Pharmacology Biochemistry & Behavior, Vol. 13, pp. 597–599. Printed in the U.S.A.

Temporal Properties of the Rewarding and Aversive Effects of Amphetamine in Rats[1]

JACK E. SHERMAN[2], TERE ROBERTS, SHERRY E. ROSKAM AND ERIC W. HOLMAN

Department of Psychology, University of California, Los Angeles, CA 90024

Received 20 February 1980

SHERMAN, J. E., T. ROBERTS, S. E. ROSKAM AND E. W. HOLMAN. *Temporal properties of the rewarding and aversive effects of amphetamine in rats.* PHARMAC. BIOCHEM. BEHAV. 13(4) 597–599, 1980.—To associate amphetamine with a location and a flavor, rats were given amphetamine injections and then confined for 20 min in one side of a shuttlebox with access to a flavored solution; on control trials with saline injections, they were confined for 20 min on the opposite side with a different flavor. Three groups of rats were placed in the shuttlebox either 5 min, 120 min, or 240 min after the injections. In subsequent choice tests, the 5 min and 120 min groups preferred the side and avoided the flavor associated with amphetamine; the 240 min group was indifferent between the sides and the flavors.

Amphetamine Conditioned flavor aversion Conditioned location preference Rats

RECENT experiments show that amphetamine has both rewarding and aversive properties depending upon the stimuli and responses with which it is associated. Wise, Yokel and DeWit [7] trained rats to press a bar for intravenous amphetamine, and then gave them access to saccharin solution followed by an amphetamine injection; a later test indicated a moderate aversion to saccharin. Reicher and Holman [5] confined rats in one side of a shuttlebox with access to one flavored solution after amphetamine injections, and confined them in the other side with another solution on control trials without injections; in later free-choice tests, the rats preferred the side of the shuttlebox but avoided the flavor associated with amphetamine. In each of these studies, therefore, the same drug treatment had both rewarding and aversive effects in the same subjects.

One possible explanation for these effects is based on differences in the effectiveness of delayed reinforcement. Garcia, Ervin and Koelling [3] have shown that flavor aversions can be learned with much longer delays of reinforcement than can most conditioned responses to exteroceptive cues. Thus, amphetamine might have immediate rewarding effects, which would be associated mainly with exteroceptive cues, and delayed aversive effects, which would be associated mainly with flavor cues. To determine whether the reinforcing effect of amphetamine changes as a function of time since injection, an obvious procedure is to compare groups of animals trained with different time intervals separating the injection from the cue. Previous experiments of this sort [1, 2, 5] have not provided any evidence that the effect of amphetamine changes with time from rewarding to aversive. Nevertheless, a temporal change might be revealed if a wider range of intervals were explored. The present experiment therefore used a procedure similar to that of Reicher and Holman [5] except that the cues were presented at intervals of 5 min, 120 min and 240 min after the injection of amphetamine.

METHOD

Subjects

The subjects were 36 female Sprague-Dawley rats obtained from Simonsen Labs in Gilroy, CA. The rats were 90–120 days old at the start of the experiments and were maintained at 85% of their free-feeding weight.

Apparatus

Each rat was trained in one of two rectangular shuttleboxes with a grid floor and a barrier in the middle that restricted rats to the appropriate end of the shuttlebox during training periods. The sides differed both tactually and visually. Details of this apparatus are described elsewhere [6].

There were two drinking solutions: the HCl solution contained 0.1% HCl and 5% sucrose, and the NaCl solution contained 3% NaCl and 5% sucrose. They were provided to the rats in graduated test tubes with drinking spouts projecting into each end of the shuttlebox.

The amphetamine and saline injections contained, respectively, 1.4 mg/kg amphetamine sulfate in isotonic saline, and isotonic saline alone; injections were administered IP in a volume of 2 ml/kg.

[1]This work was supported by USPHS Biomedical Research Support Grant 5-SO7RR07009, and UCLA Academic Senate Research Grant 2386. J.E.S. was supported by National Research Award DA 5097 from the National Institute on Drug Abuse.

[2]Reprint requests should be addressed to J. E. Sherman, Department of Psychology, University of California, Los Angeles, CA 90024.

Procedure

The rats were housed in individual cages under conditions of constant temperature, constant illumination, and unlimited access to water. On each of three days before the first training day, the rats were given 20 ml of 5% sucrose solution in their home cages in order to reduce possible neophobic reactions to the training solutions. The drug schedule during training consisted of four injections of saline and four of amphetamine; saline on Mondays and Thursdays and amphetamine on Tuesdays and Fridays. On the other days, the rats stayed in their home cages. The rats were tested on the Sunday following the last injection of amphetamine.

On training days, the rats received a distinctive set of cues associated with either the amphetamine or saline injection. On amphetamine days, each rat was placed in one side of the shuttlebox for 20 min with access to 40 ml of either NaCl solution or HCl solution. On saline days, each rat was placed in the opposite side of the shuttlebox for 20 min with access to the other solution. The rats were randomly assigned to three groups of 12 each; the rats in the three groups were given the injection, respectively, 5 min, 120 min and 240 min before they were placed in the shuttlebox. Half the rats in each group were placed in the left side of the shuttlebox on amphetamine days and half in the right, and half the rats in each group received HCl solution on amphetamine days and half received NaCl solution. Half the rats in each group were trained and tested in one shuttlebox and half in the other.

On the test day, first location preference and then flavor preference were assessed. To determine location preference, each rat was placed in the middle of the shuttlebox without the barrier, and the side occupied by the rat was automatically recorded for 20 min; no solutions were present. Immediately thereafter, the rat was returned to its home cage and offered 30 ml each of the HCl and NaCl solutions in adjacent test tubes for 20 min; total consumption of each solution was recorded.

Statistical Analyses

All statistical tests were conducted with the analysis of variance. For flavors, the dependent variable was amount consumed; the within-subject factor was flavor (HCl vs NaCl); between-subject factors were reinforced cue (amphetamine with HCl vs amphetamine with NaCl) and group (injection-cue interval). For location, the dependent variable was time spent on the left side; the between-subject factors were reinforced cue (amphetamine with left side vs amphetamine with right side), group (injection-cue interval), and shuttlebox. The rejection criterion was $p<0.05$.

RESULTS

The mean daily consumption during the 4 days of training with each flavor are presented in Table 1 for each group. The rats drank overall significantly less on amphetamine days than on saline days, $F(1,30)=81.99$, indicating the anorexic effect of the drug. The magnitude of this effect differed significantly among the three groups, $F(2,30)=3.74$. The effect was also significant in each group considered separately, $F(1,10)\geq 6.19$.

The mean consumption of each flavor for each group in the test also appears in Table 1. The rats drank overall significantly less of the amphetamine flavor than of the saline flavor, $F(1,30)=5.88$, indicating a conditioned aversion. The magnitude of this aversion did not differ significantly among the groups ($F<1$). Considering each group separately, the aversion was significant in the 5 min and 120 min groups, $F(1,10)\geq 5.21$, but not in the 240 min group ($F<1$).

TABLE 1

MEAN CONSUMPTION (ml), IN TRAINING AND TEST, OF FLAVORS ASSOCIATED WITH AMPHETAMINE AND SALINE, AND MEAN TIME (min) SPENT IN TEST ON SIDES ASSOCIATED WITH AMPHETAMINE AND SALINE

	Groups		
	5 min	120 min	240 min
Training flavor			
Amphetamine	1.1	3.4	4.3
Saline	4.9	6.6	6.0
Test flavor			
Amphetamine	2.9	4.2	7.1
Saline	6.2	7.7	8.0
Test side			
Amphetamine	11.7	11.4	10.1
Saline	8.3	8.6	9.9

Table 1 also presents the mean time spent for each group on each side of the shuttlebox in the test. The rats spent overall significantly more time on the amphetamine side than on the saline side ($F(1,24)=17.51$), indicating a conditioned preference. The magnitude of this preference differed significantly among the groups ($F(2,24)=3.51$). The preference was significant in the 5 min and 120 min groups ($F(1,8)\geq 9.18$), but not in the 240 min group ($F<1$).

DISCUSSION

The present results confirm and extend previous data showing that injections of amphetamine administered 0 or 20 min before exposure to compound flavor and location cues produced conditioned flavor aversions and location preferences [5]. The present experiment showed conditioned location preferences and flavor aversions at 5 and 120 min intervals, and indifference to both cues at the 240 min interval. In contrast, Carey [1] found that injections of amphetamine administered 30 min before exposure to a flavor did not produce an aversion. Carey used a single flavor in training and a one flavor consumption test, whereas the experiments showing an aversion used discrimination training and a choice test between two flavors. The latter procedure has been shown to provide a more sensitive test of a flavor aversion [4].

The present experiment was designed to test whether the rewarding and aversive effects of amphetamine for different cues might be explained by the tendency for exteroceptive and flavor cues to be differentially associable with immediate and delayed reinforcers, respectively. This hypothesis predicts that the effect of amphetamine should change from rewarding shortly after injection to aversive at later intervals. No such changes, however, appeared in the data. Instead, at both intervals where amphetamine had any conditioned effects, these effects were rewarding for location cues and aversive for flavor cues.

REFERENCES

1. Carey, R. J. Long-term aversion to a saccharin solution induced by repeated amphetamine injections. *Pharmac. Biochem. Behav.* **1:** 265–270, 1973.
2. D'Mello, G. D., I. P. Stolerman, D. A. Booth and C. W. T. Pilcher. Factors influencing flavour aversions conditioned with amphetamine in rats. *Pharmac. Biochem. Behav.* **7:** 185–190, 1977.
3. Garcia, J., F. R. Ervin and R. A. Koelling. Learning with prolonged delay of reinforcement. *Psychon. Sci.* **5:** 121–122, 1966.
4. Grote, F. W., Jr. and R. T. Brown. Conditioned taste aversions: two-stimulus tests are more sensitive than one-stimulus tests. *Behav. Res. Meth. Instrum.* **3:** 311–312, 1971.
5. Reicher, M. A. and E. W. Holman. Location preference and flavor aversion reinforced by amphetamine in rats. *Anim. Learn. Behav.* **5:** 343–346, 1977.
6. Sherman, J. E., C. Pickman, A. Rice, J. C. Liebeskind and E. W. Holman. Rewarding and aversive effects of morphine: temporal and pharmacological properties. *Pharmac. Biochem. Behav.* **13:** 501–505, 1980.
7. Wise, R. A., R. A. Yokel and H. DeWit. Both positive reinforcement and conditioned aversion from amphetamine and apomorphine. *Science* **191:** 1273–1274, 1976.