Role of Instrumental Learning in Tolerance to Cathinone Hypophagia

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The effects of dl-cathinone on milk intake and motor activity were investigated in bottle- and cannula-fed rats. Acute injections of cathinone produced dose-dependent increases in activity in both groups but only produced decreased intake in bottle-fed rats. With chronic injections, tolerance to the suppression of intake developed in the bottle-fed group, accompanied by decreased activity. After the tolerance phase, switching from bottle to cannula feeding produced further increases in intake, whereas switching from cannula to bottle feeding produced decreased intakes. These results suggest that (a) cathinone suppresses intake by inducing locomotion and stereotypy, which interfere with the appetitive phase of feeding, and (b) tolerance to drug-induced hypophagia involves learning to suppress such movements, as proposed by the instrumental learning model.

Keywords: contingent tolerance, amphetamine, appetitive behavior, sensitization

Tolerance to the hypophagic effects of psychostimulants—including amphetamine, cocaine, methylphenidate and cathinone—is contingent on having access to food while in the drugged state; tolerance does not develop if the drug is given in the absence of food (Bowen, Fowler, & Kallman, 1993; Carlton & Wolgin, 1971; Demellweek & Goudie, 1983; Emmett-Oglesby & Taylor, 1981; Felton & Schuster, 1982; Woolverton, Kandel, & Schuster, 1978). Two models have been proposed to explain this contingency. The Pavlovian homeostatic model (Poulos & Cappell, 1991; Poulos, Wilkinson, & Cappell, 1981) proposes that rats given amphetamine in the presence of food initially experience a loss of appetite (anorexia). The resulting decrease in food intake triggers a conditionable compensatory increase in appetite (hyper-hunger), resulting in an increase in food intake (tolerance). In the absence of food, no functional disturbance in nutritional homeostasis occurs, and therefore, no compensatory increase in hunger is recruited. In contrast, the instrumental learning model (Wolgin, 1989, 2000) proposes that food intake is initially disrupted because drug-induced locomotion and/or stereotyped responses interfere with the appetitive phase of feeding (i.e., locating, approaching, and orienting to food). Because the motivation to eat remains largely intact, rats gradually learn to inhibit these movements during chronic drug treatment, resulting in an increase in food intake (tolerance). In the absence of food, there is no incentive to inhibit stereotypy, and therefore, no learning occurs.

Thus, there are two critical differences between the two models: One is the mechanism by which food intake is suppressed. According to the homeostatic model, the suppression of intake is due to a loss of appetite (“food has lost its appeal”; Poulos & Cappell, 1991, p. 392), which results in a failure to seek food (appetitive behavior) or to eat it (consummatory behavior). According to the instrumental learning model, amphetamine has little effect on the motivation to consume food; rather, the drug induces motor effects that compete with the rat’s ability to acquire food. The second difference is the mechanism of tolerance. According to the homeostatic model, tolerance is mediated by a compensatory increase in the motivation to eat, which results in increased food intake. According to the instrumental learning model, tolerance is mediated by learning to suppress stereotyped movements, a process that is reinforced by the ingestion of food. Note that this mechanism assumes that the motivation to eat is not significantly diminished by the drug.

One strategy for evaluating the two models is to compare the effects of a drug on the intake of milk delivered either intraorally, through a chronically implanted cannula, or in a standard drinking tube. According to the homeostatic model, it should make little difference how milk is provided because the drug is assumed to reduce the appetite for food. However, if the drug suppresses food intake indirectly, by inducing movements that interfere with the appetitive phase of feeding, then delivering the milk intraorally should bypass the problem. Studies involving both amphetamine (Salisbury & Wolgin, 1985; Wolgin, Thompson, & Oslan, 1987) and cocaine (Wolgin & Hertz, 1995) have supported the instrumental learning model. Rats fed intraorally showed near-normal intakes at doses of the drug that produced substantial hypophagia in bottle-fed rats. Furthermore, rats injected with amphetamine learned to suppress stereotyped movements when reinforced with intraoral infusions of milk for maintaining a stationary head position, and they learned to do so at a rate that was similar to the rate at which bottle-fed rats developed tolerance (Wolgin & Wade, 1995). In contrast, rats injected with amphetamine and given infusions of milk noncontingently did not show a decrease in

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stereotyped head movements over time (Salisbury & Wolgin, 1985; Wolgin et al., 1987).

Analyses of the microstructure of feeding also have supported the view that amphetamine primarily disrupts the appetitive phase of feeding (Blundell & Latham, 1980; Rososky & Geary, 1989; Wolgin & Jakubow, 2003). For example, Wolgin and Jakubow (2003) demonstrated that amphetamine increased the number of pauses within the session, which resulted in more lick bursts and fewer licks per burst (Wolgin & Jakubow, 2003). Cumulative records from tolerant rats have revealed that, unlike undrugged controls, which complete all of their licking responses within the first 10–15 min of the session, amphetamine-tolerant rats distribute their licking throughout the session, interspersed with pauses during which stereotyped movements occur (Wolgin & Jakubow, 2004). In contrast, the drug has no effect on the interlick interval within a burst or on the force per lick, indicating that the motor act of licking (i.e., the consummatory phase of feeding) is normal.

In the current study, we attempted to extend the generality of the instrumental learning model to another stimulant drug, cathinone. Cathinone, an alkaloid derived from the leaves of the khat plant, shares many properties with amphetamine (for a general review, see Kalix, 1992). In particular, it increases locomotion (Kalix, 1980) and, at higher doses, induces stereotyped movements (Zelger, Schorno, & Carlini, 1980); furthermore, it also decreases food intake (Foltin & Schuster, 1982). As with amphetamine, chronic administration of cathinone produces tolerance to its hypophagic effect only when rats have access to food during the period of drug intoxication (Foltin & Schuster, 1982). Indeed, Foltin and Schuster (1982) reported that tolerance to cathinone (4 mg/kg), as assessed by the magnitude of the shift in the dose–response (DR) function, was greater than that observed with any other psychostimulant (10 fold vs. 2–3 fold). This quantitative difference in the magnitude of tolerance may reflect underlying differences in the mechanism of tolerance.

To investigate the mechanism of tolerance to cathinone-induced hypophagia, we used two strategies. First, we compared the effect of both acute and chronic injections of the drug in both cannula- and bottle-fed rats. If cathinone produced hypophagia primarily by interfering with appetite behavior (via drug-induced stereotypy), then the drug should have had a greater effect in bottle-fed rats than in cannula-fed rats. Furthermore, tolerance in bottle-fed rats should have been accompanied by a suppression of stereotyped movements when milk was available but not when milk was not available. In contrast, stereotyped movements should not have been suppressed in cannula-fed rats because such movements did not interfere with feeding in that condition. Second, after tolerance developed to cathinone’s hypophagic effect in the bottle-fed rats, we tested each group with the alternate method of milk presentation. If tolerance was mediated by the learned suppression of stereotyped movements, then cannula-fed rats should have shown hypophagia when switched to the bottle condition despite their history of drug injections and milk drinking. This was expected because these rats would not have learned to suppress stereotyped movements when they were previously fed introrally. In contrast, bottle-fed rats should have shown normal intakes when switched to the cannula condition because no additional learning was required to ingest milk under these conditions.

Subjects

The subjects were 40 experimentally naive male albino Sprague–Dawley rats (Charles River Laboratories, Wilmington, Delaware) that weighed 296–439 g at the beginning of the experiment. The rats were housed and tested in individual stainless steel cages (17.5 cm in width 25.0 cm in length 17.5 cm in height) with wire mesh fronts and bottoms. Plexiglas panels that measured 12.5 cm high were attached to the four sides of the cages to extend the height to 30.0 cm. The rats were maintained under a 12-hr alternating light–dark cycle (lights on 0600) and were fed three Purina lab chow (Ralston Purina Company, St. Louis, Missouri) pellets (about 15 g) and unlimited water daily. On days in which milk tests were not conducted, the rats were given an extra food pellet (about 5 g).

Surgery

Intraoral cannulas that were constructed from polyethylene tubing were implanted under sodium pentobarbital anesthesia (50 mg/kg) by the method of Phillips and Norgren (1970). The cannulas were inserted just lateral and rostral to the first molar and were guided subcutaneously along the cheek to emerge at an incision made along the midline of the skull. They were positioned dorsorosally in the mouth to prevent forced swallowing of milk. The externalized end of the cannula was placed over one end of an L-shaped piece of 20-gauge stainless steel tubing, which was mounted in a teflon anchoring sleeve (Alice King Chatham Medical Arts, Los Angeles, California). After inserting four jeweler’s screws into the skull, the entire assembly was cemented into place with dental acrylic. The rats were given at least 7 days for postoperative recovery before testing resumed. Cannulas were flushed twice daily with water—once before and once again after the milk tests.

Procedure

Milk tests were conducted 6 days per week. Prior to cannula implantation, the rats were given 26 trials in which Eagle Brand sweetened condensed milk (Borden, Columbus, Ohio) diluted with water (1:3) was presented in calibrated drinking tubes attached to the front of the cages for 30 min to establish stable levels of intake. Water bottles were removed from the cages prior to each test. At the end of the test session, the drinking tubes were removed, the water bottles were returned, and, 1 hr later, the rats were fed. Following cannula implantation, the rats were given 11 additional trials in the bottle condition. During these trials, they were connected to spring assemblies, which were used during cannula feeding tests to provide mechanical linkage between the implanted anchoring sleeves and fluid swivels held in counterbalanced arms mounted above the cages. The rats were then given daily cannula feeding tests for 14 trials. Milk was gravity fed from 50-cc syringes to the cannulas through polyethylene tubing at a rate of about 1.5 cc per minute. Throughout the 30-min session, milk flowed continuously through the tubing, and the rat could either move it to the back of its mouth and swallow it or let it spill out. Spillage was recovered from trays placed beneath the cage, measured, and subtracted from the volume missing from the syringe at the end of the session.

Following the baseline tests, the rats were randomly assigned to either the bottle or cannula feeding condition, and an initial DR determination (DR 1) was conducted. We administered test doses of dl-cathinone hydrochloride (2, 4, 8, 16, and 32 mg/kg) and saline in counterbalanced order using a Latin square design, with 3–5 days between doses. On the intervening days, saline injections were given prior to the milk tests, and intakes returned to baseline levels. All injections were administered 20 min before the milk tests.

In addition to measuring milk intake at the end of each test session, the effect of cathinone on motor activity was rated 7 times during the session:
5 min before milk access; 5, 10, 15, 20, and 25 min after milk was presented; and 5 min after the milk bottles were removed. We assessed motor activity using a 6-point nominal 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 mouthing, licking, biting, or gnawing (termed oral stereotyphy hereafter). 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. During DR testing, the rater was blind to the drug condition.

Following DR 1, the rats in each feeding condition were randomly assigned to one of two subgroups. During the ensuing tolerance phase, the cathinone subgroups (bottle/cathinone and cannula/cathinone; ns 10) received daily injections of cathinone and access to milk for 30 trials, whereas the saline subgroups (bottle/saline and cannula/saline; ns 10) received daily injections of saline during these trials. A dose of 8 mg/kg of cathinone was selected as the chronic dose to extend the generality of a previous study (Foltin & Schuster, 1982), which found strong tolerance in bottle-fed rats given a dose of 4 mg/kg. Two rats in the cannula/cathinone subgroup were dropped from the experiment when their cannulas became clogged. The data from these rats were excluded from the statistical analyses. Following the tolerance phase, a second DR determination (DR 2) was conducted, in which test doses of cathinone (2, 4, 8, 16, and 32 mg/kg) and saline were given, with 3–7 days between doses. During the intervening days, the rats were given their usual chronic phase treatment. Following DR 2, each subgroup was given five additional trials with its respective feeding and drug conditions to allow intakes to normalize. They were then retested with cathinone (2, 4, 8, 16, and 32 mg/kg) and saline, but given milk via the alternate feeding method during the third DR determination (DR 3) transfer tests; that is, the cannula subgroups were given milk in bottles, and the bottle subgroups were given milk via cannulas. Prior to the completion of this phase of the experiment, two rats in the bottle/cathinone subgroup developed blockage of their cannulas and were dropped from the experiment. The data from these rats were excluded from statistical analysis of this phase of the experiment but were included in the other analyses.

**Drugs**

We dissolved dl-cathinone hydrochloride (National Institute on Drug Abuse, Research Triangle Park, North Carolina) in physiological saline and injected it in a volume of 1 ml/kg. Doses of the drug were expressed as the weight of the salt. All injections were given intraperitoneally.

**Data Analysis**

The primary dependent variable was the mean amount of milk consumed on each trial. The DR data were analyzed by two factor (DR Determination Dose) analyses of variance, with adjustments to the degrees of freedom when violations of the circularity assumption were detected (Kirk, 1982). When significant interactions were obtained, tests of simple main effects were performed.

In analyzing the activity data, the dependent measure was the frequency of each category of behavior on each day. A composite activity score that consisted of the sum of the frequencies of locomotion, sniffing, head scanning, and oral stereotypy was computed for each group and was subject to a separate analysis of variance to provide a general index of activity. 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. Data from the five 5-min intervals when milk was available were analyzed separately from those collected before and after milk access. Data from the latter two intervals were combined.

**Results**

**Milk Intake**

Mean milk intakes during DR 1 are shown in Figure 1. In the bottle condition, dl-cathinone produced a dose-dependent decrease in milk intake but had little effect in the cannula condition. Because statistical analysis of the data revealed significant differences between the feeding conditions at the saline (0 mg/kg) dose, the data were converted to percentages of intakes under saline and were reanalyzed. A significant Group Dose interaction was obtained, $F(3, 124) = 14.68, p < .0001$. Tests of simple main effects confirmed that bottle-fed rats ingested less milk than the cannula-fed rats at each of the doses of cathinone.

Mean milk intakes of the bottle-fed groups during the tolerance phase of the experiment are shown in Figure 2 (top panel). In the first trial, dl-cathinone (8 mg/kg) produced a pronounced decrease in intake, and relatively little tolerance was expressed during the period of chronic drug administration. As shown in Figure 2 (bottom panel), the drug produced much less suppression of milk intake in the first trial in the cannula group, and again, little tolerance was evident on subsequent trials.

Milk intakes during the DR tests conducted before and after chronic cathinone administration are shown in Figure 3 (top panels). In the bottle/cathinone group, there was a shift to the right in the posttolerance DR function (DR 2; see Figure 3, left panels). Statistical analysis revealed a significant DR Dose interaction, $F(3, 29) = 8.75, p < .001$, and post hoc tests indicated significant

![Figure 1: Mean (plus or minus standard error of the mean) intakes of rats injected with various doses of cathinone and saline and given milk either in bottles or via intraoral cannulas.](https://example.com/figure1.png)
increases in intake at the 2-, 4-, and 8-mg/kg doses. For the cannula/cathinone group (see Figure 3, right panels), an initial analysis revealed significant differences between DR determinations at the saline dose. Consequently, the data were converted to percentages of intake under saline and were reanalyzed. A significant DR Dose interaction was found, $F(3, 23) = 3.33, p = .04$. Further analysis indicated that rats ingested less milk at the 32-mg/kg dose on the posttolerance DR test (DR 2). At all other doses, intakes on the two DR determinations were not significantly different ($p > .05$).

Retesting the rats with the alternate method of milk presentation on the transfer tests resulted in marked changes in intakes. For the bottle/cathinone group, switching from the bottle to the cannula condition resulted in a shift of the DR function further to the right (see Figure 3, left panel). Statistical analysis revealed a significant DR Dose interaction, $F(5, 35) = 7.95, p < .001$, and post hoc tests indicated that milk intakes in the cannula condition were significantly higher than those in the bottle condition at all doses except saline. To determine whether these intakes reflected the development of tolerance, we compared the intakes of the bottle/cathinone group on DR 3 (cannula condition) with the intakes of the cannula/cathinone group on its initial DR determination (see Figure 4, top panel). After normalizing the data due to differences in intake at the saline dose, statistical analysis revealed a significant Group Dose interaction, $F(2, 33) = 5.80, p < .005$. Post hoc comparisons indicated that the bottle/cathinone group ingested more milk than the cannula/cathinone group at the 4-mg/kg dose but less milk at the 32-mg/kg dose. At all other doses, intakes did not differ. Thus, in general, tolerance to drug-induced hypophagia in the bottle condition did not result in correspondingly higher intakes (i.e., tolerance) when the bottle/cathinone group was given milk in the cannula condition.

*Figure 2.* Mean (plus or minus standard error of the mean) intakes of rats injected with either cathinone (8 mg/kg) or saline and given milk in bottles (top panel) or via intraoral cannulas (bottom panel) during the tolerance phase of the experiment.
For the cannula/cathinone group, switching from the cannula to the bottle condition resulted in a leftward shift in the DR function (see Figure 3, right panel). Statistical analysis revealed a significant DR × Dose interaction, $F(3, 24) = 5.18, p = .004$. Post hoc tests indicated that intakes on the final DR determination (DR 3) were lower than on the previous one (DR 2) at all doses except saline. To determine whether these intakes reflected the expression of sensitization to drug-induced hypophagia, we compared the intakes of the cannula/cathinone group on DR 3 (bottle condition) with those of the bottle/cathinone group on their initial DR test (cf. DR 1 in Figure 3, left panel). There were no significant differences between the groups. Thus, the lower intakes of the cannula/cathinone group when tested in the bottle condition did not reflect sensitization to drug-induced hypophagia.

Groups given saline during the tolerance phase showed little change in milk intake during the DR tests (see Figure 5, top panels). For the bottle/saline group, milk intakes on the posttolerance phase DR determination (DR 2) were slightly lower than on the initial DR determination (DR 1), as shown by a significant main effect of DR, $F(1, 9) = 9.87, p = .02$. The magnitude of this effect may have been constrained by a floor effect (see below). For the cannula/saline group, an initial analysis revealed significant differences between DR determinations at the saline dose, so the data were converted to percentages of intake under saline and were reanalyzed. A significant main effect of DR was found, $F(1, 9) = 8.42, p = .02$, which indicated that intakes on the posttolerance phase DR determination (DR 2) were lower than on the initial one (DR 1); that is, sensitization of hypophagia developed.

When tested with the alternate method of feeding during the transfer tests, the control groups also showed marked changes in milk intake. For the bottle/saline group, switching from the bottle to the cannula condition resulted in increased intakes compared with those on the previous DR determination (see Figure 5, left panel). This was confirmed by a significant DR × Dose interac-

![Figure 3. Effect of saline and various doses of cathinone on mean (plus or minus standard error of the mean) milk intakes (top panels) and on the mean frequency of composite motor activity (locomotion plus stereotyped responses; bottom panels) in the bottle/cathinone group (left panels) and the cannula/cathinone group (right panels) prior to the tolerance phase (the initial dose–response [DR] determination [DR 1]), after the tolerance phase (the second DR determination [DR 2]), and during the third DR determination (DR 3) transfer tests. The activity data are expressed as a percentage of the frequencies of all categories of behavior.]
Figure 4. (Top panel) Effect of various doses of cathinone on mean (plus or minus standard error of the mean) milk intakes of the bottle/cathinone group on the transfer tests, when they were tested in the cannula condition (the third dose–response [DR] determination [DR 3]), and of the cannula/cathinone group on the initial DR determination (DR 1). (Bottom panel) Effect of various doses of cathinone on mean (plus or minus standard error of the mean) milk intakes of the bottle/saline group on the transfer tests, when it was tested in the cannula condition (DR 3), and of the cannula/saline group on the DR 1. The data are expressed as percentages of intakes at the saline dose.

For the cannula/saline group, switching from the cannula to the bottle condition resulted in a profound decrease in milk intakes compared with those on the previous DR determination (see Figure 5, right panel). Because differences were also found at the saline dose, the data were converted to percentages of intake under saline and were reanalyzed. Again, significant decreases were obtained at each dose level, $F(2, 15) = 5.07, p = .03$, and post hoc analysis. The apparent sensitization of hypophagia reflected in this data was difficult to confirm statistically (by comparing intakes with those of the bottle/saline group on DR 1) because of floor effects. During the course of the tolerance phase of the experiment, the bottle/cathinone group lost 75 g, the cannula/cathinone group lost 19 g, the bottle/saline group gained 12 g, and the cannula/saline group gained 22 g.

Motor Activity

The effect of dl-cathinone on composite motor activity during the DR tests while milk was available is shown in Figures 3 and 5 (bottom panels). For the bottle/cathinone group, cathinone produced a dose-dependent increase in composite activity on the initial DR determination (DR 1), with asymptotic levels of activity occurring at doses of 8 mg/kg and higher. Following chronic administration of the drug, there was a shift in the DR function to the right. Statistical analysis revealed a significant DR Dose interaction, $F(3, 25) = 9.34, p = .0003$, and post hoc tests showed that activity scores were significantly lower on DR 2 at the 2-, 4-, and 8-mg/kg doses. On the transfer tests (DR 3), the DR function shifted back to the left. Statistical analyses indicated a significant DR Dose interaction, $F(2, 13) = 5.17, p = .03$, with significantly higher activity at the 4- and 8-mg/kg doses.

Cathinone also produced a dose-dependent increase in composite activity in the cannula/cathinone group, with asymptotic levels at doses of 4 mg/kg and higher. Following chronic administration of the drug, activity decreased on DR 2, as confirmed by a significant main effect of DR determination, $F(1, 7) = 7.30, p = .04$. It is apparent from Figure 3 (bottom panel), however, that this effect was primarily at the 2- and 4-mg/kg doses. On the transfer tests (DR 3), activity was not significantly different than on DR 2 ($p = .05$).

During the 5-min periods before and after milk was available, cathinone produced similar dose-dependent increases in composite activity on DR 1 in both the bottle- and cannula-fed groups (see Figure 6). No decreases in activity were found for either group on the subsequent DR determinations. Indeed, activity increased at the lowest dose (2 mg/kg).

As shown in Figure 5 (bottom panels), in the saline control groups, cathinone produced dose-dependent increases in activity on DR 1, with asymptotic levels observed at 4 mg/kg (cannula/saline group) or 8 mg/kg (bottle/saline group). On DR 2, activity was little changed except for increases at the lowest dose. Activity remained unchanged on the transfer tests (DR 3).

Discussion

The instrumental learning model (Wolgin, 1989, 2000) proposes that psychostimulant drugs suppress food intake primarily by inducing locomotion and stereotyped movements that interfere with the appetitive phase of feeding. Tolerance to stimulant-induced hypophagia involves learning to suppress such movements, a process that allows for, and is reinforced by, the ingestion of food. The current results provide strong support for this model. First, rats given acute injections of cathinone and access to milk in bottles displayed a dose-dependent suppression of milk intake, whereas rats given the drug and access to milk intraorally showed very little suppression of intake across a wide range of doses. Because both the bottle and cannula conditions involved consum-
matory behavior (i.e., ingestion), whereas only the bottle condition involved appetitive behavior, these results support the view that cathinone primarily disrupts the appetitive phase of feeding. Second, bottle-fed rats given chronic injections of cathinone showed a rightward shift in their DR function, indicating the development of tolerance to drug-induced hypophagia, and this effect was accompanied by a decrease in composite activity at the same doses at which tolerance was displayed. This decrease occurred only during the periods when milk was available. In contrast, cannula-fed rats did not develop tolerance, and although composite activity declined at the lower doses, these changes were not associated with increases in milk intake.

Data from the transfer tests are also consistent with the model. When tolerant bottle-fed rats were tested under the cannula condition, intakes increased even further. This increase can be attributed to the elimination of the appetitive phase of feeding and not to the transfer of learned behavioral adaptations previously acquired in the bottle condition. This conclusion is supported by two pieces of evidence. First, the increase in milk intake was accompanied by an increase in composite activity, which is incompatible with tolerance in the bottle condition. Indeed, this increase in activity during cannula feeding demonstrates that the decrease in activity during the previous period of bottle feeding was instrumental (i.e., purposive and goal directed). Second, the increased

Figure 5. Effect of saline and various doses of cathinone on mean (plus or minus standard error of the mean) milk intakes (top panels) and on the mean frequency of composite motor activity (locomotion plus stereotyped responses; bottom panels) in the bottle/saline group (left panels) and the cannula/saline group (right panels) prior to the tolerance phase (the initial dose–response [DR] determination [DR 1]), after the tolerance phase (the second DR determination [DR 2]) and during the third DR determination (DR 3) transfer tests. The activity data are expressed as a percentage of the frequencies of all categories of behavior.
intake in the cannula condition was not greater than that of the cannula/cathinone group on its initial DR determination and, therefore, does not represent tolerance. However, when the cannula/cathinone group was switched to the bottle condition, milk intake was decreased. This effect is also consistent with the model because this group had not learned to suppress stereotyped movements during the tolerance phase of the experiment when it received milk intraorally.

The data are less compatible with the homeostatic model of tolerance (Poulos & Cappell, 1991; Poulos et al., 1981). According to this model, the initial suppression of milk intake induced by cathinone is due to drug-induced anorexia and tolerance results from a homeostatically driven compensatory increase in appetite. On the basis of this model, one would expect a dose-dependent decrease in milk intake with both methods of feeding. However, cathinone produced only a small decrease in intraoral milk intake, which was unaffected by the dose.

Because the bottle/cathinone group lost more body weight than the cannula/cathinone group during the chronic phase of the experiment, it is possible that cumulative food deprivation contributed to the development of tolerance in the former group. This possibility was initially raised regarding contingent tolerance to amphetamine-induced hypophagia (Panksepp & Booth, 1973), but subsequent experiments demonstrated that systematic manipulations of deprivation level could not account for tolerance (Demellweek & Goudie, 1982, 1983). Because amphetamine and cathinone have shown cross-tolerance (Foltin & Schuster, 1982), it seems unlikely that tolerance to cathinone-induced hypophagia can be explained by increased hunger. Moreover, the cannula/cathinone group, which also lost weight during the chronic phase (although not as much as the bottle/cathinone group), showed no tolerance during the transfer tests when it was tested in the bottle condition. Nevertheless, it seems likely that deprivation does contribute to tolerance by enhancing the incentive properties of food and, in that way, motivating the rat to learn to suppress locomotion and stereotyped movements.

Taken together, the effects of both acute and chronic cathinone on milk intake and motor activity were qualitatively similar to those reported for amphetamine (cf. Wolgin, 2000). As noted above, there is cross-tolerance between the two drugs (Foltin & Schuster, 1982), suggesting a similar mechanism of action. Quantitatively, however, the level of tolerance obtained during the chronic phase of the current experiment was less than is typically found with amphetamine and much less than that reported for cathinone in the previous study by Foltin and Schuster (1982). With regard to the latter study, the difference may be a function of the chronic dose of cathinone (4 mg/kg vs. 8 mg/kg) or the length of the daily milk tests (15 min vs. 30 min). With regard to comparisons with amphetamine, d-amphetamine is about twice as potent as dl-cathinone (Foltin & Schuster, 1982); therefore, the dose of cathinone used in the current study (8 mg/kg) is equivalent to a dose of 4 mg/kg of amphetamine. In a previous study (Wolgin & Salisbury, 1985), bottle-fed rats given chronic injections of 4 mg/kg amphetamine recovered baseline levels of milk intake in 3 weeks, whereas in the current study, minimal recovery of intake was found after 4 weeks of treatment. Thus, at this relatively high dose, tolerance to the hypophagic effect of cathinone appears to be much less than to an equipotent dose of amphetamine.

Another difference between cathinone and amphetamine was their effects on rats given chronic injections of saline during the tolerance phase. In both the bottle/saline and cannula/saline groups, cathinone produced greater suppression of milk intakes on the second DR determination than on the first, indicating that sensitization of hypophagia had developed. This effect was demonstrated most clearly during the transfer tests, when the bottle/saline group was switched to the cannula condition. As shown in Figure 4 (bottom panel), cathinone produced a dose-dependent decrease in feeding in this group, which was much more severe than in the cannula/saline group on the first DR determination. In contrast, it is unusual to find sensitization of hypophagia to amphetamine following chronic injections of saline and access to milk. For example, a review of the DR data from nine previous

Figure 6. Effect of saline and various doses of cathinone on mean frequency of composite motor activity (locomotion plus stereotyped responses) in the bottle/cathinone group (left panel) and the cannula/cathinone group (right panel) during the 5-min periods preceding and following access to milk on the initial dose–response (DR) determination (DR 1; which was prior to the tolerance phase), the second DR determination (DR 2; which was after the tolerance phase), and the third determination (DR 3; which was during the transfer tests). The data are expressed as a percentage of the frequencies of all categories of behavior.
publications from David L. Wolgin’s laboratory revealed only one case of sensitization of hypophagia, and the effect was limited to a single dose of amphetamine. It is interesting that cathinone is considerably less potent than amphetamine in producing a conditioned taste aversion (Foltin & Schuster, 1981; Goudie & Newton, 1985); therefore, it seems unlikely that sensitization of hypophagia is related to a drug-induced change in the hedonic properties of the milk. The reason for this effect, therefore, remains unexplained.

In summary, cathinone produced a dose-dependent suppression of milk intake in bottle-fed rats but not in cannula-fed rats, suggesting that the drug interferes with the appetitive phase of feeding. Tolerance to the initial suppression of intake developed in bottle-fed rats and was accompanied by a suppression of composite motor activity, supporting the instrumental learning model. These results are qualitatively similar to those obtained with amphetamine, but the extent of tolerance is less, even when differences in potency are taken into account. In addition, cathinone induced sensitization of hypophagia in saline-treated controls, an effect not generally found with amphetamine.

References