing drugs predictably affect behavior despite the absence of a formal response contingency. Psychomotor stimulants enhance those categories of behaviors that happen at the time of drug delivery (5,6,9,22). Predominant behaviors would be expected to increase in fre-

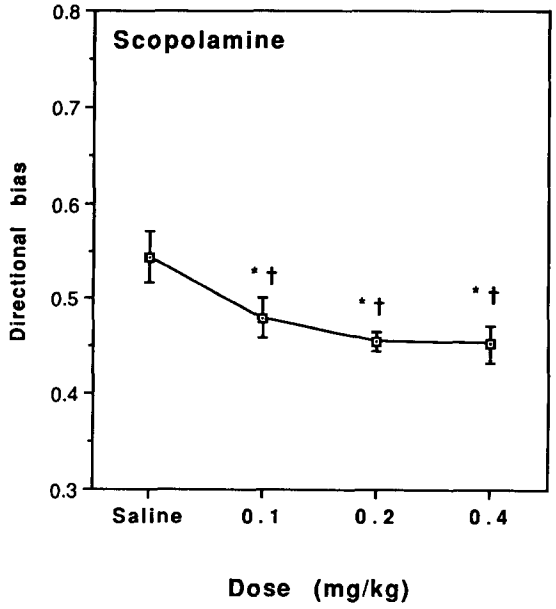

FIG. 6. Effect of scopolamine on directional bias in the radial arm maze. Points represent means (±SEM) for rats pretreated with scopolamine (0.0, 0.1, 0.2, and 0.4 mg/kg) 20 min prior to testing. *Significant difference from the vehicle group. †Significant difference from baseline testing.

quency, forcing less frequent behaviors out of the repertoire; put another way, there may be "an increased frequency in a decreased number of categories." This description is precisely that used by Lyon and Robbins (15) to describe stimulant-induced stereotypy. We suggest that some of the highly repetitive response patterns seen after high doses of amphetamine or cocaine may be an extreme extension of perseveration, which is also evident at low doses. Other reinforcing drugs may produce similar effects, although the degree to which they alter ongoing behavior would be influenced by such factors as speed of drug onset, clearance rate, and other competing responses.

In summary, drugs of abuse, including ethanol, diazepam, amphetamine, heroin, and nicotine, increase perseveration, suggesting that perseveration may be related to drug reinforcement. The reinforcing effects that influence ongoing behavior should be considered an important aspect of the addictive process and may account for "habits" and "superstitious" response patterns associated with drug-taking behavior. It appears that exploratory behavior in the radial arm maze can be used to detect and quantify drug-induced perseveration. This may provide a useful tool to investigate how reinforcing and other centrally acting drugs influence behavior.

ACKNOWLEDGEMENTS

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