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Cocaine-Induced Sniffing Stereotypy Changes in Response to Threat

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BLANCHARD, R. J., M. HEBERT, L. DULLOOG, C. MARKHAM, R. FIGUEIRA, O. NISHIMURA, K. NEWSHAM, J. N. KAAWALOA AND D. C. BLANCHARD. *Cocaine-induced sniffing stereotypy changes in response to threat.* PHARMACOL BIOCHEM BEHAV **66**(2) 249–256, 2000.—"Cocaine-induced stereotypies" have been extensively investigated on the basis that they may be capable of providing insights into behavioral and neurochemical mechanisms relevant to drug abuse and addiction. Recent work has indicated that cocaine enhances a number of defensive behaviors, and, that cocaine-enhanced sniffing may be a functional behavior pattern, potentially related to defense, prompting an investigation of the effects of threat stimuli on cocaine-enhanced sniffing. When behaviors of saline control rats were evaluated in their home cages (HC), or on exposure to a toy cat (TC) or real cat (RC), they showed minimal crouching in the HC; initial crouching declining over 5 days of repetitions to the TC; and continued, high-level crouching to the RC. Cocaine (30 mg/kg, IP) enhanced defensiveness in situations in which it had declined in the TC and RC groups. It also produced high-level sniffing, declining over 5 test days, in the HC; initial low-level sniffing to the TC, increasing over 5 test days; and very low levels of sniffing to the RC. These and previous data contribute to a view that cocaine enhances, but does not directly induce, defensive behaviors. They also indicate that external threat stimuli such as the RC, or initial presentation of the TC suppress sniffing, with sniffing returning as habituation to novel but not intrinsically dangerous stimuli reduces defensiveness. This view suggests that some component of "sensitization of cocaine-induced sniffing stereotypy" may reflect a release from defensiveness-mediated suppression of sniffing over repeated injection/testing as the subject becomes habituated to the injection procedure and to novel test situations. © 2000 Elsevier Science Inc.

Cocaine Sniffing Stereotypy Defensive behavior Sensitization Crouching Freezing Fear Anxiety

THE "stereotyped" behaviors associated with administration of cocaine have been described as ". . . highly repetitive, purposeless, compulsive, and restricted in variations" (28). Such cocaine stereotypies have been variously measured, and some of these measures such as repetitive interruptions of a single photobeam [e.g., (22)], or total photocell beam counts minus those attributable to locomotion (33), are difficult to interpret in terms of changes in specific and potentially functional behaviors. However, moderate to high doses of cocaine do tend to increase both locomotor activity (11,36) and a group of behaviors including sniffing (30,35), rearing (32,35), grooming, and "head bobbing" (10). However, in part because it is often regarded as providing an index of the activity of the mesolimbic dopaminergic system (9,28), sniffing behavior has been the focus of particular experimental attention as a focal stereotypy associated with cocaine.

An important rationale for investigating cocaine stereotypies is that they may change in intensity or magnitude over repeated administrations. In particular, decreases in stereotypical behavior are often interpreted as representing tolerance to drug effects, potentially relevant to understanding why progressively higher drug doses may be self-administered with repeated drug use; while increases in stereotypical responding are regarded as representing sensitization to the effects of the drug, a potential factor in drug addiction. These sensitization/tolerance phenomena of cocaine stereotypies have been extensively investigated, with findings of differences in parameters of change over repeated drug use for dif-

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ferent rodent strains (32); ontogenetic development (21); cross-sensitization to other drugs (1); and as a function of the familiarity or novelty of the testing situation (17,23). A particularly extensive literature has involved attempts to determine the effects of extraneous drug manipulations on the parameters of cocaine sensitization [e.g., (13,18,19,25)].

Cocaine-induced stereotypical sniffing has also been shown to respond appropriately to environmental stimuli: when sniffing and rearing were evaluated after cocaine (30 mg/kg IP) administration to rats in cages that were open only at the top or only at the bottom, cocaine enhanced sniffing overall, but this sniffing was also directed appropriately, toward the incoming air stream: in top-open cages, rats sniffed up; in bottom-open cages, they sniffed down. Rear and sniff behavior was higher in rats in top-open, as opposed to bottom-open cages (4). These findings suggest that the "stereotypical" sniffing associated with cocaine is directed toward relevant environmental stimuli, and may be part of a functional behavior pattern, for example, to sample odorants from the air. Sniffing, as an important component of the process of olfactory investigation, is particularly marked in novel situations. This raises the possibility that when animals given cocaine are tested in novel situations, changes over time/exposure to the test site may diminish situational novelty, and thus reduce the elicitation of sniffing. This view is consonant with findings that manipulations of the test situation and its familiarity serve as an important determinant of the variability of results in sensitization (17,24).

A potentially important additional factor is that cocaine can facilitate or enhance defensiveness in rats and mice. Although studies have long suggested that cocaine can increase fearfulness or anxiety [e.g., (14,26,31,37)], a more comprehensive evaluation of cocaine effects on a variety of defensive behaviors has arisen from recent experiments directed specifically toward evaluating these effects in both rats and mice, and with different modes of drug administration. In a Mouse Defense Test Battery (MDTB), specifically designed to elicit and measure flight, freezing, defensive threat and attack, and risk assessment to an oncoming predator (6), cocaine (30 mg/kg, IP) produced substantial and consistent increases in flight and escape (3). Also, rat subjects in a Rat Runway Test similar to the MDTB showed a dramatic and explosive increase in directed flight responses to an oncoming threat stimulus following intravenous (IV) administration of 4 mg/kg cocaine. Although other defenses were not elevated immediately following IV drug administration in the RRT, or after IP drug administration in the MDTB, this may have been due to the predominance of flight, which had the effect of removing the subject from the oncoming threat stimulus: when rats were tested in the RRT 30 min after IV cocaine, at a time when flight—although still significantly enhanced—had declined considerably from its initial magnitude, increased defensive threat/attack responding to the approaching threat stimulus was seen (16).

These findings of enhanced defensiveness with cocaine are particularly interesting in that high-level threat stimuli and the defensiveness that they elicit may act to suppress other behaviors, including sniffing (5,7). This suggests that high level, inescapable threat stimuli to which rat subjects show little habituation, such as a cat, may elicit a crouching or freezing response that shows little change over repeated presentations, simultaneously acting to suppress cocaine-enhanced sniffing. However, highly salient novel stimuli, such as a toy plush cat, initially elicit a high level defensiveness, but this response declines over repeated presentation, enabling enhancement of suppressed behaviors.

The present study examines the effects of cocaine on crouching and sniffing, in response to stimuli designed to show, in controls, the above relationships. Specifically, we anticipate that exposure to a highly threatening predator stimulus, a cat, will enhance freezing and reduce cocaine-enhanced sniffing both initially and over repeated presentations, but that a novel toy cat will produce these effects only on initial exposures, permitting a later decline in freezing and a sensitization-like increase in sniffing associated with cocaine exposure.

METHOD

Subjects and Treatment Groups

Subjects were 90 90–100-day-old, male Long–Evans rats maintained and bred by the University of Hawaii Laboratory Animal Services. Subjects were singly housed in clear plastic cages (46.5 × 21 × 25 cm) with wood chip bedding and ad lib access to food and water. The subjects were kept on a 12L:12D cycle, with constant temperature and humidity. Fifteen animals each were randomly assigned to one of six conditions. Three groups were administered saline, while three were given 30 mg/kg cocaine. Each animal of one saline and one drug group was observed in its home cage (HC group); animals of one saline and one drug group were transported in its cage to a novel room and exposed to a toy cat (TC group); animals of the remaining saline and drug groups were similarly transported and exposed to a real, live, cat (RC group).

Drug Administration

Cocaine hydrochloride was dissolved in a vehicle of isotonic saline. Intraperitoneal (IP) injections of saline or 30 mg/kg cocaine were given at a constant volume of 1.0 ml/kg.

Apparatus

The test apparatus for the RC and TC groups consisted of a Plexiglas cat compartment (55 cm long × 40 cm wide × 35 cm high) with a wire mesh floor, elevated 19 cm, such that the subject's home cage could be slid underneath. The subjects' home cages were made of clear Plexiglas, which enabled videotaping during testing for all groups.

Procedure

Three days prior to the first test day, all subjects were transported into a holding room, where they remained, except for testing for the RC and TC groups, for the duration of the experiment. This room was maintained under the same conditions as the animal colony rooms, but enabled testing of HC animals without disturbing colony animals that were not part of this study. The HC animals were tested in the holding room and the RC and TC subjects were transported into two additional rooms, respectively. These two rooms were identical, and identical to the holding room as well, except that one was used for TC testing and the other for RC testing, to avoid exposure of TC subjects to cat odor.

On the test day, each subject was removed from its home cage and injected with 0 or 30 mg/kg of cocaine, IP, then replaced in its home cage. The HC subjects were videotaped for 2 h without further disturbance. The TC and RC subjects were immediately transported to their testing rooms and placed under an empty cat/toy cat apparatus. Following a 30-min prestimulus period, the cat or toy cat, as appropriate, was placed into the apparatus for a period of 60 min. The stimulus was then removed and videotaping continued for an addi-

tional 30 min, for a total testing period of 120 min. After testing, the subjects were returned in their cages to the holding room. These procedures were followed for 5 consecutive days, with video taping on days 1 and 5. This experiment protocol was approved by an Institutional Review Committee for the Use of Animal Subjects.

Analysis

Videotapes were scored using time sampling. The behaviors were rated for a 1-s period, every 30 s, for the entire 2-h period. Scorers were blind to the animals' drug treatment. The following behavior categories were scored and recorded.

Lie. The animal rests with its weight on the grid of the apparatus with no elevation due to either its forepaws or hind legs.

Crouch. The animal has elevation of the forelimbs off the grid and arching in the back.

Stand. The animal is immobile with both fore and hind limbs extended.

Rear. The animal has its forepaws off the floor and is supported by its hind legs.

Locomote. Movement that is greater than 1 cm during the 1-s time period scored.

Sniffing Analysis

The location of the cameras enabled direct measurement of sniffing. Sniffing was indexed by four basic behaviors: polypnea (rapid respiration); tip of snout movement; vibrissae movement; and head movement, integrated into a com-

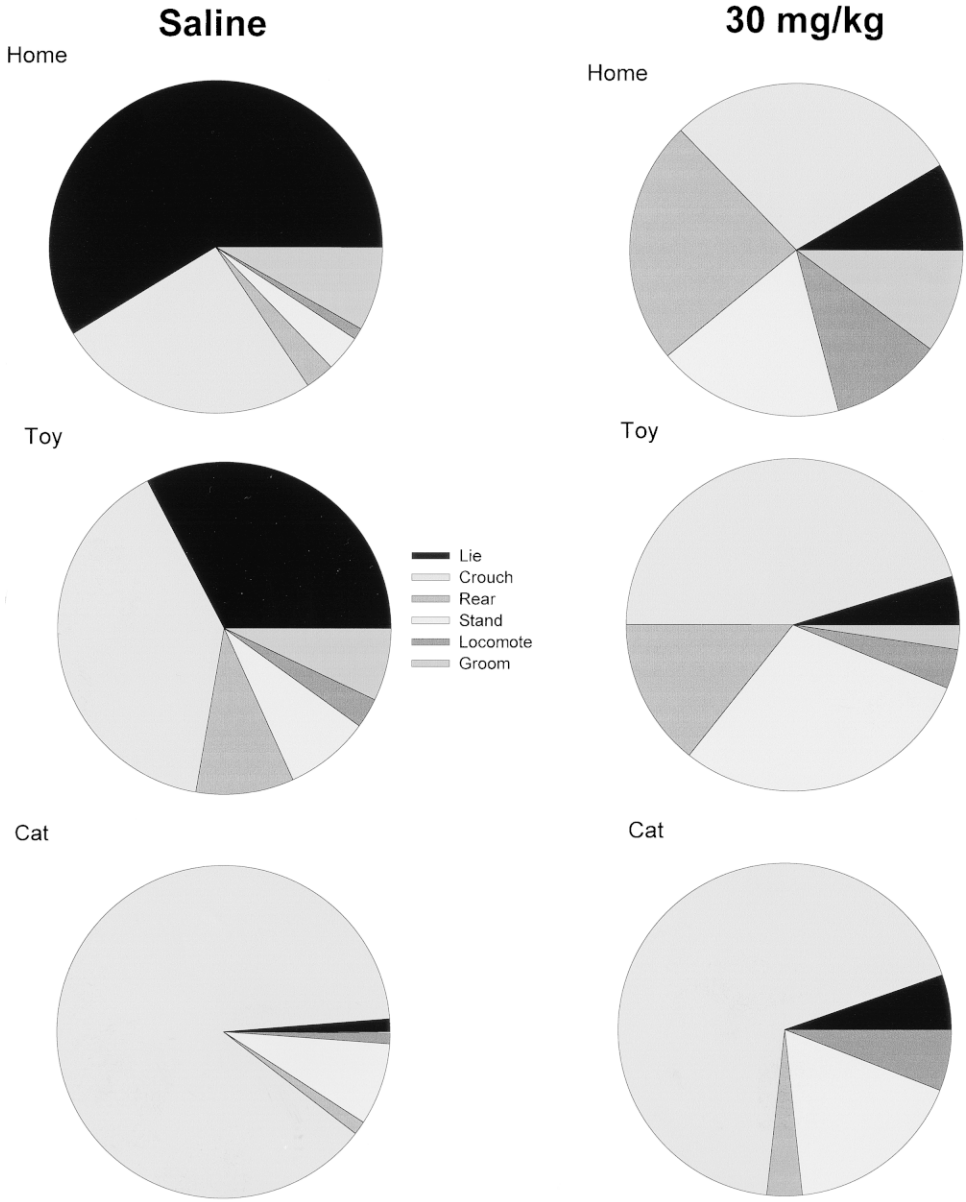

FIG. 1. Percentage of ratings of each behavior (lie, crouch, rear, stand, locomote, and groom) during the 60-min stimulus period, for subjects of the three stimulus exposure groups, under saline or cocaine, on test day 1. Ratings were made every 60 s, of the behaviors occurring during a 1-s period.

plex but relatively fixed pattern, and occurring about 8–12 times per second, during a sniffing bout. These bouts are separated by pauses of greater than 0.5 s. Although individual sniffs could not be accurately counted, we recorded the number of sniffing bouts; these were scored continuously during the following periods. Prestimulus period: minutes 20–30; stimulus period: minutes 0–10, 20–30, and 40–50; and poststimulus period: minutes 0–10 and 20–30.

Statistics

All time sampling data and sniffing data in the stimulus period were evaluated using analysis of variance (ANOVA), with exposure condition (HC, TC, or HC) as one factor, and dose (cocaine or saline) as the other. Because of the large number of groups and time periods involved, subsequent two-group analyses during specific time periods used Tukey tests.

RESULTS

Lying, Locomotion, Rearing, Standing, and Grooming

Because crouching and sniffing are the two behaviors most relevant to the hypotheses of this study, only abridged analyses are presented of the other behaviors measured (lying, locomotion, rearing, standing, and grooming). The proportion of time spent in each of these behaviors (as well as crouching) during the stimulus presentation period, on days 1 and 5 for

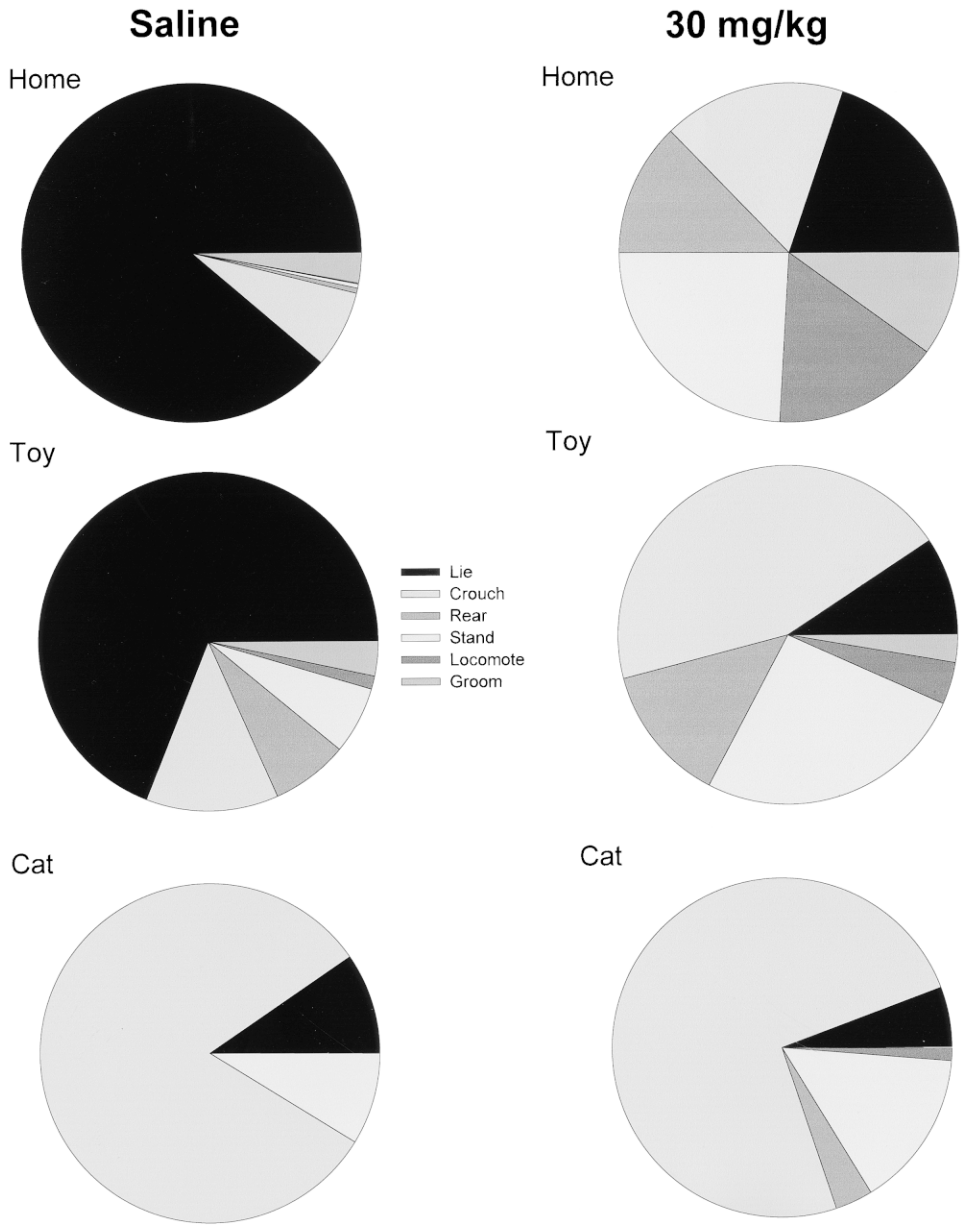

FIG. 2. Percentage of ratings of each behavior (lie, crouch, rear, stand, locomote, and groom) during the 60-min stimulus period, for subjects of the three stimulus exposure groups, under saline or cocaine, on test day 5. Ratings were made every 60 s, of the behaviors occurring during a 1-s period.

the saline and cocaine groups of the different stimulus exposure conditions, are presented in Figs. 1 and 2.

ANOVA indicated that cocaine reduced lying, $F(1, 74) = 111.97$, $p < 0.0001$; increased locomotion, rearing, and standing, $F(1, 74) = 21.11$, 10.99, and 25.15, respectively, $p < 0.01$, or less in each case; and failed to have a significant effect on grooming. ANOVA for exposure condition indicated that this was significant for lying, locomote, and rear, $F(2, 74) = 46.38$, 6.25, and 6.73, respectively, $p < 0.01$, or less; but not for standing or grooming.

Cocaine × exposure condition interactions were significant for lying, $F(2, 74) = 29.20$, $p < 0.0001$, with no differences among the groups for cocaine animals, while saline animals showed HC > TC > RC groups. For locomotion, this interaction was significant, $F(2, 74) = 8.36$, $p < 0.001$, with the HC cocaine group showing more locomotion than any other group. Rearing showed a significant interaction, $F(2, 74) = 3.25$, $p < 0.05$, with more rearing for cocaine-dosed animals in the HC condition, but not in the TC or RC conditions. For grooming, the significant interaction, $F(2, 74) = 5.18$, $p < 0.01$, reflected higher levels of grooming for cocaine-dosed animals, but only in the HC condition. The interaction of cocaine and exposure condition was not significant for standing.

The day effect (day 1 vs. 5) was significant for lying, $F(1, 74) = 23.48$, $p < 0.00001$, as was the dose × day interaction, $F(1, 74) = 10.46$, $p < 0.02$. However, the dose × stimulus exposure × day interaction was not significant.

Crouching

Figure 3 presents the percentage of behavior ratings that indicated crouching or freezing, for subjects of the three stimulus exposure groups, under saline or cocaine, on days 1 and 5. Cat exposure produced a clear increase in crouching, which persisted for the 1-h stimulus exposure period for both saline and cocaine subjects, $F(2, 74) = 64.09$, $p < 0.00001$. The RC group showed more crouching than TC and HC groups ($p < 0.001$ for both comparisons), and the TC group also showed more crouching than the HC group ($p < 0.01$). Although the main effect of cocaine was not significant, there was a significant cocaine × exposure condition interaction, $F(2, 74) = 4.35$, $p < 0.05$, reflecting that cocaine RC animals tended to show less crouching than saline RC subjects. However, this difference was significant only during the second 15 min of day 1 ($p < 0.01$). Effects of test day, $F(1, 74) = 4.37$, $p < 0.05$; time within period, $F(3, 74) = 7.35$, $p < 0.001$; and the quadruple interaction of drug, condition, day, and time, $F(6, 222) = 2.22$, $p < 0.05$, were all significant. In general, there was a wider discrepancy between the high crouching scores of the RC group, and the lower scores of the HC and TC groups on day 5, compared to day 1, with this tendency more apparent for saline groups than for cocaine groups. The saline TC group showed more crouching than the HC group on day 1 ($p < 0.05$), which habituated by day 5 ($p > 0.05$). However, in the cocaine groups the higher levels of TC animals compared to HC animals persisted throughout the experiment ($p < 0.05$ for days 1 and 5). Cocaine did not increase crouching in the home cage at any time period on days 1 or 5. During the poststimulus period (data not shown) there was a significant interaction of drug dose and condition, $F(2, 74) = 4.04$, $p < 0.05$, and RC saline animals showed reduced levels of crouching in comparison to those seen during the stimulus period, while RC cocaine animals persisted in this behavior.

Thus, during the stimulus period, cat exposure produced crouching or freezing. Cocaine, alone (i.e., in the HC group) did not. Exposure to the toy cat enhanced freezing in both cocaine and saline animals on first exposure. This habituated for the saline, but not cocaine, TC animals. Finally, cocaine-dosed rats did not show the poststimulus decrement in crouching that was shown by the saline rats of the RC group.

Sniffing

Figure 4 presents the mean number of sniffing bouts, during each of the time periods in which this was measured, for animals receiving saline or 30 mg/kg cocaine in their home cage, for test days 1 and 5. These data show the temporal course of cocaine effects following the initial handling/injection experience for these animals, and after repeated experience with this procedure, in groups receiving no additional manipulation or stimulation. Cocaine clearly increased sniffing, with the increase diminishing over time. ANOVA showed a significant dose effect, $F(1, 26) = 218.07$, $p < 0.00001$, and a dose × time interaction, $F(5, 130) = 48.46$, $p < 0.00001$. There was also a significant decrease within the session, $F(5, 130) = 74.94$, $p < 0.00001$, and less sniffing on day 5, $F(1, 26) = 8.69$, $p < 0.01$ compared to day 1. Thus the behavior (lying, locomotion, rearing, standing, grooming, and crouching) changes seen in the stimulus exposure period, described above, occurred during periods of sharply elevated sniffing for the cocaine HC animals.

Figure 5 presents the mean number of sniffing bouts during the stimulus period for all groups on the first and last day

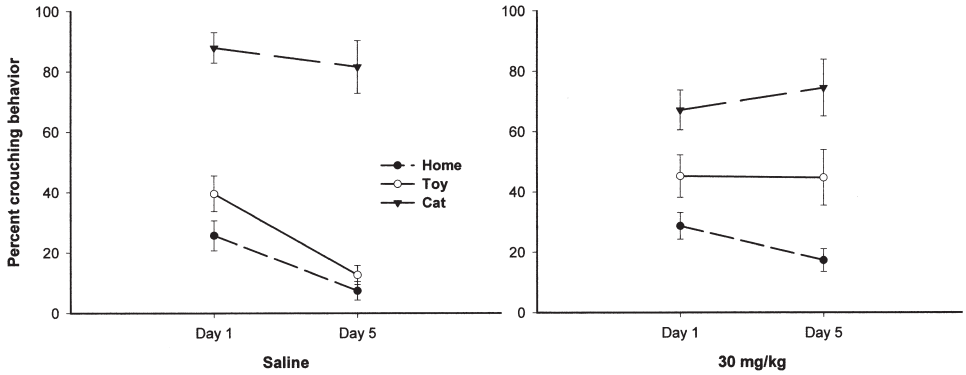

FIG. 3. Percentage of crouching ratings (1 rating/60 s) during the 60-min stimulus period for subjects of the three stimulus exposure groups, under saline or cocaine, on test days 1 and 5.

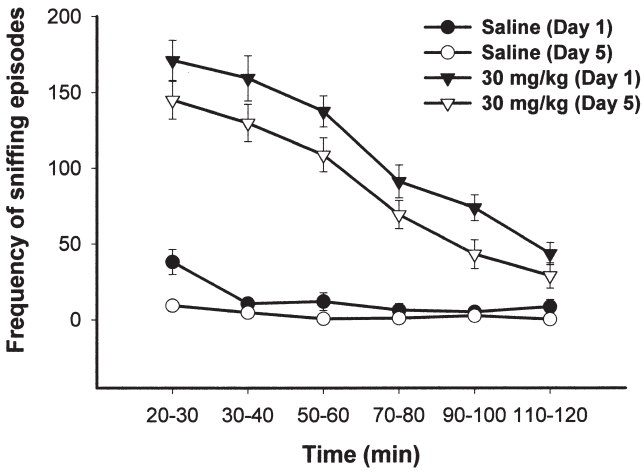

FIG. 4. Mean number of sniffing bouts during each period in which this was rated, for animals receiving saline or 30 mg/kg cocaine and evaluated in their home cages (HC group), for test days 1 and 5.

of testing. ANOVA showed a clear potentiation of sniffing by cocaine, $F(1, 80) = 199.17$, $p < 0.00001$, and a significant interaction of cocaine effects with exposure condition and days, $F(2, 80) = 7.29$, $p < 0.01$. There was also a significant interaction of cocaine, exposure condition, and time within the session, $F(4, 160) = 11.70$, $p < 0.00001$. Subsequent Tukey tests showed no significant differences in sniffing between day 1 and 5 for saline animals. Cocaine HC animals showed reduced sniffing on day 5 compared to day 1. In contrast, cocaine-dosed animals shifted to a new experimental room but only exposed to a toy cat showed a significant increase in sniffing over the 5 day period. The TC group showed significantly less sniffing than HC animals and significantly more sniffing than RC animals on both days 1 and 5. Cat exposed animals showed almost a total suppression of sniffing, not differing from the saline HC group on either test day, and showed significantly less sniffing than home cage and TC groups on both days.

SUMMARY AND DISCUSSION

Behavioral Effects of Cat Exposure

For the saline group, cat exposure produced clear behavioral effects. There was a marked reduction of lying, grooming, rearing, and locomotion, coupled with a highly significant increase in crouching or freezing, a finding reported frequently by this lab [e.g., (5,8)] and others [e.g., (29)]. Compared to saline HC controls, the saline TC group showed a transient elevation of crouching that disappeared by day 5. However, the crouching difference between the saline TC and RC groups was of high magnitude and persistent, being highly significant at all times. These results indicate that moving the subject's cage to another room and exposing the subject to a TC did produce an initial crouching response, albeit not as great as seen to the real cat. Crouching habituated with continued experience of the procedure of being moved and exposed to the toy cat. However, responsivity to the real cat showed no evidence of habituation over sessions, again, in accord with previous results (5).

Cocaine Effects

The effect of cocaine on the groups tested in their home cages was clear. On day 1, cocaine produced an almost total initial suppression of lying, and immediate increases in locomotion,standing, and rearing. This pattern of increases in active behaviors and decreased lying is generally in agreement with previous findings on cocaine effects in rats tested in initially novel test cages but not exposed to specific threat stimuli (4).

Exposure to a cat dramatically suppressed locomotion, rearing, and grooming in the cocaine-treatment groups. Crouching was significantly increased during cat exposure for both saline and cocaine animals. However, during the post-stimulus period, saline animals showed reduced levels of crouching in comparison to those seen during the stimulus period, while cat exposed cocaine animals persisted in this behavior. Similarly, while the incidence of crouching rapidly habituated in the TC groups receiving saline, crouching remained at elevated levels for the TC cocaine group. Thus, in both the RC and TC groups, cocaine increased defensiveness, as indexed by crouching or freezing, during periods in which the equivalent saline groups showed a reduction in this behavior. These findings are consonant with recent results indicating that cocaine can produce high magnitude increases in flight, in both rats and mice (3,16), and, in defensive threat/attack, in rats (16). The present crouching enhancement by cocaine appears to be somewhat more subtle than the dramatic flight increases seen at high dose cocaine levels, but this may also reflect differential effects of the enhanced activity associated with cocaine, which facilitates flight but interferes with crouching. A similar pattern was obtained for defensive threat/attack in cocaine-treated rats, in that these behaviors

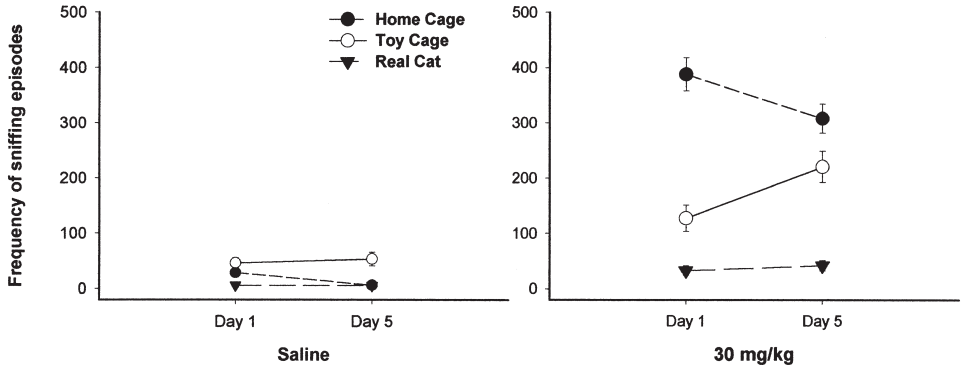

FIG. 5. Mean number of sniffing bouts for control and saline groups in ratings made during the stimulus exposure period for RC, TC, and HC groups on days 1 and 5.

only became more prevalent, relative to controls, in periods after the initial burst of flight had somewhat subsided (16). These data thus add to the view that cocaine enhances a variety of defensive behaviors, a factor that may be related to reports that cocaine can produce anxiety, panic, and paranoia in human users (12,15,27).

Stereotyped Sniffing

Cat exposure virtually eliminated the sniffing shown by cocaine animals tested in their home cages, which was initially very high and, although significantly attenuated, remained high on day 5. In contrast, the cocaine TC group's low level of sniffing on day 1 significantly increased by day 5, a pattern directly opposite to that seen for crouching in this group.

A conventional interpretation of these data, discounting any relationship between sniffing and defensiveness, might view the decline in cocaine-induced sniffing for the HC group over repeated exposure as reflecting tolerance; while the cocaine TC group's enhanced sniffing over the same exposures would be interpreted as sensitization. However, this view offers no suggestion as to how transportation and exposure to a toy cat could induce sensitization to cocaine in animals that, left undisturbed, would show tolerance to the same doses and dose schedule. The present finding that cat exposure dramatically suppresses sniffing in cocaine-dosed animals suggests a partial explanation of this seeming paradox, in that the enhanced sniffing of the cocaine TC group over repeated testing may reflect habituation to the moderately threatening transportation/toy cat exposure experience, reducing the defense-induced suppression of sniffing.

What this interpretation does not explain is why the home cage group showed a significant decrease in sniffing over the 5 test days. However, if, as the present crouching data, and previous flight and defensive threat/attack data (3,16) suggest, cocaine potentiates a variety of defensive behaviors, then it should be noted that one very prominent defense pattern includes sniffing. This is risk assessment, which includes visual, auditory, and olfactory "scanning" as well as tactile investigation of potential threat stimuli, with sniffing a major component of this pattern in rodents. Thus, cocaine-induced sniffing (and perhaps the "rear-sniff" behaviors that are also sometimes used as an index of cocaine "stereotypy") may potentially be related to risk assessment activity.

This interpretation, that cocaine-induced sniff and rear-sniff behaviors may represent attempts to sample odorants is consonant with findings (4) that these behaviors are appropriately oriented with reference to the incoming air stream in the test situation: when the test cage was open only at the top, cocaine-enhanced rear-sniff was more common, and sniffs were oriented upwards. When the test cage was open only at the bottom, rear-sniff was less common, and sniffs were oriented downwards. These findings are contrary to a view that either sniffing or the rear-sniff combination is a purely "stereotypical" behavior having no functional component, but are consonant with an interpretation of cocaine-enhanced sniffing as potentially related to enhanced defensiveness. This is not to say that the cocaine-facilitated behaviors are necessarily identical in all respects except magnitude to normal defensive behaviors; indeed, flight appears to be selectively facilitated at the expense of less active defenses (2). However, while the functional basis of cocaine-facilitated defenses as adaptive behaviors remain to be investigated, it is clear that these behaviors are characterized by an appropriate relationship to relevant features of the environment. Lyon and Robbins (20) emphasized that, for amphetamine effects, normal determinants of behavior such as unconditioned stimuli and the type of test situation may have a profound effect on the quality and development of stereotyped behavior, a view that, applied to cocaine effects, is strongly supported by present findings.

In the context of a view (2,16) that cocaine facilitates or magnifies the defensiveness seen in response to particular tests situations, it would be expected that cocaine-enhanced sniffing would be strongly dependent on the presence of some degree of threat. In the context of the HC group, this would be provided by the unfamiliar handling/injection procedure, producing enhanced alterness/defensiveness and potentiation of sniffing on day 1. If this habituates over the 5 test days, in addition to a reduction in sniffing, reduced crouching and enhancement of relaxed behaviors such as lying would be expected. This view is consonant with present data indicating significant day effects on both crouching and lying, as well as sniffing: in the absence of significant triple interactions for crouching and lying, the day 1 to day 5 changes in these behaviors for the HC group alone could not be evaluated. However, it is notable that the HC group's increase in lying over repeated exposure was proportionately larger than that for the other cocaine groups, as was its decrease in crouching. Thus, the pattern of change in all three behaviors for the HC group from day 1 to day 5 is consonant with the view that cocaine-enhanced sniffing may decline with repeated exposure to a mild and quickly habituated threat stimulus.

These data thus add to previous findings indicating that cocaine can enhance a variety of potentially defense-linked behaviors, and that these cocaine-enhance behaviors are also extremely sensitive to the threat characteristics of the test environment. The apparent suppression by high-level threat stimuli (real cat or, on first appearance, toy cat) of sniffing is consonant with a defensiveness interpretation of cocaine effects, and suggests a potential mechanism for cocaine-induced "stereotypical" sniffing, that it may reflect reductions in suppression due to defensiveness to handling/injection procedures, and, especially, to novel test stimuli, as such defensiveness habituates over repeated drug administration and testing. This interpretation raises questions of whether other instances of sniffing "sensitization" may also reflect reduction of fearfulness or defensiveness to an initially novel testing situation, through habituation, and, moreover, if manipulations shown to alter sniffing "sensitization" may actually do so through effects on fearfulness or fear conditioning and habituation [e.g., (34)].

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