Effects of acute and chronic cocaine on milk intake, body weight, and activity in bottle- and cannula-fed rats

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The effects of cocaine on the milk intake, body weight and activity of bottle- and cannula-fed rats was compared under both acute and chronic dosing conditions. Bottle-fed rats were initially more hypophagic than cannula-fed rats when given acute injections of cocaine (4–40 mg/kg). Following chronic injections of the drug (16 mg/kg), bottle-fed rats developed tolerance, as shown by a rightward shift in the dose-response function for milk intake. Such tolerance was accompanied by a decrease in drug-induced motor activity. In contrast, cannula-fed rats showed marked sensitization of stereotyped movements. Bottle-fed rats also lost weight during the chronic phase, while cannula-fed rats did not. However, weight loss *per se* was not a determining factor in tolerance development, because cannula-fed rats given chronic injections of 32 mg/kg cocaine lost even more weight, but did not become tolerant. These results suggest that, at moderate doses, cocaine suppresses feeding primarily by inducing behaviors that are incompatible with the appetitive phase of feeding, and that tolerance involves learning to inhibit such responses in order to feed.

Keywords: Appetitive behavior – Body weight – Cocaine – Locomotion – Milk intake – Rat – Sensitization – Stereotypy – Tolerance

INTRODUCTION

Tolerance to the hypophagic effects of both amphetamine (Carlton and Wolgin, 1971; Demellweek and Goudie, 1983) and cocaine (Woolverton *et al.*, 1978; Bowen *et al.*, 1993) is contingent on having access to food while in the drugged state. Although it is generally assumed that such tolerance represents a learned compensation for the initial loss of reinforcement produced by the drug (Schuster *et al.*, 1966; Carlton and Wolgin, 1971), the precise mechanism by which tolerance is acquired is not well understood. With respect to amphetamine, tolerance may involve learning to suppress stereotyped head movements, which interfere with feeding (Wolgin, 1989). Preliminary support for this hypothesis was obtained by comparing the effects of amphetamine on the milk intakes of cannula- and bottle-fed rats (Salisbury and Wolgin, 1985; Wolgin *et al.*, 1987). Although amphetamine (2 and 4 mg/kg) induced comparable levels of stereotyped head movements in both feeding conditions, the drug produced far greater suppression of intake in the bottle-fed groups. These results suggest that amphetamine has a greater effect on the appetitive phase of feeding (orientation and approach to food) than on the consummatory phase (ingestion of food). This conclusion is consistent with previous results showing that, following acute injection of amphetamine (1 mg/kg), rats had longer latencies to initiate feeding and frequently interrupted their meals with bouts of activity (Blundell and Latham, 1980).

Although bottle-fed rats were initially more hypophagic than cannula-fed rats, they showed rapid recovery of milk intake when amphetamine was given chronically, suggesting that they learned to suppress stereotyped behaviors in order to feed. In contrast, cannula-fed rats, which initially showed little hypophagia, showed no change in the frequency of stereotyped behavior and little tolerance during the same period of time (Salisbury and Wolgin, 1985; Wolgin *et al.*, 1987). Using a paradigm that dissociates the suppression of stereotypy from the act of licking a drinking tube, we recently confirmed that rats can suppress stereotyped behavior in order to feed. In that study, amphetamine-treated rats learned to hold their heads stationary in an area of space

defined by intersecting photobeams in order to self-administer intraoral infusions of milk (Wolgin and Wade, 1995).

Like amphetamine, cocaine also induces stereotyped movements at doses that suppress feeding (Woolverton *et al.*, 1978). To date, however, no studies have addressed the potential role of stereotypy in cocaine-induced hypophagia and tolerance. In an analysis of the acute effects of cocaine, Cooper and Van der Hoek (1993) found that the decrease in feeding induced by the drug (10–30 mg/kg) was accompanied by an increase in the latency to initiate feeding and an increase in the frequency of bouts of locomotion. However, the local rate of feeding, when it occurred, was normal. As the authors noted, these results suggest that cocaine, like amphetamine, affects the appetitive phase of feeding more than the consummatory phase.

If this conclusion is correct, then cocaine should induce greater hypophagia in bottle-fed rats, which are more dependent on appetitive behavior, than in cannula-fed rats. Furthermore, since cocaine and amphetamine display cross-tolerance to their hypophagic effects (Woolverton *et al.*, 1978), a common behavioral mechanism (i.e. learned suppression of stereotyped movements) may underlie the development of tolerance to both drugs. If so, tolerance to cocaine-induced hypophagia should develop more rapidly in bottle-fed rats than in cannula-fed rats, and such tolerance should be accompanied by a decrease in stereotyped movements only in the bottle condition. The following experiment was designed to test these predictions.

METHODS

Subjects

The subjects were 36 adult male albino Sprague-Dawley rats (382–457 g), housed individually in stainless steel cages under a 12 h alternating light-dark cycle (lights on 06.00 h) in a room maintained at about 24°C. The rats were maintained on three Purina Lab Chow pellets (approximately 15 g) daily, with free access to water.

Surgical procedure

Intraoral cannulae, constructed from polyethylene tubing (PE 90), were implanted in all of the rats under sodium pentobarbital anaesthesia (50 mg/kg), as previously described by Wolgin *et al.* (1987). The cannulae were positioned just lateral and rostral to the first maxillary molar. The externalized end of each cannula was connected to an L-shaped piece of 20 gauge stainless steel tubing mounted in a Teflon anchoring button (Alice King Chatham Medical Arts, Los Angeles), and embedded in cranioplastic cement along the midline of the skull. Throughout the experiment, the cannulae were flushed twice daily with warm water to keep them clean.

Procedure

Tests were conducted in cages identical to those in which the rats were housed, except that the food hoppers were removed and slotted Plexiglas covers were attached overhead. Prior to each test, the rats were weighed and then connected via a 12 in long spring tether to a miniature single channel fluid swivel (20 gauge; Alice King Chatham Medical Arts) suspended over the center of the cage. The spring was attached to the rat by threading it onto a hub protruding from the top of the cannula assembly. Although tethering was required only for the cannula-fed rats, bottle-fed rats were also tethered to control for potential restrictions in movement produced by the spring.

Each group was given daily 30 min tests with its respective method of feeding for 17 days, to establish baseline levels of milk intake. In the bottle condition (Group B; $n = 13$), sweetened condensed milk diluted with water (1:3) was provided in calibrated drinking tubes fitted with stainless steel spouts attached to the fronts of the cages. In the cannula condition (Group C; $n = 23$), milk was infused by gravity from a 50 ml glass syringe positioned about 50 cm above the floor of the cage. The syringe was connected to the miniature fluid swivel, and from there to the cannula assembly, by PE 90 tubing. The rate of milk flow was approximately 1 ml/min. Spillage was recovered in compartmentalized aluminum pans placed beneath the test cage. The pans were weighed before and after the session (after removing feces and blotting urine, if any) and the difference in weight expressed as ml using a conversion factor. The amount of milk ingested was calculated by subtracting spillage, if any, from the difference in the volume of the syringe before and after the session. During this phase, one rat in Group C died of unknown causes and another was dropped from the experiment when its cannula became blocked.

Following the baseline period, an initial dose-response determination (DR 1) was conducted. Test doses of cocaine hydrochloride (Group B: 4, 8, 16 and 32 mg/kg; Group C: 8, 16, 32 and 40 mg/kg) and saline were administered in counterbalanced order at four-day intervals. On the intervening days, saline injections were given. All injections were administered 20 min before the milk test.

In addition to measuring milk intake at the end of each session, the effects of cocaine on motor activity were assessed at 5 min intervals during the 30 min session using a rating scale with the following categories: 0 = immobile, whether awake or asleep; 1 = stationary activity (e.g. grooming, drinking); 2 = movement invol-

ving one or both forelimbs without concurrent stereotyped head movements (e.g. pivoting, rearing, walking; termed 'locomotion' hereafter); 3 = stereotyped darting head movements accompanied by sniffing, and generally covering a wide area (termed 'sniffing' hereafter); 4 = focused stereotyped head scanning movements covering a small area of the wall or floor of the cage; and 5 = stereotyped licking or biting of the walls or floor of the cage (oral stereotypy). Each rat was observed for 10–15 s by a trained observer, who recorded the dominant behavior that occurred in that interval. The reliability of the rating scale was established using videotaped recordings and in pilot work; interobserver agreement on these tests was consistently greater than 0.9.

During DR 1, two rats in Group C died following doses of cocaine (32 and 40 mg/kg) that induced seizures. At the conclusion of this phase, the remaining rats in each group were divided into subgroups. During the next 60 days (the tolerance phase), Group BS ($n = 6$) and Group B16 ($n = 7$) were injected with saline and cocaine (16 mg/kg), respectively, and given access to milk in bottles for 30 min each day. Similarly, Group CS ($n = 6$) and Group C16 ($n = 6$) were injected with saline and cocaine (16 mg/kg), respectively, and given intraoral infusions of milk for 30 min each day. Because cocaine (16 mg/kg) produced greater hypophagia in bottle-fed rats than in cannula-fed rats on DR 1 (cf. Fig. 1), a second cannula-fed group (Group C32; $n = 7$) was given daily injections of 32 mg/kg cocaine, a dose that was equipotent to 16 mg/kg in the bottle-fed groups. Following the tolerance phase, a second dose-response determination (DR 2) was conducted in which test doses of cocaine and saline were substituted for the chronic treatment at four-day intervals.

During the tolerance phase, one rat in Group BS died of unknown causes. In addition, two rats in Group C32 and one rat in Group CS developed either leaks or blockage in their cannulae and were dropped from the experiment. Four other cannula-fed rats were lost during DR 2. Two rats from Group C32 died following doses of cocaine (40 mg/kg) that induced seizures, while two other rats (one from Group C32 and one from Group CS) were dropped from the experiment when their cannula assemblies loosened.

Data analysis

The data were analyzed by analysis of variance (ANOVA). When violations of the circularity assumption were detected, the Geisser-Greenhouse conservative F test and Huyn-Feldt adjusted F test were used (Kirk, 1982). Apparent discrepancies in degrees of freedom reported for different analyses for the same group are attributable to the use of these tests. In general, planned comparisons were made using the test of Dunn and Sidak (Kirk, 1982). Post-hoc analyses of daily changes in intake and body weight during the tolerance phase were assessed using Fisher's least significant difference test (Kirk, 1982).

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 and head scanning was computed for each group and subjected to a separate ANOVA, in order to provide a more general index of activity. In presenting the data graphically, the frequency of these categories of behavior was expressed as a percentage of the total number of observations from all categories.

Because only two rats in Group C32 survived the experiment, statistical analysis of the dose-response data for this group was not possible and the data are not presented. Data for the tolerance phase are included, however, because five rats completed this phase of the experiment.

Drugs

Cocaine hydrochloride (obtained from the National Institute on Drug Abuse) 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. All injections were given i.p.

RESULTS

Milk intake and body weight

The effect of acute injections of cocaine and saline on the milk intakes of cannula- and bottle-fed rats during DR 1 is shown in Fig. 1. Intakes were similar following injection of saline. Although cocaine produced a dose-dependent decrease in milk consumption in both groups, the effect was greater in the bottle-fed rats. Statistical analysis of the data from the doses common to both groups (0, 8, 16 and 32 mg/kg) revealed a significant main effect of Group [$F(1,30) = 63.42$, $p < 0.001$] as well as a significant Group X Dose interaction [$F(3,90) = 12.14$, $p < 0.001$] with significant differences between the groups at the 8, 16 and 32 mg/kg doses.

The effect of chronic injections of cocaine or saline on the milk intake and body weight of bottle-fed rats is shown in Fig 2. Rats given saline (Group BS) showed no significant changes in intake during the tolerance phase. In contrast, Group B16 showed a marked decrease in intake on the first block and only partial recovery of intake by the end of the tolerance phase. A significant main effect of Group [$F(1,10) = 83.69$, $p < 0.001$] as well as a significant Group X Block interaction [$F(17,168) = 1.97$, $p < 0.02$] confirmed that Group BS

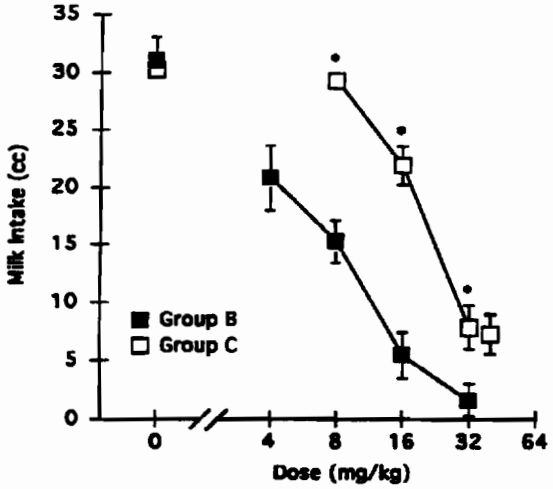

FIG. 1. Effect of saline and various doses of cocaine on the milk intakes of bottle-fed (Group B) and cannula-fed (Group C) rats. Each data point represents the mean ± 1 SE. *Group C > Group B, $p < 0.05$.

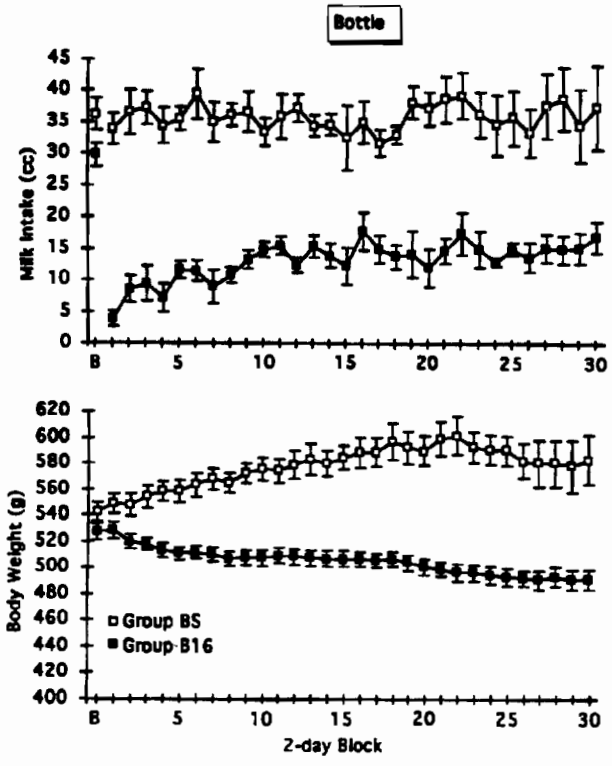

FIG. 2. Mean milk intakes (top) and body weights (bottom) of bottle-fed rats given chronic injections of either saline (Group BS) or 16 mg/kg cocaine (Group B16) during the tolerance phase. B = mean of last three baseline trials. All other data points represent the mean (± SE) of two trials.

and Group B16 differed during the tolerance phase. For Group B16, intakes exceeded those on block 1 from block 3 onwards, and remained stable from block 9 through block 30.

Group BS gained 59 g through block 22, but then lost

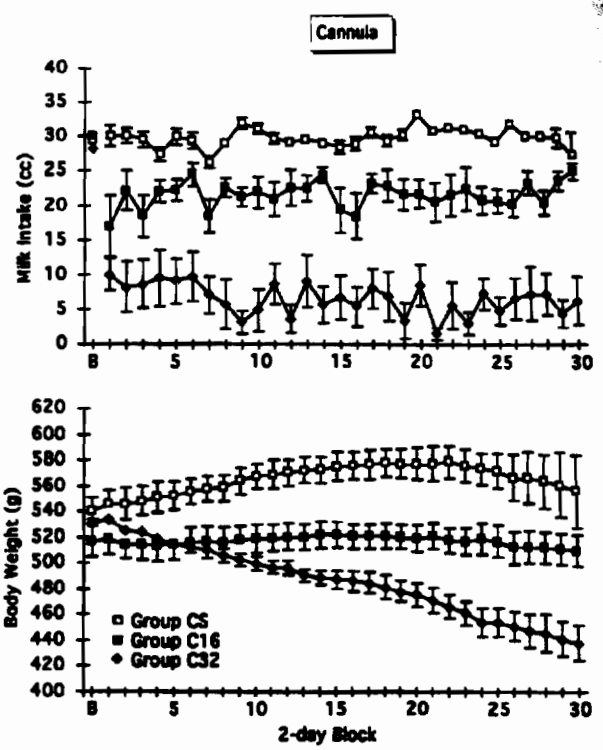

FIG. 3. Mean milk intakes (top) and body weights (bottom) of cannula-fed rats given chronic injections of either saline (Group CS), 16 mg/kg cocaine (Group C16), or 32 mg/kg cocaine (Group C32) during the tolerance phase. B = mean of last three baseline trials. All other data points represent the mean (±1SE) of two trials.

weight over the remaining trials for a net gain of 41 g. In contrast, Group B16 showed a gradual weight loss throughout the tolerance phase, ultimately losing 35 g. Differences between the groups were confirmed by a significant main effect of Group [$F(1,10) = 48.40$, $p < 0.001$] and by a significant Group X Block interaction [$F(2,22) = 13.79$, $p = 0.001$].

Like their bottle-fed counterparts, cannula-fed rats given saline injections (Group CS) showed no significant changes in milk intake during the tolerance phase (Fig. 3). In contrast, the groups given chronic injections of cocaine showed dose-dependent decreases in intakes on block 1. By block 30, the intake of Group C16 did not differ from that of Group CS, while the intake of Group C32 remained depressed. Differences between the groups were confirmed by a significant main effect of Group [$F(2,13) = 68.16$, $p < 0.001$] and by a significant Group X Block interaction [$F(30,198) = 2.19$, $p = 0.001$]. Within-group comparisons revealed that for Group C16, intakes were significantly higher on block 2 than on block 1. However, during the remainder of the tolerance phase the range of intakes remained quite narrow (18–25 ml) and there were no further significant changes in intakes from block 2 to block 30. For Group C32, intakes never exceeded those on block 1, and were significantly lower

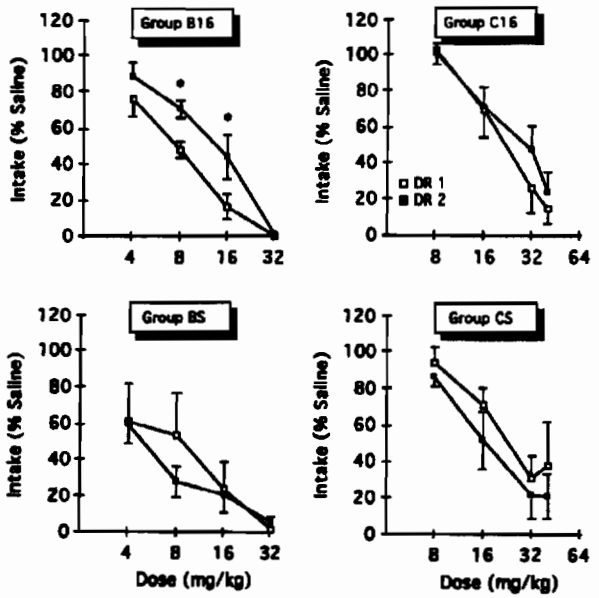

FIG. 4. Effect of various doses of cocaine on milk intakes during DR 1, conducted prior to the tolerance phase, and DR 2, conducted after the tolerance phase. During the tolerance phase, Group B16 and Group C16 received daily injections of cocaine (16 mg/kg); Group BS and Group CS received daily injections of saline. The data are expressed as a percentage of intakes at the 0 mg/kg (saline) dose. Each data point represents the mean ±1 SE. *DR 2 > DR 1, $p < 0.05$.

on six of the blocks. Thus, sensitization developed to the hypophagic effect of cocaine in this group, rather than tolerance.

By block 21, Group CS gained 32 g, but then lost all but 6 g of the gain by the end of the tolerance phase. Group C16 showed no significant changes in body weight during this period, while Group C32 steadily lost 93 g during the tolerance phase. Differences between the groups were confirmed by a significant main effect of Group [$F(2,13) = 6.73$, $p < 0.01$] and by a significant Group X Block interaction [$F(5,30) = 12.57$, $p < 0.001$].

Comparisons between feeding conditions showed that Group C16 drank significantly more than Group B16 throughout the tolerance phase, as indicated by a significant main effect of Group [$F(1,11) = 32.86$, $p < 0.001$]. In contrast, Group CS drank slightly less than group BS during much of the chronic phase, although the differences fell just short of statistical significance [$F(1,8) = 4.97$, $p < 0.056$].

Dose-response data for each of the groups are presented in Fig. 4. Only Group B16 showed a significant change in milk intake on DR 2 relative to DR 1. However, post-hoc analysis revealed that intakes were significantly higher at the saline dose as well. To control for this apparent baseline shift, the intakes at each cocaine dose were converted to percentages of the intakes under saline. Reanalysis of the data revealed a significant main effect of Dose Response [$F(1,6) = 29.41$, $p < 0.002$] as well as a significant Group X Dose Response interaction [$F(3,15 = 3.80$, $p < 0.05$]. Post-hoc comparisons indicated that intakes were significantly higher on DR 2 than on DR 1 at the 8 and 16 mg/kg doses.

Motor activity

Cocaine produced dose-dependent increases in locomotion and/or stereotyped behavior in all of the groups on DR 1 (Fig. 5). On DR 2, following the tolerance phase, Group B16 showed a decreased level of composite activity at the 8 and 16 mg/kg doses (Fig. 5, upper left). Statistical analysis of the data revealed a significant Dose Response × Dose interaction [$F(4,24) = 2.97$, $p < 0.05$]. Post-hoc comparisons indicated significant differences between DR 1 and DR 2 at the 16 mg/kg dose.

Further analysis of the individual behavioral categories revealed that stationary activity increased on DR 2, as indicated by a significant main effect of Dose Response [$F(1,6) = 12.44$, $p < 0.02$; data not shown]. This change was accompanied by decreases in locomotion [$F_{interaction}$ $(2,14) = 11.02$, $p = 0.001$; 8 and 16 mg/kg doses] and stereotyped sniffing [$F_{interaction}$ $(2,13) = 5.55$, $p < 0.02$; 32 mg/kg dose], and increases in focused stereotyped head scanning [$F_{interaction}$ $(2,12) = 9.37$, $p < 0.005$; 32 mg/kg dose]. Taken together, this pattern of results suggests that, although the overall level of activity decreased on DR 2, sensitization of stereotypy developed at the higher doses.

In contrast to their bottle-fed counterparts, Group C16 showed no significant changes in the level of composite activity on DR 2 (Fig. 5, upper right panel). Moreover, analysis of the individual behavioral categories revealed that there was no change in the level of stationary activity (data not shown). Although decreases in locomotion [$F_{main\ effect}$ $(1,5) = 9.89$, $p < 0.05$] and stereotyped sniffing [$F_{main\ effect}$ $(1,5) = 8.26$, $p < 0.05$] were observed in this group, these changes were accompanied by a marked increase in focused stereotyped head scanning movements [$F_{interaction}$ $(4,20) = 10.63$, $p = 0.001$; 16, 32 and 40 mg/kg doses]. Taken together, this pattern indicates that sensitization developed to cocaine-induced stereotypy in Group C16.

The two control groups showed little change in the level of composite activity when retested with cocaine on DR 2 (Fig. 5, lower left and lower right panels). For Group BS, stationary activity, locomotion and stereotyped behavior were not significantly different than on DR 1, although stereotyped head scanning showed a small but nonsignificant increase. For Group CS, stationary activity and locomotion were not significantly different than on DR 1. However, stereotyped sniffing

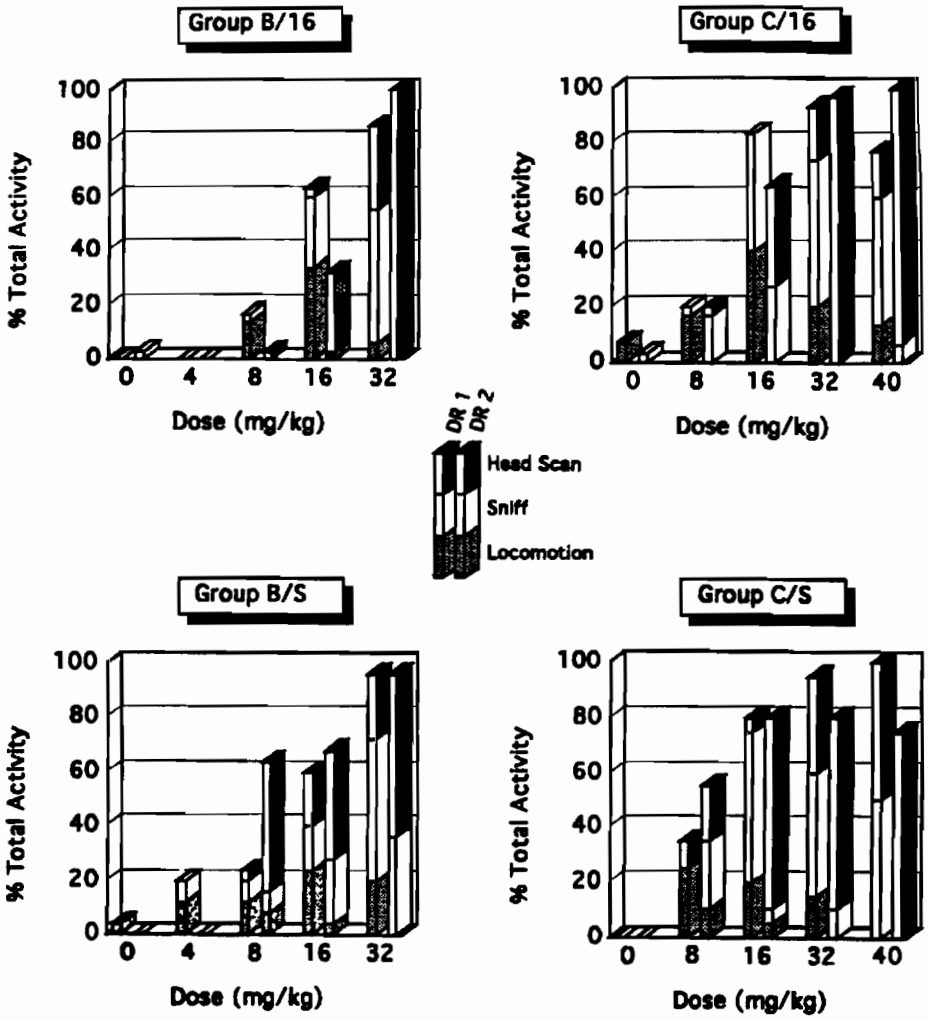

FIG. 5. Effect of saline and various doses of cocaine on total motor activity (locomotion + stereotyped sniffing + stereotyped head scanning) on DR 1, conducted prior to the tolerance phase, and DR 2, conducted after the tolerance phase. Each histogram indicates the relative amounts of each movement category at each dose. The data are expressed as a percentage of the total number of responses from all of the behavioral categories (maximum raw scores: Group B16 = 35; Group C16 = 30; Group BS = 25; and Group CS = 20). *DR 2 < DR 1, $p < 0.05$.

decreased [$F_{interaction}$ (2,7) = 4.80, $p < 0.05$; 16 and 40 mg/kg doses] while stereotyped head scanning increased, although not significantly. Because head scanning is generally observed at higher doses than sniffing, this shift implies that some degree of sensitization developed in the control groups, presumably due to prior exposure to the drug on DR 1.

DISCUSSION

Although cocaine initially induced comparable increases in locomotion and stereotyped movements in bottle- and cannula-fed rats, the drug suppressed feeding to a greater extent in the bottle-fed group. Because movement is incompatible with feeding when milk is presented in a bottle, but not when it is delivered intraorally, these results suggest that cocaine, like amphetamine (Salisbury and Wolgin, 1985; Wolgin *et al.*, 1987), disrupts ingestion primarily by interfering with the appetitive phase of feeding. Similarly, Cooper and Van der Hoek (1993) found that cocaine increased the frequency of locomotion and increased the latency to initiate feeding, but did not affect the local rate of ingestion when feeding occurred. Although these results support the conclusion that cocaine disrupts feeding nonspecifically, Rapoza and Woolverton (1991) reported that cocaine (16 mg/kg) suppressed milk intake to a greater extent than water intake, suggesting that cocaine has a more specific inhibitory effect on food intake. As the authors noted, these results are not conclusive because it is difficult to equate the deprivation states for the two ingestants. It should also be noted, however, that the decreased intakes of cannula-fed rats at the higher doses in the present experiment

suggest that cocaine can also affect consummatory responses and this effect may be more specific to food intake.

Although bottle-fed rats were initially more hypophagic than their cannula-fed counterparts, they developed partial tolerance to the suppression of feeding when cocaine was given chronically. Such tolerance was accompanied by an increase in stationary activity (primarily drinking) and a decrease in the overall level of movement, except at the highest dose, at which the rats remained completely hypophagic. Interestingly, the decrease in overall activity was accompanied by a shift in the pattern of locomotion and stereotypy characteristic of sensitization (i.e., decreased locomotion and stereotyped sniffing, and increased focused stereotyped head scanning movements). These results suggest that the ability of rats to suppress movement in order to drink (learned tolerance) does not preclude the concurrent development of sensitization. Indeed, previous studies with amphetamine have shown that, contrary to initial expectations, prior sensitization of stereotypy does not retard the subsequent development of tolerance to the hypophagic effect of the drug (Wolgin and Hughes, in preparation; Wolgin and Kinney, 1992).

In contrast to the bottle-fed group, cannula-fed rats given the same chronic dose of cocaine showed little evidence of tolerance to the hypophagic effect of the drug. The lack of substantial recovery in these rats during the tolerance phase, coupled with the absence of a rightward shift on DR 2, suggests that tolerance to the drug's effect on consummatory behavior does not occur to an appreciable extent. Moreover, the fact that these rats showed no decrease in overall activity and developed marked sensitization to cocaine-induced stereotypy demonstrates that the decreased level of activity in the bottle-fed group was not simply due to repeated exposure to cocaine *per se*. Taken together, then, these results provide strong support for the view that tolerance in bottle-fed rats involves learning to suppress movements that are incompatible with feeding, as proposed by the instrumental learning model (Wolgin, 1989).

In general, relatively little tolerance developed to the hypophagic effect of cocaine, despite the prolonged period of chronic administration. In part, this may have been a function of deprivation conditions. As Bowen *et al.* (1993) noted, differences in supplemental food intake during the course of an experiment may influence the extent of tolerance development. For example, Bowen *et al.* (1993) found little tolerance to 16 mg/kg cocaine in their rats, which were maintained on a free-feeding schedule that resulted in intakes of 17 g/day, whereas Woolverton *et al.* (1978) reported substantially more tolerance in their rats, which were maintained on a deprivation schedule (4–6 g/day). In the present experiment, in which the rats were maintained on 15 g/day, the degree of tolerance to 16 mg/kg was intermediate between that reported in the two other studies. On the other hand, neither the Bowen *et al.* (1993) study nor the present study found tolerance when rats were given chronic injections of cocaine at the 32 mg/kg dose. Indeed, evidence of sensitization was found in both studies. The failure to observe tolerance at this dose in the present experiment is particularly striking, considering that the milk was infused directly into the rats' mouths. The fact that tolerance failed to develop in this group, despite a substantial weight loss, suggests that cumulative deprivation *per se* is not a sufficient explanation for tolerance to cocaine-induced hypophagia. A similar conclusion was reached with respect to tolerance to amphetamine-induced hypophagia (Demellweek and Goudie, 1983).

In addition to deprivation level, pharmacokinetic factors affecting the disposition of cocaine may have influenced the development of tolerance. Several studies have demonstrated that rats given daily i.p. or s.c. injections of cocaine have higher concentrations of cocaine and its metabolites in both plasma and brain tissue than acutely treated rats, and that these higher levels are correlated with sensitization of locomotion and stereotypy (Estevez *et al.*, 1979; Reith *et al.*, 1987; Pettit *et al.*, 1990; Pan *et al.*, 1991; but see Orona *et al.*, 1994). These effects may have limited the extent of tolerance development in the groups given 16 mg/kg and blocked it entirely in the group given 32 mg/kg.

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