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# Loss of Tolerance to Amphetamine-Induced Hypophagia in Rats: Homeostatic Readjustment vs. Instrumental Learning

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HUGHES, K. M., L. POPI AND D. L. WOLGIN. *Loss of tolerance to amphetamine-induced hypophagia in rats: Homeostatic readjustment vs. instrumental learning.* PHARMACOL BIOCHEM BEHAV 64(1) 177–182, 1999.—According to the homeostatic model, the loss of tolerance to amphetamine-induced hypophagia requires a period of unrestricted feeding in the drug-free state, which transforms the compensatory response mediating tolerance ("hyperhunger") into a functional disturbance to homeostasis. In the absence of such a disturbance, tolerance should be retained. To test this prediction, rats tolerant to amphetamine's hypophagic effect were given a 4-week tolerance retention period during which milk intakes were restricted and deprivation levels held relatively constant. During this period the rats were assigned to one of the following drug treatment conditions: 1) saline injections both before and after daily milk tests (saline group); 2) saline injections before, and amphetamine injections after, daily milk tests (after group); 3) no injections and no milk tests (no-treatment group); or 4) amphetamine injections before, and saline injections after, milk tests (before group). Despite the restricted feeding regimen, both the saline and after groups lost tolerance. These results do not support the homeostatic model, but are consistent with the instrumental learning model, which views drinking milk in the undrugged state as analogous to receiving noncontingent reinforcement. © 1999 Elsevier Science Inc.

Amphetamine Anorexia Feeding Homeostatic theory Hypophagia Instrumental learning Retention of tolerance Tolerance

IT is well established that the acquisition of tolerance to many psychoactive drugs is not merely a function of repeated pharmacological exposure, but is subject to the influence of behavioral variables as well [for reviews, see (5,12,15,16,18,24)]. It is now becoming increasingly evident that the loss of tolerance following the cessation of drug treatment is equally subject to behavioral influences. For example, tolerance to the anticonvulsant effects of ethanol (8), carbamazepine (17), and diazepam (6) dissipates if subjects experience convulsions in the absence of the drug, even if they continue to get the drug at other times. Similarly, tolerance to the hypophagic effect of amphetamine (14) and to the hypodipsic effect of scopolamine (13) is diminished if rats are given feeding or drinking tests while drug injections are suspended, but not if such tests are also discontinued during this period. Thus, engaging in the criterion response in the absence of the drug in some way promotes the loss of tolerance.

In recent studies, we confirmed that tolerant rats given feeding tests in the undrugged state lose tolerance to amphetamine-induced hypophagia (20,21). In addition, we showed that the loss of tolerance was not due to the absence of the drug per se, but rather to the absence of the drug during feeding. Tolerant rats given injections of amphetamine after their daily feeding tests also lost tolerance, despite continued drug exposure. The loss of tolerance was equivalent to that of a group given injections of saline. When again given amphetamine prior to feeding, both groups developed tolerance faster than a control group given chronic amphetamine for the first time (21). These findings are consistent with an instrumental learning model, which proposes that tolerance to amphetamine hypophagia involves learning to suppress locomotion and stereotyped responses that interfere with the appetitive phase of feeding [for supporting evidence, see (22,23)]. From this perspective, rats given feeding tests in the

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undrugged state learn that they no longer have to suppress such movements in order to feed. This learning would not occur if both feeding tests and drug injections were discontinued. Furthermore, the faster rate of tolerance development during the reacquisition phase (11 trials vs. 55 trials) presumably reflects the benefit of prior learning because no overt extinction procedures were enacted.

An alternative explanation for the loss of tolerance to amphetamine has been proposed by Poulos and Cappell (12). According to their homeostatic model, deprived rats given amphetamine in the presence of milk initially experience anorexia, which causes a decrease in caloric intake. This disturbance in nutritional homeostasis engenders a conditioned compensatory increase in appetite ("hyperhunger"), resulting in tolerance. If rats are then given ad lib food and allowed to drink milk in the absence of the drug, the compensatory response ("hyperhunger") itself serves as a functional disturbance to homeostasis. This induces a counteradaptation ("hypohunger"), which results in a loss of tolerance when the drug is later given prior to feeding.

If the loss of tolerance to amphetamine-induced hypophagia results from overeating due to an adaptive compensatory response while in a nutritionally homeostatic state, then tolerance should not be lost if overeating occurs in a nonhomeostatic state. That is, if rats are still food deprived when drug treatment is either discontinued or given after feeding, the conditioned increase in appetite should not constitute a functional disturbance to nutritional homeostasis and tolerance should not be lost. In contrast to the homeostatic model, the instrumental learning model predicts that maintaining a state of food deprivation during feeding tests in the undrugged state should not prevent the loss of tolerance. As long as the rats drink milk in the undrugged state, they should learn that they no longer have to suppress stereotyped movements.

The primary purpose of the following experiment was to determine whether tolerance is lost if deprivation conditions are held relatively constant across a retention period. In the previous experiment (21), rats were given unlimited access to milk when tested during the retention phase. The increased intakes during the initial trials of this period relative to those during the preceding tolerance phase could be viewed as creating a state of nutritional repletion required by the homeostatic model for the loss of tolerance. Accordingly, in the present experiment intakes during the retention phase were restricted to the mean amount of milk ingested during the preceding tolerance phase. In addition, a group was included that was given no treatment during the retention phase [cf. (14)].

## METHOD

### *Subjects*

The subjects were 34 experimentally naive male albino Sprague–Dawley rats (Charles River Laboratories, Wilmington, DE) weighing 397–544 g at the beginning of the experiment. Housing conditions were similar to those described by Wolgin (19). 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.

### *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 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 a 7-week baseline period during which intakes stabilized, an initial dose–response 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 IP 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 six-point 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 dose–response testing, raters were blind to the drug condition.

Following DR 1, the rats were given saline injections and milk tests for 5 days to allow milk intakes to stabilize. The rats were then divided into two groups. During the ensuing tolerance phase, one group ($n$ = 28) received injections of amphetamine (2 mg/kg) for 110 trials, while a yoked control group ($n$ = 9) received saline injections. The long duration of this phase was intended to ensure that tolerance was well established prior to the retention phase. 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 dose–response 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, three rats in the amphetamine group that were not tolerant were dropped from the experiment. The remaining rats were assigned to one of four groups, matched on the basis of milk intakes on DR 2. During the ensuing 4-week retention period, the saline group ($n$ = 6) received injections of saline both before and after the milk tests; the after group ($n$ = 6) received saline injections before the milk tests and amphetamine injections afterward; and the no-treatment group ($n$ = 6) received neither injections nor milk tests. The before group ($n$ = 7) continued to receive injections of amphetamine (2 mg/kg) prior to milk tests (as they had during the tolerance phase) and saline injections after the tests, while the nontolerant control group ($n$ = 9) received saline injections before and after the tests. During this phase, each rat in the saline, after, before, and control groups was given the mean amount of milk it consumed during the last 2 weeks of the tolerance phase. Because rats in the no-treatment group were not given milk tests during the retention phase, they continued to receive an additional rat chow pellet each day to maintain their weight.

TABLE 1
SUMMARY OF EXPERIMENTAL DESIGN

| | Amphetamine group | | | | Control group |
|---|---|---|---|---|---|
| | DR 1 | | | | DR 1 |
| Tolerance phase: | Chronic Amphetamine (2 mg/kg) | | | | Chronic Saline |
| | DR 2 | | | | DR 2 |
| Retention phase: | Before A-S | After S-A | Saline S-S | No Trt. | Control S-S |
| | DR 3 | | | --- | DR 3 |
| Reacquisition phase: | Chronic Amphetamine (2 mg/kg) | | | | Chronic Amphetamine (2 mg/kg) |
| | DR 4 | | | | DR 4 |

A-S, S-A, S-S: order of injections during the retention phase. The first letter indicates the injection given before the milk test, the second letter indicates the injection given after the test. A–amphetamine; S–saline. The no-treatment group was not injected during the retention phase.

After the retention interval, a third dose–response determination (DR 3) was conducted to assess any change in the level of tolerance. Rats in all of the groups were given injections of saline and test doses of amphetamine prior to milk tests, with at least 3 days between each dose. On the intervening days, all groups received their usual retention phase treatment. Thus, rats in the no-treatment group were not given milk tests on these days, but received an extra pellet of food. Following DR 3, the tolerance reacquisition phase began. Rats in all groups were given injections of amphetamine (2 mg/kg) prior to milk tests for 22 trials. A final dose–response determination (DR 4) was then conducted in which saline and test doses of amphetamine were substituted for the usual dose (2 mg/kg).

A summary of the experimental protocol is presented in Table 1.

### *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.

### *Data Analysis*

The DR data were analyzed by two-factor (dose–response determination × dose) analyses of variance (ANOVA), with adjustments to the degrees of freedom when violations of the circularity assumption were detected (7). When significant interactions were obtained, tests of simple main effects were performed followed by individual comparisons using the test of Dunn and Sidak (7). Intakes under amphetamine were converted to percentages of intakes under the saline dose measured during that DR determination prior to statistical analysis. Changes in body weight during the retention phase were analyzed with Student's *t*-test.

To analyze the activity data, 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 was expressed as a percentage of the total number of observations from all categories.

## RESULTS

### *Body Weight*

There were no significant changes in body weight during the tolerance phase except in the control group, which gained 23 g, $t(8) = 4.17$, $p = 0.003$. Because the milk intakes of the control group were yoked to those of the other groups, the absence of weight gain in the drugged groups can be attributed to the increased energy expenditure induced by amphetamine. There were no significant changes in body weight during the retention phase for the before, after, or no-treatment groups. Both the saline and control groups gained weight [saline group: 15 g, $t(5) = 4.49$, $p = 0.006$; control group: 9 g, $t(8) = 4.32$, $p = 0.0025$].

### *Milk Intake*

Mean milk intakes during the final week of the baseline phase and on the first and last trial of the tolerance phase are shown in Table 2; dose–response data is presented in Fig. 1. On DR 1, conducted prior to the tolerance phase, amphetamine produced dose-dependent decreases in milk intake in each group, with almost complete suppression of intake at the 2 mg/kg dose. Similar suppression was found with this dose on the first trial of the tolerance phase, but by the last trial mean intakes recovered to 60–78% of baseline levels (Table 2). Tolerance was confirmed in the before, after, saline, and no-treatment groups by increased intakes on DR 2, conducted after the tolerance phase (Fig. 1).

Statistical analysis of the dose–response data revealed significant dose–response × dose interactions [before: $F(9, 54) = 7.13$, $p < 0.0001$; after: $F(7, 36) = 4.08$, $p < 0.002$; saline: $F(9, 45) = 3.08$, $p < 0.006$; no treatment: $F(6, 31) = 3.28$, $p < 0.02$]. For the before and after groups, significant increases in milk intake were found at 1 and 2 mg/kg, while for the saline and

TABLE 2
MEAN MILK INTAKES (cc) BEFORE AND DURING THE TOLERANCE PHASE

| Group | Baseline | Tolerance Day 1 | Tolerance Day 110 | Tolerance Last 2 Weeks |
|---|---|---|---|---|
| Before | 33 | 0 | 24 | 20 |
| After | 35 | 0 | 21 | 22 |
| Saline | 30 | 0 | 21 | 21 |
| No Treatment | 31 | 1 | 24 | 18 |
| Control | 32 | 0 | 20 | 20 |

Baseline = mean intakes during the last week of the baseline phase. During the tolerance phase, the control group was given the mean amount of milk ingested by the before, after, saline, and no-treatment groups on the previous day.

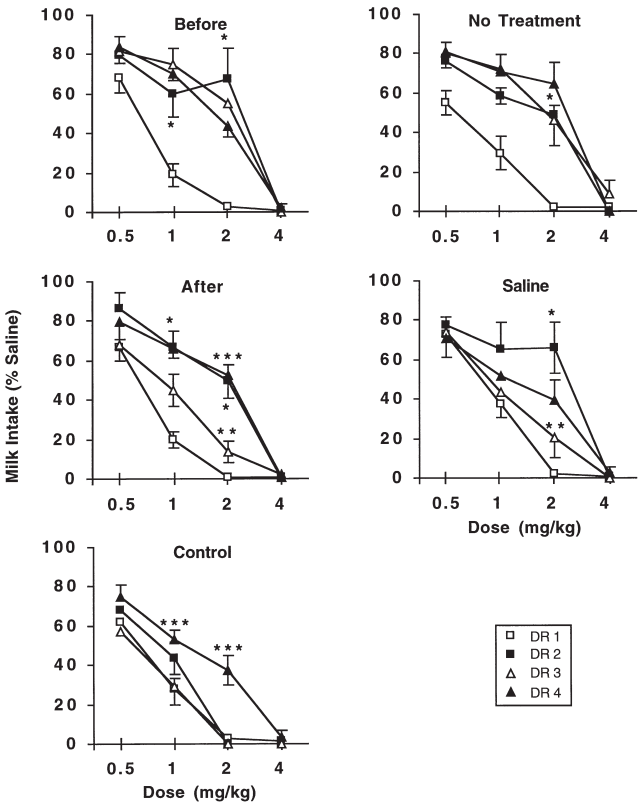


FIG. 1. Effect of various doses of amphetamine on mean milk intakes in the before, after, saline, no-treatment, and control groups prior to the tolerance phase (DR 1), after the tolerance phase (DR 2), after the retention phase (DR 3), and after the reacquisition phase (DR 4). The data are expressed as a percentage of intakes under the saline doses for each DR determination. Mean intakes under saline for DR 1, 2, 3, and 4, respectively, for each group were as follows: before: 36, 38, 40, 39 cc; after: 43, 43, 45, 46 cc; saline: 35, 37, 43, 40 cc; no treatment: 37, 39, 37, 39 cc; control: 34, 37, 40, 41. Vertical lines indicate 1 SE. *>DR 1, $p < 0.05$; **<DR 2, $p < 0.05$; ***> DR 3, $p < 0.05$.

no-treatment groups, intakes were significantly higher only at 2 mg/kg. No significant changes in milk intake were found for the control group, which received injections of saline during the tolerance phase.

During the retention phase, each rat in the before, after, saline, and control groups was given the mean amount of milk it consumed during the final 2 weeks of the tolerance phase (for group means, see Table 2). With rare exceptions, all of the daily milk ration was ingested each day. Following this phase, both the after and saline groups lost tolerance, as evidenced by decreased milk intakes on DR 3 compared to DR 2 (Fig. 1). In both cases, the effect was statistically significant only at 2 mg/kg. Neither the before group, which received amphetamine injections during the retention phase, the nontolerant control group, which received saline injections during the retention phase, nor the no-treatment group, which was not tested during the retention phase, displayed significant changes in milk intake on DR 3. It should be noted, however, that despite the absence of a significant change in the mean intake of the no-treatment group, two rats in this group did show decreases of 17 and 11 cc, respectively.

Following the reacquisition phase, in which all groups were given amphetamine injections prior to milk tests, the after and control groups showed increased milk intakes on DR 4 relative to DR 3 (Fig. 1). For the after group, intakes were significantly higher at 2 mg/kg, whereas for the control group, intakes were significantly higher at both 1 and 2 mg/kg. Although milk intakes were also higher at 2 mg/kg in the saline group, the increased intakes relative to DR 3 did not reach statistical significance due to the complete lack of tolerance in one rat. There were no significant changes in milk intake on DR 4 for the before and no-treatment groups, which had not previously lost tolerance.

*Motor Activity*

The frequency of composite activity (locomotion + stereotypy) during each of the dose–response determinations is shown in Fig. 2. The data are expressed as a percentage of the frequencies of all categories of behavior. In general, changes in activity were inversely related to changes in milk intake. On DR 2, each of the tolerant groups (before, after, saline, and no treatment) showed less motor activity than on DR 1, although the effect was statistically significant only at the 2 mg/kg dose. The before and no-treatment groups, which retained tolerance for the remainder of the experiment, showed no further changes in activity on DR 3 or DR 4. In contrast, the after group, which lost tolerance on DR 3 and then regained it on DR 4, showed a corresponding increase and decrease in activity. Although the saline group also lost tolerance on DR 3, the increase in activity was not statistically significant. Finally, the control group showed no decrease in activity until DR 4, when it developed tolerance for the first time. Changes in activity were reflected in significant dose–response × dose interactions for each group [before: $F(6, 37) = 4.93$, $p = 0.0008$; after: $F(6, 31) = 17.97$, $p < 0.0001$; saline: $F(11, 54) = 5.30$, $p < 0.0001$; no treatment: $F(12, 58) = 2.96$, $p = 0.003$; control: $F(7, 56) = 5.44$, $p = 0.0001$].

## DISCUSSION

According to the homeostatic model (12), nutritional repletion is a prerequisite to losing tolerance because it transforms what was initially a compensatory response (hyperhunger) into a homeostatic disturbance. It follows that if the deprivation conditions that fostered the development of tolerance are maintained, tolerance should not be lost. In the present experiment, milk intakes during the retention phase were held constant at the mean amount ingested during the last 2 weeks of the tolerance phase. Because mean intakes at the end of the tolerance phase were only 60–78% of baseline levels, these intakes should not have been sufficient to cause nutritional repletion. Nevertheless, both the after and saline groups lost tolerance when they were retested with amphetamine following the retention phase. These results do not support the homeostatic model.

We believe that the underlying assumption of the model, that amphetamine suppresses food intake primarily by decreasing appetite (anorexia), is incorrect. Comparisons between cannula- and bottle-fed rats suggest that, at a dose of 2 mg/kg, drug-induced anorexia is quite weak, and that behavioral interference from locomotion and stereotyped movements plays a major role in the suppression of intake [(23); see also (1,3)]. Moreover, there is little evidence that an imbalance in nutritional homeostasis, as reflected in decreased food intake or body weight loss, is systematically related to the degree of tolerance. For example, Demellweek and

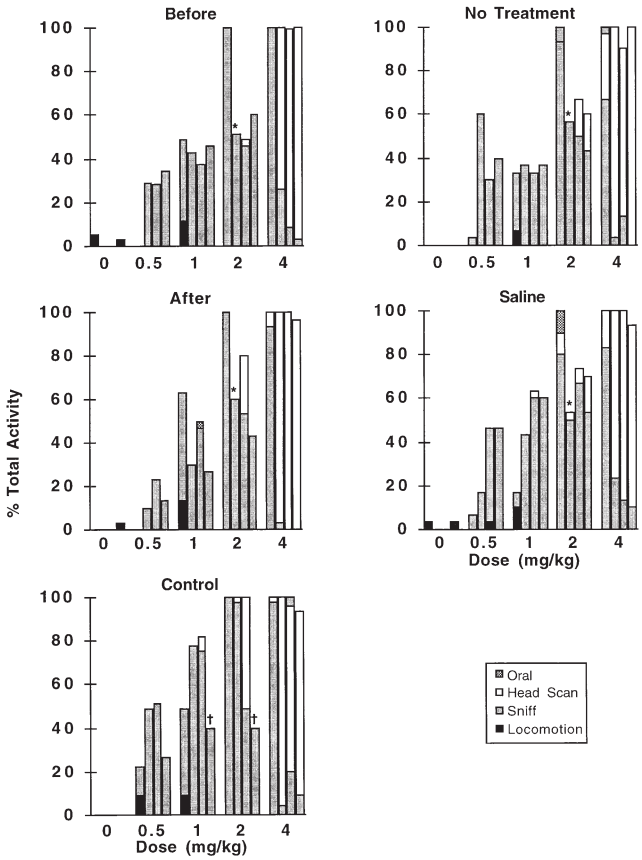


FIG. 2. Effect of saline and various doses of amphetamine on composite motor activity (locomotion + stereotyped sniffing + stereotyped head scanning + oral stereotypy). The data were collected while milk was available. Each histogram indicates the relative amounts of each movement category, expressed as a percentage of the total number of responses from all of the behavioral categories. At each dose, the first histogram represents data collected before the tolerance phase (DR 1), the second, data collected after the tolerance phase (DR 2), the third, data collected after the retention phase (DR 3), and the fourth, data collected after the reacquisition phase (DR 4). The maximum score was 35 for the before group (seven rats × five rating periods), 30 for the after, saline, and no-treatment groups (six rats × five rating periods), and 45 for the control group (nine rats × five rating periods). *<DR 1, $p < 0.05$; †<DR 3, $p < 0.05$.

Goudie (4) found that rats maintained under varying degrees of food supplementation all developed tolerance to amphetamine, even though two groups lost weight while another gained weight during chronic administration of the drug. This does not mean, however, that food deprivation has no affect on tolerance development. From the perspective of the instrumental learning model, deprivation is important in establishing the motivational conditions for learning to suppress stereotypy.

An additional finding in this experiment was the retention of tolerance in the no-treatment group, which was given neither milk tests nor drug injections during the retention phase. These results confirm and extend those of Poulos et al. (14), who first demonstrated that the loss of tolerance to amphetamine is contingent on having access to food during a drug-free period. The present study differed from that of Poulos et al. (14) in several respects. First, a lower chronic dose was administered (2 vs. 4 mg/kg), and the drug was given daily, rather than on alternate days. Second, the loss of tolerance was assessed across a range of doses, rather than on the basis of a single dose. Finally, the deprivation conditions during the retention phase were different in the two studies. Poulos et al. (14) gave their groups unlimited food during the retention period, whereas in the present case, the deprivation level was held relatively constant.

Despite these methodological differences, the results of both experiments are consistent in demonstrating that the loss of tolerance to amphetamine-induced hypophagia is contingent on ingesting milk in the undrugged state. In general, tolerance was retained when amphetamine injections were discontinued during the retention phase provided that milk tests were also suspended (no-treatment group). In contrast, tolerance was lost if rats drank milk in the undrugged state, whether or not they received injections of amphetamine at another time (after and saline groups).

These results are consistent with the instrumental learning model. According to this model, tolerance to the hypophagic effects of moderate to high doses of psychostimulants involves learning to suppress behaviors (primarily stereotyped sniffing and head scanning movements) that are incompatible with the appetitive phase of feeding (18). Simply put, rats are reinforced with milk for inhibiting stereotyped movements [for supporting evidence, see (22)]. When tolerant rats are later given milk while undrugged, they learn that they no longer have to utilize whatever behavioral strategies they have adopted to suppress these movements to feed. This is analogous to the loss of operant responding that occurs when rats are given noncontingent reward, and results in a loss of tolerance when the rats are later offered milk in the drugged state. Without the experience of drinking milk in the undrugged state, however, no new learning takes place, and tolerance is retained even if drug injections are suspended.

This model is supported by the finding that the frequency of locomotion and stereotyped movement was inversely related to milk intake, particularly at the chronic dose (2 mg/kg). That is, activity decreased when groups became tolerant (before, after, saline, and no-treatment groups on DR 2), and increased when tolerance was lost (after and saline groups on DR 3). In groups that did not lose tolerance, activity remained suppressed (before and no-treatment group on DR 2, 3, and 4), whereas in the nontolerant control group, activity remained high until DR 4, when tolerance developed.

Although taken as a whole the data support the instrumental learning model, it should be noted that two rats in the no-treatment group showed a loss of tolerance despite the absence of drinking tests during the retention period. This finding is not consistent with the instrumental learning model because no opportunity for new learning was provided. Because individual differences in tolerance development are well known [cf. (5,18)], it is perhaps not surprising that such differences also exist with respect to the retention of tolerance. It is also possible, however, that even in the absence of drinking experience, tolerance will eventually be lost as a function of the passage of time ("forgetting"). This possibility has not been systematically investigated and, therefore, cannot be excluded at the present time.

The preceding point notwithstanding, the data presented above are consistent with a growing body of evidence showing that the loss of tolerance to a variety of drugs is contingent on engaging in the criterion response while in the undrugged state (6,8,13,14,17,20,21). Conversely, the acquisition of toler-

ance to these drugs is contingent on engaging in the criterion response while in the drugged state (2,9,10,14). It is noteworthy that the criterion measures in these studies range from seizures (6,8,17) to feeding and drinking (13,14,20,21). This suggests that neurobehavioral adaptations to a drug's effect, and the functional disturbances that trigger them, can occur at any of various levels of neural organization, from the cellular to the behavioral (11,16). In the present context, the loss of milk reward constitutes the functional disturbance, and the learned suppression of stereotypy, the neurobehavioral adaptation.

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