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ORIGINAL INVESTIGATION

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Effect of sensitization of stereotypy on the acquisition and retention of tolerance to amphetamine hypophagia

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Abstract The purpose of this study was to determine whether prior sensitization of stereotypy interferes with the development and retention of tolerance to amphetamine-induced hypophagia. Rats were given intermittent injections of either amphetamine (2.5 mg/kg) to induce sensitization of stereotypy, or saline. Subgroups from each group then received daily injections of either amphetamine (2 mg/kg) or saline and access to milk for 30 min. Both sensitized and nonsensitized groups became tolerant to drug-induced hypophagia at about the same rate and to about the same extent. Such tolerance was accompanied by a decrease in the frequency of stereotyped movements while milk was available. The rats were then given daily milk tests for 4 weeks without injections. Subsequent tests with amphetamine revealed that both groups lost tolerance to drug-induced hypophagia and displayed more intense stereotypy than they had prior to drug withdrawal. We conclude that sensitization of stereotypy produced by intermittent injections of amphetamine (2.5 mg/kg) does not retard the development of tolerance to drug-induced hypophagia and does not alter the rat's ability to suppress stereotyped movements. However, the loss of tolerance following drug withdrawal may have been due to the development of more intense stereotypy and/or the "unlearning" of previously acquired strategies for suppressing stereotypy.

Key words Amphetamine · Tolerance · Sensitization · Stereotypy · Retention of tolerance

Introduction

Although amphetamine is classified as an anorexigen, its inhibitory effect on feeding may be due more to its psychostimulant effects than to a decreased motivation to eat (Wolgin 1989). For example, when amphetamine-treated rats are given milk intraorally through implanted cannulae, they consume substantially more milk than when fed in standard drinking tubes (Salisbury and Wolgin 1985; see also Wolgin and Hertz 1995). This difference can be attributed to the fact that in the cannula condition, drug-induced stereotyped movements do not interfere with feeding, as they do in the bottle condition. The fact that bottle-fed rats ultimately recover feeding when amphetamine is given chronically (i.e., become tolerant) implies that they can learn to suppress stereotypy in order to feed (Wolgin et al. 1987; Wolgin and Wade 1995). This conclusion is supported by the finding that tolerance to the hypophagic effect of psychostimulant drugs is contingent on having access to food while intoxicated (Carlton and Wolgin 1971; Woolverton et al. 1978; Foltin and Schuster 1982). Access to food provides both the context and the incentive to suppress stereotyped movements.

If tolerance to amphetamine-induced hypophagia involves learning to suppress stereotyped movements, then sensitization of stereotypy might be expected to retard the subsequent development of tolerance. In an initial test of this hypothesis, however, sensitized rats became more tolerant than nonsensitized rats (Wolgin and Kinney 1992). Although this finding is inconsistent with the hypothesis, the interpretation of the results was complicated by the fact that the nonsensitized rats drank less milk on the dose-response tests conducted after the sensitization phase than they did prior to that phase. This unexpected increase in sensitivity to the hypophagic effect of the drug may have retarded the subsequent development of tolerance in this group.

A subsequent experiment attempted to re-examine this issue (Wolgin 1995). The procedure for inducing sensitization was identical to that in the Wolgin and Kinney (1992) study, except that 36 trials were given,

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rather than 14. Although only the amphetamine-treated group showed sensitization of stereotypy, both groups showed sensitization of hypophagia at the end of this phase. Because even the saline-treated group showed such sensitization, this effect may have been induced by prior exposure to the drug during the initial dose-response tests. If this interpretation is correct, then omitting dose-response testing prior to the sensitization phase should preclude the development of this effect.

Accordingly, in the following experiment, we employed a design similar to that in the Wolgin and Kinney (1992) study except that the initial dose-response tests, conducted prior to the sensitization phase, were omitted. In addition, at the conclusion of the experiment, we examined the retention of tolerance following a 4-week period of drug withdrawal.

Materials and methods

Subjects

The subjects were 32 experimentally naive male albino Sprague-Dawley rats (Charles River Laboratories, Wilmington, Del.) weighing 305–370 g at the beginning of the experiment. Housing conditions were similar to those described by Wolgin (1995).

Procedure

The rats were given Eagle Brand sweetened condensed milk (Borden, Columbus, Ohio) diluted with water (1:3) in their home cages for 30 min each day for 10 weeks to establish robust and stable drinking. Preceding each test, food and water bottles were removed, the rats were injected with isotonic saline (1 cc/kg), and 20 min later, milk was provided in calibrated drinking tubes attached to the front of the cages. At the end of the session, milk intakes were measured, the drinking tubes were removed, water bottles were returned, and the rats were fed. Following the baseline period, the rats were randomly assigned to one of two groups. During the ensuing sensitization phase, one group (group A) received 36 injections of amphetamine (2.5 mg/kg) at 3-day intervals, whereas the other group (group S) received injections of saline. An intermittent schedule of injections was used to facilitate the development of sensitization (cf. Robinson and Becker 1986). An identical schedule was employed in the Wolgin and Kinney (1992) study. On sensitization trials no milk was given, but ratings of motor activity were taken at 10-min intervals for 60 min. On the days intervening between sensitization trials, both groups were given injections of saline and access to milk for 30 min in order to maintain high levels of milk intake.

The effects of amphetamine on motor activity were assessed using a 6-point rating scale, which included the following categories: 0 = stationary and immobile; 1 = stationary activity without stereotyped head movements (e.g., grooming, drinking); 2 = movement involving one or both forelimbs without concurrent stereotyped head movements (e.g., pivoting, rearing, walking; termed "locomotion" hereafter); 3 = stereotyped head darting movements accompanied by sniffing, and generally covering a wide area (termed "sniffing" hereafter); 4 = focused stereotyped head scanning movements covering a small area of the wall or floor of the cage; and 5 = stereotyped licking or biting of the walls or floor of the cage (oral stereotypy). At each rating interval, each rat was observed for about 10 s by a trained observer, who scored the dominant behavior that occurred in that interval. In addition, the intensity (1 = mild; 2 = moderate; 3 = intense) and continuity (1 = discontinuous; 2 = continuous) of each behavioral category were also assessed. The reliability of the raters was established using videotaped recordings and in pilot work. Interobserver agreement on these tests exceeded 90%. During dose-response testing, raters were blind to the drug condition.

At the end of this phase, drug injections were terminated and both groups were given access to milk for 1 week to re-establish a daily regimen of milk tests. In addition, a period of drug withdrawal is thought to enhance the degree of behavioral sensitization (cf. Post 1980; Robinson and Becker 1986). An initial dose-response determination (DR 1) was then conducted. Test doses of *d*-amphetamine sulfate (0.5, 1, 2, and 4 mg/kg) and saline were administered in counterbalanced order, with at least 3 days between doses. On the intervening days, saline injections were given. All injections were administered 20 min before the milk test. In addition to measuring milk intakes at the end of each session, motor activity was rated beginning 5 min before milk access, at 5-min intervals during milk access, and 5 min after the bottles were removed.

Following DR 1, the rats in each group were subdivided into two subgroups, matched on the basis of their mean baseline milk intakes. During the tolerance phase, one subgroup from each group (group A/A and group S/A) was given daily injections of amphetamine (2 mg/kg) and access to milk for 48 trials, while the other subgroup (group A/S and group S/S) was given injections of saline, but otherwise treated similarly. To control for potential differences in milk intakes between amphetamine- and saline-treated subgroups, the intakes of group A/S and group S/S were yoked to those of group A/A and S/A, respectively. This was accomplished by testing the groups in shifts and offering each saline group the mean amount of milk consumed by its corresponding amphetamine group earlier that day.

At the conclusion of the tolerance phase, a second dose-response determination (DR 2) was conducted, in which test doses of amphetamine and saline were substituted for the usual chronic treatment. On these tests, the tolerant groups (group A/A and group S/A) were tested with a higher range of doses (0.5–8 mg/kg) than they were on DR 1. The continuation of the chronic treatment on the days between test doses was designed to maintain the level of tolerance previously established. Following DR 2, drug and saline injections were terminated and all groups were given daily 30-min milk tests for 4 weeks. During this period the yoking procedure was suspended. A final dose-response determination (DR 3) was then conducted to assess the retention of tolerance. During these tests, amphetamine (0.5, 1, 2, and 4 mg/kg) and saline were injected in counterbalanced order with at least three days between doses. On the intervening days, milk tests were conducted but no injections were given. In addition to measuring milk intakes, ratings of motor activity were made at 5-min intervals as previously described.

Drugs

d-Amphetamine sulfate (Sigma, St Louis, Mo.) was dissolved in physiological saline and injected in a volume of 1 ml/kg. Doses of the drug were expressed as the weight of the salt. All injections were given IP.

Data analysis

Except where otherwise noted, the data were analyzed by analyses of variance (ANOVA), with adjustments made to the degrees of freedom when violations of the circularity assumption were detected (Kirk 1982). Planned comparisons were made using the test of Dunn and Sidak (Kirk 1982).

Sensitization of stereotypy was defined as a change in the pattern of movement during the sensitization phase from primarily locomotion and sniffing to one dominated by focused head

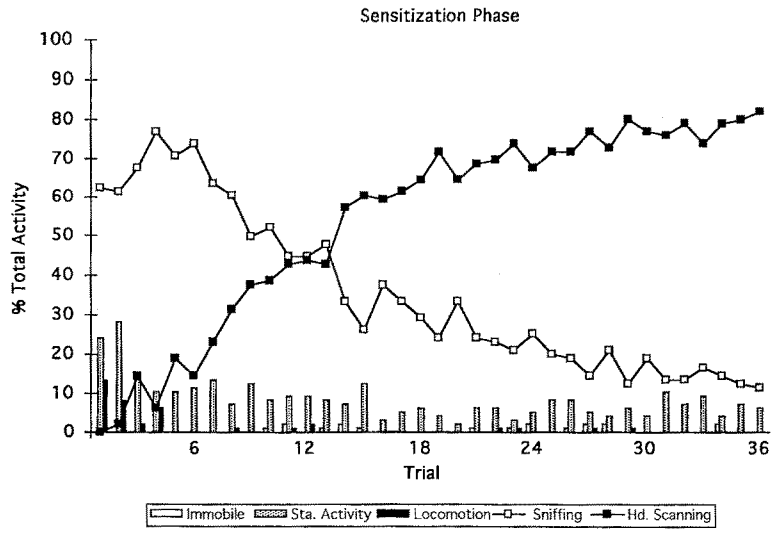

Fig. 1 Frequency of various components of motor activity in amphetamine-treated rats (group A) during the sensitization phase. The data are expressed as a percentage of the total responses on each trial. Non-stereotyped responses are displayed as histograms, stereotyped responses as line graphs. The maximum raw score for each category on each trial was 96 (16 rats × 6 rating periods)

scanning movements. In addition, a more quantitative assessment of sensitization was made by comparing group A and group S with respect to the relative frequency of each behavioral category on DR 1. In analyzing the activity data, the primary dependent measure was the frequency of each category of behavior on each day. Separate ANOVA were conducted for each of the behavioral categories. During the tolerance phase, data from the five 5-min intervals when milk was available were analyzed separately from those collected before and after milk access. In addition, a composite activity score consisting of the sum of the frequencies of locomotion, sniffing, and head scanning was computed for each group and subject to a separate ANOVA in order to provide a more general index of activity. In presenting these data graphically, the frequency of these categories of behavior was expressed as a percentage of the total number of observations from all categories. To assess changes in the intensity of stereotyped sniffing and head scanning, the intensity and duration scores of each rat at each observation period were multiplied, summed, and the total divided by the frequency of that response to yield an average intensity score for each behavior (cf. Rebec and Segal 1980). Because these data may be considered ordinal, they were analyzed with a nonparametric test (the Wilcoxon test; Ferguson 1959).

Results

Sensitization phase

Motor activity

During the early trials of the sensitization phase, group A displayed stereotyped sniffing during 60–80% of the observation periods, and either stationary activity or locomotion during the remaining periods (Fig. 1). On subsequent trials, the frequency of stereotyped sniffing gradually declined to <20%, while the frequency of focused stereotyped head scanning increased to about 80%. In addition, there was a shift in the onset of stereotyped behavior (Table 1). For example, at 10 min postinjection, head scanning increased from 0% of all observations on trial 1, to 19% on trial 12, 38% on trial 24, and 50% on trial 36. These changes in the latency of stereotyped movements, coupled with the alterations in response topography, demonstrate that sensitization of stereotypy developed in group A.

In contrast, group S showed varying degrees of immobility (range: 1–21% of all observations), stationary activity (range: 61–93%), and locomotion (range: 5–26%), but no stereotypy (data not shown). There were no apparent systematic changes in the frequency of these responses over trials.

Direct comparisons between the groups on DR 1, conducted at the conclusion of the sensitization phase, revealed significant differences in head scanning [$F_{\text{interaction}}$ (3, 86) = 7.78, $P = 0.0002$], sniffing [$F_{\text{interaction}}$ (3, 92) = 6.50, $P = 0.0004$], and locomotion [F_{group} (1, 30) = 4.35, $P < 0.05$]. Post hoc tests confirmed that group A displayed more head scanning than group S at the 1, 2, and 4 mg/kg doses, whereas group S showed more locomotion across the dose range and more sniffing at the 2 mg/kg dose.

Milk intake

Amphetamine produced similar dose-dependent decreases in the milk intakes of group A and group S on DR 1 (Fig. 2).

Tolerance phase

Milk intake

The effect of daily injections of amphetamine (2 mg/kg) on the milk intakes of group A/A and group S/A during the tolerance phase is shown in Fig. 3. Because the intakes of group A/S and group S/S were yoked (and identical) to those of the experimental groups, their data are not shown. Group A/A and S/A showed comparable suppression of milk intake on the first

Table 1 Percent of time spent in various activities at 10 and 60 min after injection of amphetamine during the sensitization phase

Trial	Time (min)	Immobile	Stationary activity	Locomotion	Sniffing	Head scanning
1	10	0	63	31	6	0
	60	0	13	6	81	0
6	10	0	19	0	75	6
	60	0	6	0	69	25
12	10	0	19	6	56	19
	60	0	0	6	56	38
18	10	0	19	0	63	19
	60	0	0	0	25	75
24	10	13	0	0	50	38
	60	0	6	0	19	75
30	10	0	13	0	38	50
	60	0	0	0	25	75
36	10	0	13	0	38	50
	60	0	0	0	6	94

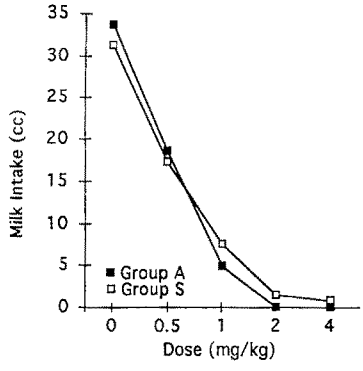

Fig. 2 Effect of saline and various doses of amphetamine on mean milk intake during DR 1, conducted after the sensitization phase

four blocks of trials. On subsequent blocks, intakes gradually recovered, but did not reach baseline levels by the end of the tolerance phase. There were no statistically significant differences between the groups ($P > 0.05$). There was, however, a significant main effect of Trial [$F(6, 84) = 18.72$, $P < 0.0001$], indicating that tolerance developed to the initial hypophagic effect of the drug in both groups.

The development of tolerance in group A/A and group S/A was confirmed by a rightward shift in DR 2 relative to DR 1 (Fig. 4). Statistical analyses revealed a significant Dose-response × Dose interaction for both groups [group A/A: $F(8, 56) = 5.98$, $P < 0.0001$; group S/A: $F(5, 34) = 4.56$, $P < 0.003$], with significant differences at 0.5, 1, and 2 mg/kg. The control groups also showed a rightward shift on DR 2 [group A/S: $F_{\text{interaction}}(6, 43) = 3.68$, $P < 0.005$; group S/S: $F_{\text{interaction}}(6, 39) = 3.21$, $P < 0.02$], but significant differences were limited to the 0.5 and 1 mg/kg doses.

All of the groups lost weight during the tolerance phase (group A/A: 67 g; group S/A: 44 g; group A/S: 43 g; group S/S: 38 g).

Motor activity

Although group A/A and group S/A displayed different patterns of activity on DR 1, both groups showed decreased levels of composite activity on DR 2 during the periods in which the milk was available [group A/A: $F_{\text{interaction}}(6, 44) = 2.37$, $P < 0.05$; group S/A: $F_{\text{interaction}}(7, 46) = 5.29$, $P < 0.0002$; Fig. 5]. Post hoc analyses revealed significant differences at the 1 and 2 mg/kg doses. Analysis of the individual components of activity suggested that, for both groups, the decline in composite activity was due primarily to a decrease in stereotyped sniffing [Group A/A: $F_{\text{DR}}(2, 14) = 6.06$, $P < 0.02$; group S/A: $F_{\text{interaction}}(4, 28) = 5.97$, $P < 0.002$]. For example, at the 2 mg/kg dose, the frequency of stereotyped sniffing declined to 0 on DR 2 in both groups (cf. Fig. 5). There were no significant changes in the frequency of head scanning for either group.

Despite these statistical findings, a more detailed analysis of each subject's data revealed that the changes in the frequency of stereotyped behavior were actually more complex. For example, in group A/A, some rats, which displayed stereotyped sniffing on DR 1, showed head scanning on DR 2, while other rats, which engaged in head scanning on DR 1, suppressed such activity on DR 2. Thus, it is an oversimplification to conclude that sniffing declined while head scanning remained constant during the chronic phase. Furthermore, during the observation periods before and after access to milk, rats in group S/A showed significantly more head scanning on DR 2 than they had on DR 1 [$F_{\text{interaction}}(8, 56) = 3.40$, $P < 0.003$], suggesting that sensitization of stereotypy developed during the tolerance phase. For example, at the 2 mg/kg dose, head scanning rose from 25% of all observations on DR 1 to 63% on DR 2. In contrast, when milk was available, head scanning on DR 2 occurred only 20% of the time at this dose. This difference suggests that the rats in group S/A were actually suppressing stereotyped head scanning movements

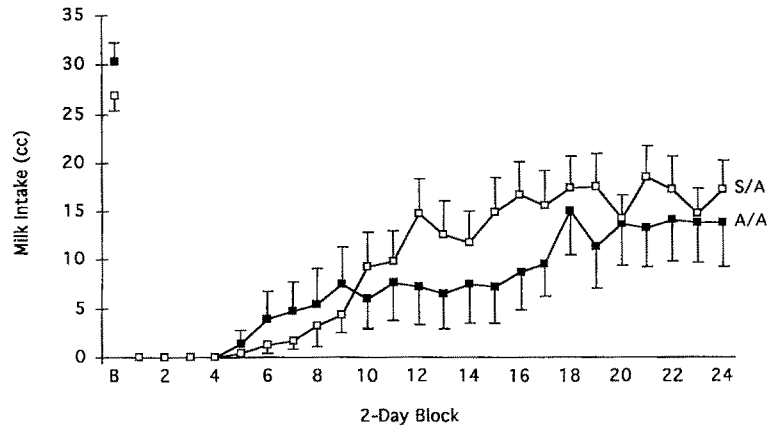

Fig. 3 Mean milk intakes of sensitized (A/A) and non-sensitized (S/A) groups during the tolerance phase. *B* mean of last three baseline trials. The data are expressed as 2-day blocks. *Vertical lines* indicate 1 SE

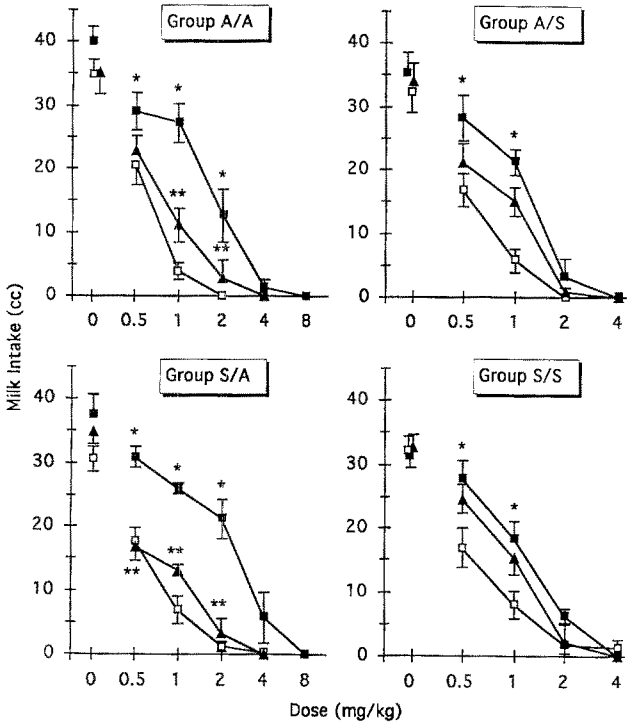

Fig. 4 Effect of saline and various doses of amphetamine on mean milk intake prior to the tolerance phase (□, Pretolerance), after the tolerance phase (■, Post Tolerance), and after drug withdrawal (▲, Retention). *Vertical lines* indicate 1 SE. *Differs from Pretolerance; **differs from Post Tolerance

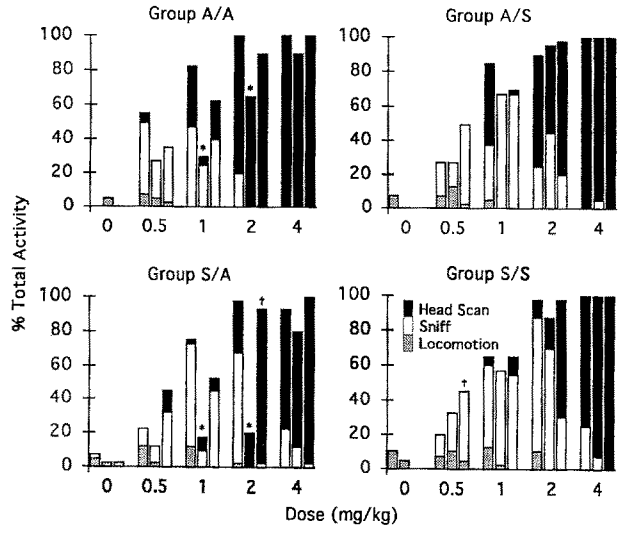

Fig. 5 Effect of saline and various doses of amphetamine on composite motor activity (locomotion + stereotyped sniffing + stereotyped head scanning). Each histogram indicates the relative amounts of each movement category, expressed as a percentage of the total number of responses from all of the behavioral categories. At each dose, the *left histogram* represents data collected before the tolerance phase, the *middle histogram*, data collected after the tolerance phase, and the *right histogram*, data collected following drug withdrawal. The maximum score was 40 (eight rats × five rating periods). *Differs from Pretolerance; †differs from Post Tolerance

when milk was available, even though the frequency of this response did not appear to change from DR 1.

No significant decreases in composite activity were found for group A/S or group S/S.

Retention of tolerance

Milk intake

Following a 4-week period in which injections were suspended while milk tests were conducted, group A/A and group S/A showed leftward shifts on DR 3 relative to DR 2 (Fig. 4). Statistical analysis revealed significant Dose-response × Dose interactions for both groups [group A/A: F (8, 56) = 5.98, $P < 0.0001$; group S/A: $F(5, 34) = 4.56$, $P < 0.003$]. For group A/A intakes were significantly lower at the 1 and 2 mg/kg doses whereas for group S/A, intakes were depressed at the 0.5, 1, and 2 mg/kg doses. Intakes on DR 3 did not differ from those on DR 1. In contrast, there were no significant changes in intake on DR 3 for group A/S or group S/S.

Motor activity

The loss of tolerance in group A/A and group S/A was accompanied by an increased frequency of head scanning and/or sniffing on DR 3 (cf. Fig. 5). For group

Table 2 Average intensity of stereotyped head scanning and sniffing (maximum score = 6.00)

	Dose (mg/mg)				
	0	0.5	1	2	4
Head scanning					
Group A/A					
DR 2	0.00	0.00	0.25	2.86	5.30
DR 3	0.00	0.00	2.33	4.80*	5.90
Group S/A					
DR 2	0.00	0.00	0.38	1.35	3.88
DR 3	0.00	0.63	0.69	4.32*	5.59
Group A/S					
DR 2	0.00	0.00	0.00	2.32	4.80
DR 3	0.00	0.00	0.25	3.53	5.80
Group S/S					
DR 2	0.00	0.00	0.00	0.94	4.35
DR 3	0.00	0.00	0.63	2.12	4.85
Sniffing					
Group A/A					
DR 2	0.00	1.06	1.00	0.00	0.00
DR 3	0.00	1.42	2.44	0.00	0.00
Group S/A					
DR 2	0.00	0.75	0.63	0.00	0.18
DR 3	0.25	1.78	2.56*	0.50	0.25
Group A/S					
DR 2	0.00	0.81	2.44	2.48	0.88
DR 3	0.00	1.89*	2.66	1.75	0.00
Group S/S					
DR 2	0.00	0.94	2.25	3.14	0.58
DR 3	0.00	2.33*	2.58	2.45	0.00

*DR 3 > DR 2, $P < 0.05$

A/A, these changes did not achieve statistical significance, in part due to a "ceiling effect" at the higher doses. For group S/A, there was a significant increase in composite activity [$F_{\text{interaction}}$ (7, 46) = 5.29, $P < 0.0002$], which was limited to the 2 mg/kg dose. In addition, there were increases in the frequency of individual components of stereotypy. Head scanning increased [$F_{\text{interaction}}$ (8, 55) = 5.98, $P < 0.0001$] at both the 2 and 4 mg/kg doses, and sniffing increased [$F_{\text{interaction}}$ (4,28) = 5.97, $P < 0.0002$], at the 1 mg/kg dose.

These increases in the frequency of head scanning and sniffing were accompanied by changes in the intensity of these movements (Table 2). The intensity of head scanning was significantly higher at the 2 mg/kg dose in both groups, while the intensity of sniffing was higher only in group S/A, and only at the 1 mg/kg dose (Wilcoxon test, $P < 0.05$).

In contrast, there were only minor changes in the frequency and/or intensity of motor activity in group A/S and group S/S on DR 3 (cf. Fig. 5 and Table 2).

Discussion

Although group A and group S clearly differed in their response to the psychomotor effects of amphetamine at the conclusion of the sensitization phase, they showed similar dose-dependent decreases in milk intake prior to the tolerance phase. Moreover, both the sensitized (group A/A) and nonsensitized (group S/A) groups developed tolerance to the hypophagic effect of the drug at about the same rate and showed comparable rightward shifts on DR 2. Thus, sensitization of stereotypy neither facilitated nor retarded the subsequent development of tolerance under conditions in which initial sensitivity to the hypophagic effect of the drug was equal.

Although sensitization of stereotypy did not affect the development of tolerance to drug-induced hypophagia, both group A/A and group S/A showed a decrease in composite activity on DR 2, suggesting that they had learned to suppress stereotyped movements in order to feed. Paradoxically, during the same time frame, group S/A displayed increased head scanning and decreased sniffing when milk was not available. Thus, sensitization of stereotypy developed in this group concurrently with the development of tolerance to hypophagia. Similar results have been found with cocaine (Wolgin and Hertz 1995). Taken together, these findings suggest that sensitized stereotyped movements are not more difficult to suppress than nonsensitized movements. It is possible, however, that more intense sterotypy would interfere with the development of tolerance. Some preliminary evidence supporting this possibility is discussed below.

Although both control groups (group A/S and group S/S) also showed rightward shifts on DR 2, significant increases in milk intake were found only at the lower doses. We believe that this apparent tolerance was artifactual. Because milk intakes were limited to the amounts ingested by the amphetamine-treated groups, group A/S and group S/S probably developed an increased motivation for milk during the course of the tolerance phase. This may have promoted increased milk intakes at the lower doses of amphetamine, which do not induce stereotyped movements. At the higher doses, however, increased motivation per se would not affect intake because these groups had not learned to suppress stereotypy. For groups given amphetamine during the tolerance phase, on the other hand, an increased motivation for milk would facilitate learning to suppress stereotyped movements.

The loss of tolerance in group A/A and group S/A following a 4-week period of drug withdrawal may appear, at first glance, to be inconsistent with a learning model. As others have noted (e.g., Stafford et al. 1994), if tolerance is mediated by instrumental learning, the learned response should be retained over drug-free intervals unless specific procedures are employed to diminish conditioning. Two previous studies reported that tolerance to amphetamine-induced hypophagia was retained following 6 or 26 days of drug withdrawal (Poulos et al. 1981; Demellweek and Goudie 1983), whereas other studies found a loss of

tolerance following periods of 20 or 50 days (Gotestam and Lewander 1975; Wolgin and Salisbury 1985).

However, Poulos et al. (1981) have shown that tolerance to amphetamine-induced hypophagia is retained only if feeding tests are suspended during the withdrawal period; tolerance is not retained if feeding tests are continued. In the studies cited above in which tolerance was lost, including the present study, subjects had access to food. Clearly, then, the loss of tolerance is not a function of drug withdrawal per se. To account for this finding, Poulos and Cappell (1991) propose that tolerance is mediated by a state of "hyperhunger" that is engendered to offset the initial anorexic effect of the drug. When tolerant subjects are given food during drug withdrawal, this increased motivation to eat constitutes a functional disturbance to nutritional homeostasis, and elicits a counteradaptation, causing a loss of tolerance. However, an alternative interpretation, based on the learning model, is that during the period of drug withdrawal, tolerant rats simply learn that it is no longer necessary to suppress stereotyped movements in order to obtain milk. Presumably, such "unlearning" would not take place if milk tests were suspended during the withdrawal period.

Another factor that may have contributed to the loss of tolerance is the marked increase in the frequency and/or intensity of stereotyped movements following drug withdrawal. Several previous studies have reported that such time-dependent sensitization of stereotypy is accompanied by changes in amphetamine-stimulated dopamine release in striatal tissue (Kolta et al. 1985; Segal and Kuczenski 1992; Paulson and Robinson 1995). Although sensitization of stereotypy did not retard the initial development of tolerance, the increased intensity of stereotyped movements following drug withdrawal may have rendered them more difficult to suppress. This raises the possibility that stereotypy must surpass a critical threshold of intensity before it will interfere with the development of tolerance. This notion can be tested by using higher sensitizing doses and/or by allowing time-dependent sensitization to develop by introducing a longer drug-free period between the sensitization and tolerance phases of the experiment.

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