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Long-term retention of tolerance to amphetamine hypophagia following cessation of drug injections and feeding tests

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Abstract

According to the instrumental learning model, tolerance to amphetamine hypophagia involves learning to suppress stereotyped movements that interfere with feeding. If both drug injections and feeding tests are then suspended, learning should be retained and no loss of tolerance should occur. However, previous studies have only assessed the retention of tolerance for 3–4 weeks. In the present study, retention intervals of 4–31 weeks were used. Rats were given daily injections of amphetamine (2 mg/kg) and access to milk for 30 min until tolerance developed to drug-induced hypophagia. Yoked controls were injected with saline. Both before and after this phase, dose-response (DR) tests were conducted. Drug injections and feeding tests were then suspended. At 4, 10, 18, and 31 weeks, both groups were injected with 2 mg/kg amphetamine and given access to milk for 30 min to assess the retention of tolerance. A final DR determination was then conducted. Most (88%) rats retained tolerance to 2 mg/kg amphetamine for 31 weeks. However, DR tests revealed that tolerance was not retained at 4 mg/kg. The results demonstrate that learned tolerance to amphetamine can be retained over long intervals when both drug injections and feeding tests are suspended.

Keywords: Amphetamine; Retention of tolerance; Instrumental learning model; Hypophagia; Stereotyped movements

1. Introduction

Tolerance to amphetamine-induced hypophagia is contingent on having access to food during the period of drug intoxication (Carlton and Wolgin, 1971). Several studies have now demonstrated that the loss of tolerance is contingent on, or at least facilitated by, having access to the test food during a drug-free period (Hughes et al., 1999; Poulos et al., 1981; Wolgin and Hughes, 1997). For example, tolerant rats that were allowed to drink milk in the undrugged state during a 3–4-week period lost tolerance to amphetamine hypophagia, even though they continued to receive amphetamine injections after each of the daily milk tests. In a group of rats that were neither injected with amphetamine nor given feeding tests during the same period of time, however, only two of six rats lost tolerance (Hughes et al., 1999). Studies involving other drugs have also reported that the loss of tolerance is contingent on exposure to the criterion response in the absence of the drug (Kalynchuk et al., 1994; Mana and Pinel, 1987; Poulos and Hinson, 1984; Weiss and Post, 1991).

According to the instrumental learning model (Wolgin, 1989), tolerance involves learning to suppress stereotyped responses, which interfere with the appetitive phase of feeding (Wolgin and Wade, 1995; Wolgin et al., 1987). Such learning is reinforced by the ingestion of milk. From this perspective, drinking milk in the absence of the drug would represent a change in the contingencies of reinforcement because obtaining milk would no longer be contingent on suppressing stereotyped movements. Such a change would decrease the probability of performing the learned response in the future, when the drug is reintroduced, resulting in a loss of tolerance. In contrast, if both access to milk and drug injections were suspended concurrently, no change in the reinforcement contingencies would be experienced, no new learning would ensue and, therefore, tolerance would be retained.

It is also possible, however, that with the passage of sufficient time, tolerance would decay even in the absence of contravening experience (cf. Hughes et al., 1999). In principle, this time-dependent loss of tolerance could result from pharmacodynamic changes and/or "forgetting" of the

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learned response. Because previous studies on the retention of tolerance to amphetamine-induced hypophagia used retention intervals lasting only 3–4 weeks (Hughes et al., 1999; Poulos et al., 1981), this possibility has not been adequately evaluated. Accordingly, in the present experiment we examined the retention of tolerance following the suspension of both drug injections and feeding tests over periods ranging from 4 to 31 weeks. Furthermore, unlike previous studies, in which the retention of tolerance was assessed only once, at the end of the designated interval, the present experiment probed the retention of tolerance at increasingly longer intervals, with a final dose-response (DR) determination conducted at the end.

2. Method

2.1. Subjects

The subjects were 45 experimentally naive male albino Sprague–Dawley rats (Charles River Laboratories, Wilmington, DE) weighing 312–388 g at the beginning of the experiment. Housing conditions were similar to those described by Wolgin (1995). The rats were maintained on three Purina Lab Chow pellets (about 15 g) and unlimited water on days when milk tests were conducted. On days when milk tests were not conducted, an extra food pellet (about 5 g) was given to each rat.

2.2. Procedure

Milk tests were conducted 6 days per week. Eagle Brand sweetened condensed milk (Borden, Columbus, OH) diluted with water (1:3) was presented in graduated bottles attached to the front of the home cages for 30 min. Preceding each test, the rats were weighed, injected with isotonic saline (1 cc/kg ip), and given the milk 20 min later. At the end of the test session, the drinking tubes were removed, water bottles were returned, and the rats were fed. After an 18-day baseline period during which intakes stabilized, an initial DR determination (DR 1) was 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 intraperitoneally 20 min before the milk test.

In addition to measuring milk intake at the end of each test session, motor activity was rated beginning 5 min before milk access, at 5-min intervals during milk access, and 5 min after the milk bottles were removed. Motor activity was assessed using a 6-point nominal rating scale, which included the following categories: 0 = immobile, 1 = stationary activity, 2 = locomotion, 3 = stereotyped sniffing, 4 = stereotyped head scanning, 5 = 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. The reliability of the raters was established using videotaped recordings and in pilot work. Interobserver agreement on these tests (number of concordant ratings/total number of ratings) exceeded 90%. During DR testing, raters were blind to the drug condition.

Following DR 1, the rats were given saline injections and milk tests for 10 days to allow milk intakes to stabilize. The rats were then divided into two groups. During the ensuing tolerance phase, one group ($n = 32$) received a daily injection of amphetamine (2 mg/kg) for 40 trials, while a control group ($n = 13$) received saline injections. To control for the potential effects of differences in milk intakes between the two groups, the intakes of the control group were yoked to those of the drugged group. This was accomplished by staggering the trials by 1 day so that the saline group was offered the mean amount consumed by the drugged group on the previous day. At the end of the tolerance phase, a second DR determination (DR 2) was conducted, in which test doses of amphetamine and saline were substituted for the usual chronic treatment, with at least 3 days between each dose. The continuation of the chronic treatment was designed to maintain the level of tolerance previously established.

Following DR 2, the retention phase began. During this period, injections and feeding tests were suspended and the rats were left undisturbed in their cages except for being weighed one or more times each week. At 4, 10, 18, and 31 weeks of the retention period, the rats in both groups were injected with 2 mg/kg amphetamine and given access to milk for 30 min to assess the retention of tolerance.

Three days after the final retention test, a third DR determination (DR 3) was conducted to assess more quantitatively any changes in the retention of tolerance. Rats in both groups were given injections of saline and test doses of amphetamine prior to milk tests in counterbalanced order, with at least 3 days between each dose. On the intervening days, the rats were left undisturbed in their cages.

2.3. 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 are expressed as the weight of the salt.

2.4. Data analysis

The DR data were analyzed by two-factor (DR determination × Dose) analyses of variance (ANOVA), with adjustments to the degrees of freedom when violations of the sphericity assumption were detected (Kirk, 1982). When significant interactions were obtained, tests of simple main effects were performed followed by individual comparisons using the test of Dunn and Sidak (Kirk, 1982). Intakes under amphetamine were converted to percentages of intakes under saline prior to statistical analysis.

In analyzing the activity data, the dependent measure was the frequency of each category of behavior on each day. Separate ANOVAs were conducted for each of the behavioral categories. In addition, a composite activity score consisting of the sum of the frequencies of locomotion, sniffing, head scanning, and oral stereotypy was computed for each group and subject to a separate ANOVA. In presenting these data graphically, the combined frequencies of these categories of behavior were expressed as a percentage of the total number of observations from all categories. Activity data collected during the 30-min period in which the rats had access to milk were analyzed separately from data collected before and after milk access.

3. Results

3.1. Milk intake

Mean milk intakes during the DR tests are presented in Fig. 1 (upper panels). On DR 1, conducted prior to the tolerance phase, amphetamine produced dose-dependent decreases in milk intake in both groups. At the 2-mg/kg dose, intakes were reduced to a mean of 2 cc. During the tolerance phase, intakes recovered and then stabilized at ca. 20 cc (Fig. 2). This level of intake was maintained during the intervening days of DR 2, leading up to the beginning of the retention phase. Administration of amphetamine probes to the previously tolerant group at 4, 10, 18, and 31 weeks resulted in intakes of 22.8, 19.6, 20.0, and 19.6 cc, respectively, which were not statistically different from previous levels ($P > .05$). Mean body weights on these trials were 459, 458, 457, and 461 g, respectively. In contrast, in the nontolerant control group, amphetamine almost totally suppressed intakes on each trial (Fig. 2).

Analysis of the DR data revealed that in the amphetamine group, tolerance developed to the initial hypophagic effect of amphetamine on DR 2 across the entire dose range, and was retained following the retention phase (DR 3) at all but the highest dose (4 mg/kg; Fig. 1, upper left panel). This conclusion was confirmed by a significant DR × Dose interaction, $F(6,186) = 9.34$, $P < .0001$, and post hoc comparisons. In contrast, there were no significant changes on the DR tests in the control group.

3.2. Motor activity

The frequency of composite motor activity (locomotion + stereotypy) during each of the DR determinations is shown in Fig. 1 (middle and lower panels). The data are expressed as a percentage of the frequencies of all categories of behavior. Data collected while milk was available (middle panels) are presented separately from data collected before and after milk availability (bottom panels). On DR 1, conducted prior to the tolerance phase, both groups showed dose-dependent increases in composite activity when milk was available (Fig. 1, middle). Inspection of the individual categories of behavior revealed that, at the 2-mg/kg dose, most of this activity consisted of stereotyped sniffing (91% and 88% for the amphetamine and saline groups, respectively) whereas at the 4-mg/kg dose there was

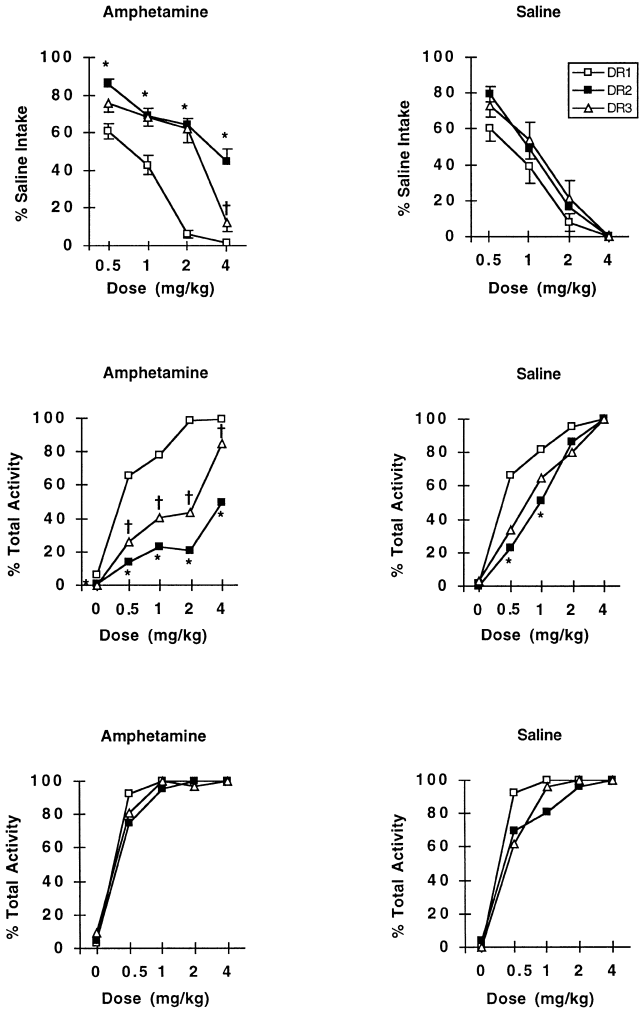

Fig. 1. Top: Effect of various doses of amphetamine on mean milk intakes (±S.E.) in the amphetamine and saline groups prior to the tolerance phase (DR 1), after the tolerance phase (DR 2), and after the retention phase (DR 3). The data are expressed as a percentage of intakes under the saline doses for each DR determination. Mean intakes under saline for DR 1, 2, and 3, respectively, for the amphetamine group were 32, 34, and 29 cc; for the saline group, 29, 35, and 25 cc. Middle and Bottom: Effect of saline and various doses of amphetamine on composite motor activity (locomotion + stereotyped responses) prior to the tolerance phase (DR 1), after the tolerance phase (DR 2), and after the retention phase (DR 3). The data are expressed as a percentage of the frequencies of all categories of behavior. Activity data collected when milk was available are shown in the middle panels; data collected before and after milk availability are shown in the bottom panels. The maximum score when milk was available was 160 for the amphetamine group (32 rats × 5 rating periods) and 65 for the saline group (13 rats × 5 rating periods). When milk was not available, the maximum scores were 64 (32 rats × 2 rating periods) and 26 (13 rats × 2 rating periods), respectively. * $P < .05$, differs from DR 1; † $P < .05$, differs from DR 2.

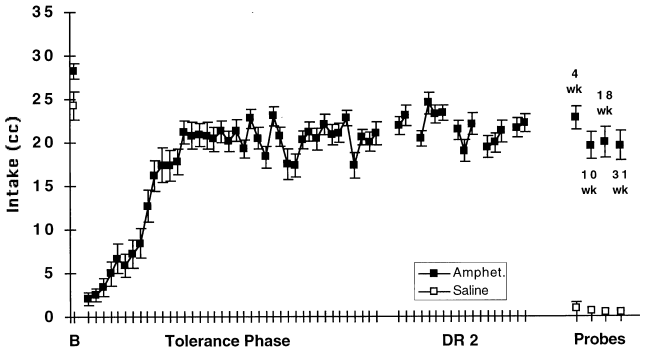

Fig. 2. Mean milk intakes (±S.E.) of the amphetamine and saline groups on the last baseline trial (B), during the tolerance phase, on the days intervening between test doses during the second DR determination (DR 2), and on retention tests conducted 4, 10, 18, and 31 weeks after completion of DR 2 (probes). During the tolerance phase, the intakes of the saline group were yoked (and equivalent) to those of the amphetamine group. On the retention tests, both groups were injected with 2 mg/kg D-amphetamine.

less sniffing (69% and 63%, respectively) and more head scanning (30% and 37%, respectively). During the tolerance phase, rats injected with amphetamine (2 mg/kg) gradually showed more head scanning and less sniffing; however, the overall frequency of composite activity declined over trials as intakes increased (Fig. 3). The decrease in activity was confirmed on DR 2, conducted after the tolerance phase, when there was a significant reduction in composite activity at all doses, as revealed by a significant DR × Dose interaction, $F(8,248) = 14.59$, $P < .0001$, and post hoc comparisons (Fig. 1, middle left). On DR 3, conducted after the retention phase, composite activity in this group increased significantly, relative to DR 2. However, the level of activity was still well below that on DR 1, except at the 4-mg/kg dose. At this dose, activity reached 85% (vs. 99% on DR 1) and was comprised primarily of stereotyped head scanning movements (78% of all responses).

Control rats, which were injected with saline during the tolerance phase, showed no stereotyped responses during this period. On DR 2, when milk was available, they displayed a significant decrease in composite activity at the two lower doses (0.5 and 1 mg/kg) compared to DR 1, $F(8,96) = 3.88$, $P < .005$ (Fig. 1, middle right). At the two higher doses, however, they showed no change in activity. No further changes in composite activity were found following the retention phase (DR 3).

The effects of amphetamine on motor activity were strongly influenced by the availability of milk. First, the dose-dependent increase in activity observed on DR 1 in both groups when milk was available (Fig. 1, middle) was not evident in the absence of milk (Fig. 1, bottom). Instead, activity levels remained asymptotic across the dose range. Second, while the amphetamine group showed decreased activity on DR 2 and DR 3 in the presence of milk (Fig. 1, middle left), they showed no decrease in activity in the absence of milk (Fig. 1, bottom left). Finally, the decreased activity shown by the saline group on DR 2 and DR 3 at the lower doses was much greater when milk was available (Fig. 1, middle right) than when milk was unavailable (Fig. 1, bottom right).

3.3. Individual differences

Although analysis of the group data showed clearly that tolerance was retained at the chronic dose (2 mg/kg)

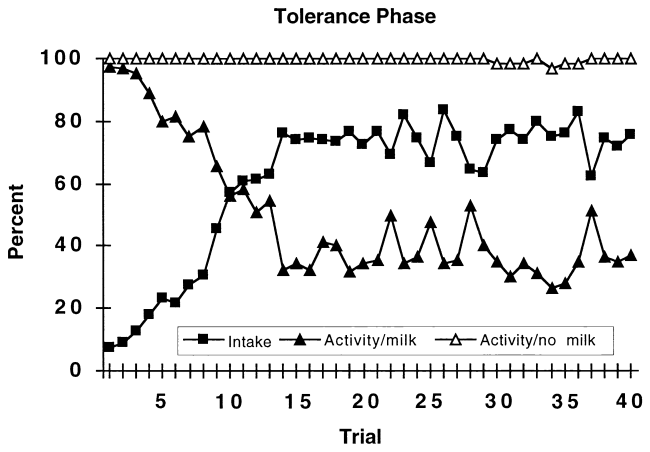

Fig. 3. Mean milk intake and composite activity of the amphetamine group during the tolerance phase. Milk intakes are expressed as a percentage of mean baseline intakes. Composite activity (locomotion + stereotyped responses) is expressed as a percentage of the frequencies of all categories of behavior. Activity data collected when milk was available are shown separately from data collected before and after milk availability. The maximum score on each trial was 160 (32 rats × 5 rating periods) when milk was available and 64 (32 rats × 2 rating periods) when milk was not available.

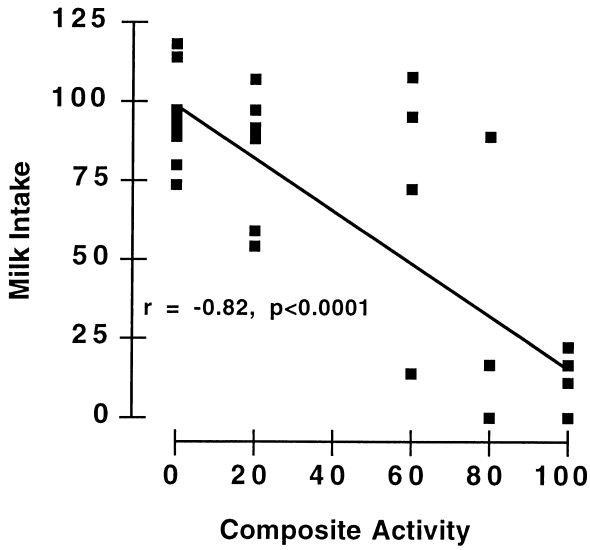

Fig. 4. Relation between the frequency of composite activity and milk intake on DR 3 at the 2-mg/kg dose for rats in the amphetamine group. Milk intake is expressed as a percentage of intake at the saline dose. Composite activity (locomotion + stereotyped responses) is expressed as a percentage of the frequencies of all categories of behavior. The maximum score was 160 (32 rats × 5 rating periods).

throughout the 31-week retention period, there were individual exceptions. Three rats showed a loss of tolerance during the final two or three retention trials. One of these rats drank 0 cc on the last three trials while two others drank a mean of 5.5 and 1.0 cc on the last two trials. The loss of tolerance in these rats was confirmed on DR 3, during which their intakes were 5, 0, and 0 cc at the 2-mg/kg dose. Seven other rats, while retaining tolerance during the retention trials, showed a loss of tolerance at the 2-mg/kg dose on DR 3. Three of these rats drank 0 cc while the remaining four drank 6, 6, 4, and 3 cc, respectively.

Rats that lost tolerance showed a corresponding increase in motor activity on DR 3. This was particularly evident at the 2-mg/kg dose, which was previously given chronically. As shown in Fig. 4, there was a significant negative correlation between the amount of milk consumed at this dose and the level of composite activity ($r = -.82$, $P < .0001$). Thus, the inverse relation between feeding and activity evident during the tolerance phase (cf. Fig. 3) was also evident in the individual differences between rats following the retention phase.

4. Discussion

If tolerance to amphetamine-induced hypophagia involves instrumental learning, then the learned response should not decay simply as a function of time. Indeed, previous findings (Hughes et al., 1999; Poulos et al., 1981) have confirmed that when both drug injections and feeding tests are suspended, tolerance is retained for up to 4 weeks. The present study was designed to explore the retention of tolerance over longer intervals. The results clearly demonstrate that, for the chronic dose (2 mg/kg), tolerance to amphetamine hypophagia is retained for 31 weeks in most rats when both drug injections and feeding tests are suspended. In contrast, when feeding tests are conducted during the retention period, tolerance is lost in as little as 3–4 weeks, even if drug injections are given after each of the feeding tests (Wolgin and Hughes, 1997).

Taken together, these two sets of results are consistent with the instrumental learning model of tolerance (Wolgin, 1989). According to this model, tolerance to amphetamine hypophagia involves learning to suppress stereotyped behaviors, which are incompatible with the appetitive phase of feeding. If rats are later given milk while undrugged, they learn that they no longer have to utilize whatever behavioral adaptations they had acquired in order to feed. Hence, when later offered food in the drugged state, they demonstrate a loss of tolerance, although they can subsequently reacquire the learned response more quickly when drug injections are reinstated (Wolgin and Hughes, 1997). If, however, both drug and feeding tests are suspended, as in the present case, no new learning takes place and tolerance is retained. It is also possible that during the tolerance phase, the learned response comes under the discriminative control of drug-related interoceptive stimuli (Stafford et al., 1994). Such stimulus control would be expected to be retained over long retention intervals in which neither drug injections nor feeding tests are given.

Unlike previous studies, in which tolerance was assessed only at the end of a fixed period, the present experiment probed the retention of tolerance at successively longer intervals. This approach is more efficient than a between groups design and allowed us to track the decay of tolerance over time. However, one potential problem with this design is that the probes themselves may influence the retention of tolerance. While this possibility cannot be totally ruled out, the fact that 10 of the rats lost tolerance suggests that the probes did not have a significant impact on the retention of tolerance.

The loss of tolerance in some of the rats despite the absence of contravening experience during the retention period suggests there may be an upper limit to how long the learned response can be retained. In a previous study (Hughes et al., 1999), two of six rats lost tolerance only 4 weeks after the suspension of drug injections and feeding tests. In the present study, of 32 rats that were tolerant at the 2-mg/kg dose, one rat lost tolerance at 10 weeks, two others lost tolerance at 18 weeks, and seven others lost tolerance on DR 3, which was conducted between 31 and 34 weeks after the tolerance phase. Furthermore, of 18 rats that were originally tolerant to the 4-mg/kg dose on DR 2, 14 showed a loss of tolerance to that dose on DR 3. The tendency for some rats to lose tolerance as the retention period progressed suggests that there may be time-dependent factors that affect the retention of tolerance. Extending the retention interval beyond 31 weeks would be necessary to establish the extent and the boundaries of this phenomenon.

There are a number of mechanisms that might account for a time-dependent decay of tolerance. One possibility is that following prolonged absence of the drug pharmacodynamic changes occur in the neural system mediating tolerance. However, the fact that tolerance is lost relatively rapidly if rats are permitted to ingest milk in the undrugged state, whether or not they continue to receive drug injections after each feeding test (Wolgin and Hughes, 1997), suggests that biochemical mechanisms that are dependent on the presence or absence of the drug per se are not importantly involved.

A related possibility is that time-dependent biochemical changes associated with the sensitization of stereotyped movements contribute to the loss of tolerance. It is well established that intermittent injections of amphetamine promote the sensitization of stereotypy (Post, 1980; Robinson and Becker, 1986; Stewart and Badiani, 1993). If the widely spaced probe doses resulted in the emergence of sensitized behavioral responses that were not previously experienced during the tolerance phase, behavioral strat-

egies for suppressing those responses would not have been acquired (cf. Hughes et al., 1998). However, inspection of the activity data revealed that, although sensitization occurred, it did not result in the emergence of new categories of behavior. These results confirm previous findings showing that rats can learn to suppress stereotyped movements even as these responses undergo sensitization (Wolgin and Hertz, 1995; Wolgin and Hughes, 1996; for a discussion of the implications of these findings, see Wolgin, 2000).

An alternative possibility, more in keeping with the important role of learning in tolerance to amphetamine, is that the ability to execute the learned response is weakened from lack of "practice." From this perspective, the gradual loss of tolerance is analogous to the deterioration that occurs with any skilled movement that is not continuously practiced. This would be more likely to occur at doses higher than the chronic dose because the rats had relatively little experience with suppressing stereotyped movements at the higher dose initially. In addition, the degree of stimulus control exerted by this dose over the learned response would be less than at the chronic dose. In contrast, the rats had considerably more practice suppressing stereotyped movements at the chronically administered dose (2 mg/kg), including the retention trials themselves. This interpretation would also explain why the vast majority of rats retained tolerance throughout the retention period.

It is important to note that the other proposed mechanisms for the loss of tolerance should be equally present in all of the rats because these mechanisms rely solely on the presence or absence of the drug. Since the majority of the rats did not lose tolerance, it could be concluded that pharmacodynamic changes in the neural system mediating tolerance and biochemical changes associated with sensitization, in general, are not sufficient to prevent the retention of a learned response that results in behavioral tolerance.

Finally, the data from this experiment provide additional support for the instrumental learning model. During the tolerance phase, the recovery of milk intake was accompanied by a corresponding decrease in the frequency of motor activity while milk was available, but not before and after the sessions when milk was not available. These results were confirmed on DR 2 and DR 3, in which the effect of amphetamine on activity was dependent on whether milk was present or absent. Furthermore, following the retention interval, rats that lost tolerance showed a corresponding increase in activity associated with their failure to drink, whereas rats that retained tolerance continued to suppress stereotyped movements when milk was available. These findings demonstrate that tolerance did not develop to the motor effects of the drug; indeed, as noted above, there was evidence that sensitization developed. Instead, the data suggest that the rats learned to suppress stereotyped movements based on the contingencies of reinforcement operating during the period of drug administration. As would be expected from the model, most rats retained this learned response for the entire 31-week retention interval.

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