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One-Trial Cocaine-Induced Behavioral Sensitization in Preweanling Rats: Role of Contextual Stimuli

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Abstract

Using a one-trial procedure, preweanling rats exhibit robust sensitization regardless of whether drug pretreatment and testing occur in the same or different environments. The purpose of the present study was to determine whether one-trial context-specific and context-independent sensitization of preweanling rats could be dissociated by varying the pretreatment dose of cocaine, by varying the pretreatment drug, or by minimizing interoceptive cues. In Experiments 1a and 1b, rats were pretreated with a broad dose range of cocaine (0–40 mg/kg) before placement in a novel activity chamber or the home cage. In Experiment 2, rats were pretreated with a locomotor-enhancing drug (e.g., methylphenidate, U50,488, or MK-801) before placement in a novel activity or anesthesia chamber. In Experiment 3, rats were anesthetized with isoflurane prior to cocaine administration in order to minimize the effects of interoceptive and injection cues. In all experiments, rats were challenged with cocaine on the test day (24 hr later), with locomotion being measured in activity chambers. Results showed that: (a) the pretreatment dose of cocaine (10–40 mg/kg) did not differentially affect context-specific and context-independent sensitization; (b) cross-sensitization between methylphenidate and cocaine was observed in the context-specific condition, but not when using a context-independent procedure; and (c) sensitization was evident if injection and interoceptive cues were minimized. One possibility is that associative processes do not modulate the one-trial sensitization of preweanling rats. Alternatively, “unitization” may cause preweanling rats to treat the different environments as equivalent, thus permitting robust sensitization even when drug pretreatment and testing occur in different environments.

Keywords

behavioral sensitization; cocaine; isoflurane; environmental context; ontogeny

Behavioral sensitization occurs when rats repeatedly exposed to a psychostimulant drug (e.g., cocaine or amphetamine) show an augmented behavioral response after a challenge injection with the same drug (Kalivas & Stewart, 1991; Robinson & Becker, 1986). In this circumstance, adult rats will exhibit a sensitized response for several months after final psychostimulant exposure (Leith & Kuczenski, 1982; Paulson, Camp, & Robinson, 1991). Cross-sensitization

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between different compounds is also possible, because adult rats given repeated injections of formaldehyde, toluene, morphine, heroin, amphetamine, methamphetamine, GBR12909, or methylphenidate show an augmented locomotor response when challenged with cocaine (Baldo & Kelley, 1991; Beyer, Stafford, LeSage, Glowa, & Steketee, 2001; Bonate, Swann, & Silverman, 1997; Cador, Bjijou, & Stinus, 1995; Kazahaya, Akimoto, & Otsuki, 1989; Leri, Flores, Rajabi, & Stewart, 2003; Lett, 1989; Smith, Greene-Naples, Felder, Iordanou, Lyle, & Walker, 2009; Sorg, Willis, See, Hopkins, & Westberg, 1998; Torres-Reverón & Dow-Edwards, 2005).

When using a standard multi-trial behavioral sensitization paradigm (i.e., psychostimulant pretreatment occurs across multiple days), adult rats exhibit a more robust sensitized response when drug pretreatment and testing occur in the same previously novel environment (Badiani, Camp, & Robinson, 1997; Carey & Gui, 1998; Post, Lockfeld, Squillace, & Contel, 1981; Tirelli & Terry, 1998). Even so, sensitized responding has often been observed even when the psychostimulant is never associated with the testing environment (Battisti, Uretsky, & Wallace, 2000; Partridge & Schenk, 1999; Vezina & Stewart, 1990). Rather than representing two qualitatively different types of behavioral sensitization (context-specific vs context-independent), it seems more likely that sensitization is mediated by a common set of neural mechanisms that are capable of being modulated by associative learning processes (Anagnostaras & Robinson, 1996; Anagnostaras, Schallert, & Robinson, 2002). The relative impact of nonassociative and associative processes can be manipulated in a variety of ways. For example, nonassociative processes can be strengthened by repeatedly administering high doses of a psychostimulant across multiple days (Browman, Badiani, & Robinson, 1998a, b; Pert, Post, & Weiss, 1990).

Adult animals are also capable of exhibiting behavioral sensitization after only a single pretreatment administration of a psychostimulant drug, but in this experimental paradigm environmental conditioning factors gain in importance (see Pert et al., 1990; White, Joshi, Koeltzow, & Hu, 1998). For example, adult rats and mice pretreated with cocaine or amphetamine in a novel environmental context showed a sensitized response when subsequently challenged with a psychostimulant in the same environment (Battisti et al., 2000; Fontana, Post, Weiss, & Pert, 1993; Jackson & Nutt, 1993; McDougall, Reichel, Cyr, Karper, Nazarian, & Crawford, 2005). In contrast, behavioral sensitization was not evident if drug pretreatment and testing occurred in distinctly different environments or if drug pretreatment occurred in the home cage (Battisti, Chang, Uretsky, & Wallace, 1999; Battisti, Uretsky, & Wallace, 1999; McDougall, Baella, Stuebner, Halladay, & Crawford, 2007; McDougall, Cortez, et al., 2009; Weiss, Post, Pert, Woodward, & Murman, 1989). Therefore, it appears that adult rats will only exhibit context-specific behavioral sensitization, but not context-independent sensitization, when tested after a single pretreatment injection of cocaine or amphetamine.

Preweanling rats exhibit a very different pattern of responding when tested using the one-trial sensitization paradigm. Specifically, rats pretreated with cocaine on postnatal day (PD) 19 and tested on PD 20 showed robust context-independent behavioral sensitization in various experimental situations. For example, context-independent sensitization was evident on the test day (PD 20) if: (1) rats were exposed to the testing chamber on PD 19 and injected with cocaine 30 min after being returned to the home cage; (2) rats were pretreated with cocaine in a novel chamber on PD 19 and then given a challenge injection of cocaine in a different novel chamber on the test day; or (3) rats were injected with cocaine and restricted to the home cage on PD 19 (McDougall et al., 2007; McDougall, Charntikov, Cortez, Amodeo, Martinez, & Crawford, 2009; McDougall, Cortez, et al., 2009). In these situations, preweanling rats exhibited a sensitized response that was similar to rats pretreated and tested with cocaine in the same environment. Although this pattern of results was not initially anticipated, the most

parsimonious conclusion is that environmental conditioning factors are unnecessary for one-trial behavioral sensitization during the preweanling period.

The overall purpose of the present study was to identify some of the critical determinants underlying the one-trial context-independent behavioral sensitization of preweanling rats. Because drug dose is an important factor determining whether adult rats exhibit context-independent sensitization (Browman et al., 1998a,b), we examined whether the context-specific and context-independent sensitization of preweanling rats could be dissociated by varying the pretreatment dose of cocaine. In Experiment 1a, context-independent sensitization was examined by administering cocaine (10–40 mg/kg) 30 min after rats were returned to the home cage from the novel activity chamber; whereas, in Experiment 1b, context-independent sensitization was assessed by injecting rats with cocaine (10–40 mg/kg) and restricting them to their home cage on the pretreatment day. In the second experiment, we tested whether simply elevating locomotor activity through pharmacological means (i.e., by administering methylphenidate, MK-801, or U50,488 on the pretreatment day) would result in context-specific or context-independent cross-sensitization to cocaine. The purpose of the third experiment was to determine whether interoceptive and injection cues are necessary for the development of context-independent behavioral sensitization in preweanling rats. To this end, some rats were briefly anesthetized with isoflurane prior to cocaine injection on the pretreatment day (i.e., to eliminate injection cues), while other rats were maintained in an anesthetized state until being returned to the home cage (i.e., to minimize interoceptive cues).

General Method

Subjects

Subjects were 240 male and female rats of Sprague-Dawley descent (Charles River, Hollister, CA) that were born and bred at California State University, San Bernardino (CSUSB). Litters were culled to 10 pups at three days of age. Preweanling rats were kept with the dam and littermates throughout behavioral testing and were housed in large polycarbonate maternity cages (56 × 34 × 22 cm) with wire lids and Tek-Fresh® bedding (Harlan, Indianapolis, IN). Food and water were freely available. The colony room was maintained at 22–24°C and kept under a 12-hr light–dark cycle, with behavioral testing occurring during the light phase of the cycle. All procedures were approved by the Institutional Animal Care and Use Committee of CSUSB.

Apparatus

Behavioral testing was done in commercially available (Coulbourn Instruments, Allentown, PA) activity monitoring chambers (25.5 × 25.5 × 41 cm, L × W × H), consisting of acrylic walls, a plastic floor, and an open top. Each chamber included an X–Y photobeam array, with 16 photocells and detectors, that was used to determine distance traveled (horizontal locomotor activity). Photobeam resolution was 0.76 cm, with the position of each rat being determined every 100 ms. Some experiments also used small animal anesthesia chambers (model: PY8 50-0108, Harvard Apparatus, Holliston, MA) made of clear Plexiglas with a sliding lid (23.5 × 10 × 10 cm, L × W × H). The activity monitoring chambers and anesthesia chambers were located in different rooms.

Drugs

(−)-Cocaine hydrochloride, methylphenidate hydrochloride, (+)-MK-801 hydrogen maleate, and (±)-*trans*-U50,488 methanesulfonate were purchased from Sigma (St. Louis, MO). All drugs were dissolved in saline and injected intraperitoneally (ip) at a volume of 5 ml/kg. Cocaine was administered to preweanling rats at doses ranging from 10 to 40 mg/kg. In comparison, one-trial behavioral sensitization experiments using adult rats most frequently

employ a 40 mg/kg dose of cocaine on the pretreatment day (Fontana et al., 1993; Jackson & Nutt, 1993; Weiss et al., 1989).

Statistics

For each experiment, omnibus repeated measures analyses of variance (ANOVAs) were used for the statistical analysis of distance traveled data. Significant higher-order interactions were further analyzed using one- or two-way ANOVAs. Post hoc analysis of behavioral data was made using Tukey tests ($p < .05$).

In all experiments, an equal number of male and female preweanling rats were assigned to each group. Unlike adults, prepubescent rats do not typically exhibit sex differences after treatment with dopamine agonists or other locomotor activating compounds (see also Bowman, Blatt, & Kuhn, 1997; Duke, Meier, Bolanos, Crawford, & McDougall, 1997; Frantz & Van Hartesveldt, 1999; McDougall et al., 2007; Scalzo & Holson, 1992; Snyder, Katovic, & Spear, 1998). Preliminary analyses indicated that distance traveled data did not differ according to sex, so this variable was not included in subsequent analyses. Litter effects were controlled through both experimental design and statistical procedures. In most circumstances no more than one subject per litter was assigned to a particular group. In cases where this procedure was not possible (e.g., analysis of the pretreatment day), a single litter mean was calculated from multiple littermates assigned to the same group (Holson & Pearce, 1992; Zorrilla, 1997). With only one exception (described below), litter was used as the unit of analysis for statistical purposes (Zorrilla, 1997). With this statistical model each litter, rather than each rat, is treated as an independent observation (i.e., a within analysis using one value/condition/litter). In order to compare the results of Experiments 1a and 1b, a between analysis was used (a 3 × 4 between-subjects ANOVA) because all groups were not represented within each litter.

Experiments 1a and 1b

Although adult rats do not exhibit context-independent behavioral sensitization when using the one-trial procedure (Fontana et al. 1993; Jackson & Nutt, 1993; McDougall et al., 2007; McDougall, Cortez, et al., 2009; Weiss et al., 1989), they are capable of showing context-independent sensitization when given repeated daily treatments with a psychostimulant (Battisti et al., 2000; Partridge & Schenk, 1999; Vezina & Stewart, 1990). In the latter circumstance, sensitization is more readily observed if adult rats are pretreated with a high dose of cocaine or amphetamine (Browman et al., 1998a, b). In the same manner, it is possible that the one-trial behavioral sensitization of preweanling rats is dependent on drug dose, with context-independent sensitization requiring a high dose of cocaine on the pretreatment day. In the first experiment, context-independent sensitization was assessed in two ways: by administering cocaine (10–40 mg/kg) 30 min after rats were returned to the home cage from the novel activity chamber (Experiment 1a) or by injecting rats with cocaine (10–40 mg/kg) and restricting them to their home cage on the pretreatment day (Experiment 1b). For comparison purposes, context-specific sensitization was assessed by pretreating rats with cocaine in a novel activity chamber (Experiment 1a).

Method

In Experiment 1a, eight litters of male and female rats ($N = 72$) were randomly assigned to one of nine pretreatment conditions on PD 19. Rats in the cocaine-activity groups were taken to the test room and injected with cocaine (10, 20, 30, or 40 mg/kg, ip) before being placed in activity chambers. Distance traveled was measured for 30 min. These rats were returned to the home cage and injected with saline 30 min later. Rats in the cocaine-home groups were injected with saline before being placed in the activity chambers and injected with cocaine (10, 20, 30, or 40 mg/kg, ip) 30 min after being returned to the home cage. The saline control group received

saline in both the activity chamber and home cage. In all cases, "home" refers to the normal maternity cage that includes both the dam and littermates.

After 24 hr (i.e., on PD 20), all rats received a challenge injection of 20 mg/kg cocaine to determine the occurrence of behavioral sensitization. After drug administration, rats were placed in activity chambers where distance traveled was measured for 60 min. Distance traveled data from the pretreatment day were analyzed using a 5 × 6 (Drug Dose × Time Block) ANOVA. Test day data were initially analyzed using an omnibus 9 × 12 (Group × Time Block) ANOVA, while 3 × 12 (Condition × Time Block) ANOVAs were used to assess the effects of the condition variable at each dose of cocaine.

In Experiment 1b, an additional eight litters of male and female rats ($N = 40$) were used to determine the effects of cocaine on the sensitized responding of rats restricted to the home cage (i.e., the home-restricted groups). On PD 19, rats were injected with cocaine (0, 10, 20, 30, or 40 mg/kg, ip) in the home cage followed, 60 min later, by an injection of saline in the home cage (half of the rats received the saline injection first followed by the cocaine injection). None of these rats were removed from the colony room on the pretreatment day. After 24 hr, all rats were taken to the test room, injected with cocaine (20 mg/kg, ip), and immediately placed in activity chambers for 60 min. Distance traveled data from the test day were analyzed using a 5 × 12 (Drug Dose × Time Block) ANOVA.

Results and Discussion

Activity chamber groups (Experiment 1a)—On the pretreatment day (i.e., PD 19), rats injected with cocaine (10–40 mg/kg) exhibited greater distance traveled scores than saline controls, Drug Dose main effect, $F(4, 28) = 20.88$, $p < .05$, and Tukey tests, $p < .05$. This effect varied across the 30-min session (see Figure 1) because rats given 40 mg/kg cocaine only differed significantly from the saline group on time blocks 1, 5, and 6, Drug Dose × Time Block interaction, $F(20, 140) = 4.23$, $p < .05$, and Tukey tests, $p < .05$. Rats injected with the lower doses of cocaine (10, 20, or 30 mg/kg) had greater distance traveled scores than saline controls on time blocks 1–6, Tukey tests, $p < .05$.

On the test day (i.e., PD 20), an omnibus ANOVA showed that distance traveled scores varied significantly according to treatment group and time block, Group main effect, $F(8, 56) = 8.68$, $p < .05$ and Time Block main effect, $F(11, 77) = 11.85$, $p < .05$, respectively. In the latter case, distance traveled scores increased across the first few time blocks and then gradually declined as the testing session progressed. Separate analysis of the 40 mg/kg groups showed that rats in the cocaine-activity and cocaine-home groups had greater distance traveled scores than rats in the saline control group, Condition main effect, $F(2, 14) = 14.01$, $p < .05$, and Tukey tests, $p < .05$ (see upper graph, Figure 2). Although a trend was apparent, the cocaine-activity and cocaine-home groups treated with 40 mg/kg cocaine did not differ significantly from each other. Context-independent sensitization was also apparent if preweanling rats were pretreated with lower doses of cocaine (see middle graphs, Figure 2). More specifically, rats exhibited elevated distance traveled scores on the test day if they had been pretreated with 20 or 30 mg/kg cocaine in the activity chambers (i.e., the cocaine-activity groups) or 30 min after being returned to the home cage (i.e., the cocaine-home groups), Condition main effects, $F(2, 14) = 18.04$, $p < .05$, $F(2, 14) = 10.81$, $p < .05$, respectively, and Tukey tests, $p < .05$]. Pretreating rats with 10 mg/kg cocaine in either the test chamber or home cage did not induce sensitized responding on the test day (see lower graph, Figure 2).

Home-restricted groups (Experiment 1b)—When assessed on the test day, rats pretreated with 30 mg/kg cocaine in the home cage exhibited significantly greater distance traveled scores than rats pretreated with 0 mg/kg cocaine, Drug Dose main effect, $F(4, 28) = 5.60$, $p < .05$, and Tukey tests, $p < .05$ (see Figure 3). Rats pretreated with lower (10 or 20 mg/

kg) or higher (40 mg/kg) doses of cocaine did not differ from controls. The effects of the pretreatment variable differed across the testing session, because rats pretreated with 30 mg/kg cocaine had greater distance traveled scores than the 0 mg/kg group on time blocks 3–5 and 7–12, Condition × Time Block interaction, $F(44, 308) = 2.35$, $p < .05$, and Tukey tests, $p < .05$.

Comparison of activity chamber and home-restricted groups—Mean distance traveled scores of activity chamber groups (Experiment 1a) and home-restricted groups (Experiment 1b) are shown in Figure 4. A 3 × 4 between-subjects ANOVA indicated that distance traveled scores varied according to dose, with the 10 mg/kg cocaine group exhibiting less locomotor activity than groups pretreated with higher doses of cocaine (20, 30, or 40 mg/kg), Drug Dose main effect, $F(3, 84) = 12.14$, $p < .001$, and Tukey tests, $p < .05$. Overall, rats in the cocaine-activity groups (dark gray bars) had greater distance traveled scores than rats in the home-restricted groups (open bars), with the cocaine-home groups (light gray bars) being intermediate between the other groups, Condition main effect, $F(2, 84) = 4.90$, $p < .01$, and Tukey tests, $p < .05$. The Condition × Drug Dose interaction was nonsignificant.

Discussion—In Experiment 1a, rats pretreated with 20–40 mg/kg cocaine in the novel activity chambers showed a sensitized locomotor response when challenged with cocaine on PD 20. The same pattern of results was apparent if rats were pretreated with cocaine (20–40 mg/kg) 30 min after they were returned to the home cage. When considered together, these two sets of findings indicate that the context-independent sensitization of preweanling rats is not dependent on a high dose of cocaine. In Experiment 1b, context-independent sensitization was also evident when cocaine-pretreated rat were maintained in the home cage on the pretreatment day, but the sensitized responding appeared weaker than if rats were exposed to the activity chambers on PD 19.

Experiment 2

The purpose of Experiment 2 was to determine whether pretreating rats with a compound other than cocaine would differentially affect the expression of context-specific and context-independent behavioral sensitization. MK-801 (an NMDA antagonist), U50,488 (a kappa opioid agonist), and methylphenidate (a psychostimulant) were used because all three drugs typically induce substantial locomotor activity in preweanling rats (Duke, Meier, et al., 1997; Frantz & Van Hartesveldt, 1999; Jackson & Kitchen, 1989; McDougall, Collins, Karper, Watson, & Crawford, 1999) and are capable of inducing a sensitized locomotor response (Collins, Zavala, Ingersoll, Duke, Crawford, & McDougall, 1998; Duke, O'Neal, & McDougall, 1997; McDougall et al., 1999). On PD 19, rats were pretreated with MK-801, U50,488, methylphenidate, or cocaine prior to placement in activity chambers or small, enclosed anesthesia chambers. On PD 20, all rats were challenged with 20 mg/kg cocaine and distance traveled scores were measured in the activity chambers. Thus, context-independent sensitization (or cross-sensitization) was tested in a different manner than in Experiment 1 (i.e., context-independent sensitization was previously assessed by pretreating rats with cocaine in the home cage rather than in a separate environment). The reasons for using different procedures to assess context-independent sensitization were twofold: (a) to better determine the generality of context-independent sensitization in preweanling rats and (b) design constraints involving Experiment 3 required that context-independent sensitization (or the lack thereof) be established using a separate, novel environment (i.e., anesthesia chambers).

Method

On PD 19, eight litters of male and female rats ($N = 80$) were randomly assigned to one of ten pretreatment conditions. Specifically, preweanling rats were injected with a test compound or

saline and then immediately placed in activity or anesthesia chambers for 30 min (no anesthesia was administered). The test compounds were MK-801 (0.3 mg/kg), U50,488 (5 mg/kg), methylphenidate (10 mg/kg), or cocaine (30 mg/kg). After 24 hr, all rats were challenged with 20 mg/kg cocaine and placed in activity chambers where distance traveled was measured for 60 min.

Distance traveled data from the pretreatment day were analyzed using a 5 × 6 (Drug × Time Block) ANOVA. Test day data were analyzed using separate 5 × 12 (Drug × Time Block) ANOVAs for each pretreatment environment.

Results and Discussion

Activity chamber groups—On the pretreatment day (i.e., PD 19), rats injected with MK-801 (*M* = 7,429 cm, *SEM* = ±1,096), methylphenidate (*M* = 10,547 cm, *SEM* = ±1,561), or cocaine (*M* = 6,487 cm, *SEM* = ±823) had significantly greater distance traveled scores than saline controls (*M* = 2,502 cm, *SEM* = ±324), Drug main effect, $F(4, 28) = 11.61$, $p < .05$, and Tukey tests, $p < .05$. Unexpectedly, U50,488 (*M* = 3,660 cm, *SEM* = ±545) did not enhance the locomotor activity of preweanling rats when compared to the saline group.

On the test day (i.e., PD 20), rats pretreated with methylphenidate (10 mg/kg) or cocaine (30 mg/kg) showed a sensitized locomotor response when challenged with 20 mg/kg cocaine (see upper graph, Figure 5). Specifically, when collapsed across the test session the distance traveled scores of the methylphenidate- and cocaine-pretreated rats were significantly greater than the saline controls, Drug main effect, $F(4, 28) = 10.48$, $p < .05$, and Tukey tests, $p < .05$. Rats pretreated with MK-801 or U50,488 did not show a sensitized locomotor response after cocaine challenge, nor did the methylphenidate and cocaine groups differ from each other. Although distance traveled scores showed a general decline across the testing session, Time Block main effect, $F(11, 77) = 19.08$, $p < .05$, the drug variable did not interact with time to affect performance.

Anesthesia chamber groups—Rats pretreated with cocaine (30 mg/kg) in the anesthesia chambers exhibited significantly more locomotor activity than control rats on the test day, Drug main effect, $F(4, 28) = 4.95$, $p < .05$, and Tukey tests, $p < .05$ (see lower graph, Figure 5). In contrast, rats pretreated with MK-801, U50,488, or methylphenidate did not differ significantly from saline controls. Overall, distance traveled scores declined across the session, Time Block main effect, $F(11, 77) = 14.71$, $p < .05$.

Separate statistical analyses showed that rats pretreated with methylphenidate in the activity chambers had significantly greater distance traveled scores on the test day than rats given an injection of methylphenidate in the anesthesia chambers, Condition main effect, $F(1, 7) = 5.67$, $p < .05$ (compare the upper and lower graphs, Figure 5). None of the other compounds (cocaine, U50,488, or MK-801) induced differential amounts of locomotor activity in the two chambers.

Discussion—When drug pretreatment occurred in the activity chambers, a single exposure to cocaine or methylphenidate was sufficient to induce behavioral sensitization on the test day. In contrast, a sensitized locomotor response was only evident when cocaine, but not methylphenidate, was administered in the anesthesia chambers (see also McDougall, Cortez, et al., 2009). Simply enhancing locomotor activity on the pretreatment day was not sufficient to induce behavioral sensitization, because rats pretreated with MK-801 (in either the activity or anesthesia chambers) did not show a sensitized locomotor response when challenged with cocaine on the test day.

Experiment 3

Results from Experiments 1 and 2 suggest that environmental conditioning is unnecessary for the one-trial behavioral sensitization of preweanling rats. Instead, interoceptive and/or injection cues may be critical factors modulating the context-independent behavioral sensitization of preweanling rats (see Crombag, Badiani, & Robinson, 1996; Pert et al., 1990). According to this hypothesis, changes in the internal state of the rat or the injection procedure itself could serve as potent conditioned stimuli (CS) or occasion-setters necessary for behavioral sensitization. To test this idea, rats were pretreated with saline or cocaine in the same anesthesia chambers as described previously. Some of these rats were briefly anesthetized with isoflurane prior to the injection procedure; other rats were maintained in an anesthetized state until being returned to the home cage; while still other rats were never exposed to isoflurane. Behavioral sensitization was assessed one day later in the novel activity chambers.

Method

On PD 19, eight litters of male and female rats ($N = 48$) were randomly assigned to one of six groups. Rats in the extended isoflurane condition were placed in the anesthesia chambers and given isoflurane (a 5% concentration mixed with oxygen) prior to cocaine (30 mg/kg) or saline injections. These rats were then maintained under 1% isoflurane anesthesia for the entire pretreatment period and remained unresponsive until they were returned to the home cage. Rats in the brief isoflurane condition were placed in the anesthesia chambers and given isoflurane before being injected with cocaine or saline. Isoflurane administration was quickly discontinued and rats became responsive soon after the injection procedure was completed (approximately 5 min). Rats in the no-isoflurane condition were placed in the anesthesia chambers and injected with cocaine or saline, with no isoflurane being administered. In all conditions, rats were kept in the anesthesia chambers for 30 min and then returned to the home cage.

After 24 hr (i.e., on PD 20), all rats were challenged with 20 mg/kg cocaine and placed in activity chambers where distance traveled was measured for 60 min. Distance traveled data from the test day were analyzed using a 3 × 2 × 12 (Drug × Condition × Time Block) ANOVA.

Results and Discussion

Anesthesia chamber groups—On the test day (i.e., PD 20), an omnibus 3 × 2 × 12 ANOVA indicated that there were significant effects for only time block, $F(11, 77) = 16.02$, $p < .05$, and drug. Regardless of anesthesia condition, cocaine-pretreated rats showed greater distance traveled scores on the test day than saline-pretreated rats, Drug main effect, $F(1, 7) = 17.84$, $p < .05$ (see Figure 6). To ensure that this overall main effect was truly representative, we performed separate 2 × 12 ANOVAs for each anesthesia condition. When no isoflurane was administered on the pretreatment day, rats previously exposed to cocaine had greater test day distance traveled scores than saline-pretreated rats, Drug main effect, $F(1, 7) = 10.59$, $p < .05$ (see upper graph, Figure 6). This finding replicated results from Experiment 2. Likewise, cocaine-pretreated rats from the brief isoflurane condition (i.e., rats were under isoflurane anesthesia during the injection procedure) had elevated distance traveled scores when compared to saline controls, Drug main effect, $F(1, 7) = 8.51$, $p < .05$ (see middle graph, Figure 6). Rats maintained under isoflurane anesthesia for the entire pretreatment session (i.e., from before the injection procedure until 30 min after cocaine or saline treatment) also exhibited behavioral sensitization (see lower graph, Figure 6), because cocaine-pretreated rats had significantly greater distance traveled scores on the test day than saline-pretreated controls, Drug main effect, $F(1, 7) = 9.57$, $p < .05$. In no case did the drug variable interact with time block to affect performance.

Discussion—Preweanling rats showed a sensitized locomotor response on the test day regardless of whether they had been anesthetized with isoflurane during the entire pretreatment session or only during the injection procedure. Thus, these results suggest that interoceptive and injection cues are not necessary for the one-trial context-independent behavioral sensitization of preweanling rats.

General Discussion

The ability of associative processes to modulate psychostimulant-induced behavioral sensitization appears to vary across ontogeny. Unlike adult rats, preweanling rats express robust context-independent behavioral sensitization if they previously received a single 30 mg/kg cocaine injection after return to the home cage (McDougall et al., 2007; McDougall, Charntikov, et al., 2009; McDougall, Cortez, et al., 2009). Some interpretive difficulties arise from using a high dose of psychostimulant, because repeatedly administering a high dose of amphetamine or cocaine in the home cage is sufficient to induce context-independent behavioral sensitization in adult rats, even when drug administration is unsignalled (Browman et al., 1998a, b). That being said, results from Experiment 1a show that the one-trial context-independent sensitization of preweanling rats is not uniquely dependent on a high dose of cocaine, because sensitized responding was apparent regardless of whether cocaine (20, 30, or 40 mg/kg) was administered in the activity chamber or 30 min after being returned to the home cage. A lower dose of cocaine (10 mg/kg) did not induce either context-specific or context-independent behavioral sensitization. When results from these developmental and nondevelopmental studies are considered together, it appears that the ability of preweanling rats to exhibit one-trial context-independent behavioral sensitization represents a true qualitative ontogenetic difference that is not dependent on drug dose.

Similar to a previous report (McDougall, Cortez, et al., 2009), results from Experiment 1b showed that cocaine-pretreated rats restricted to the home cage on PD 19 exhibited a sensitized locomotor response when challenged with cocaine on the test day (PD 20). Two features of these data are of special note: first, the strength of the sensitized response did not increase linearly according to dose. Specifically, only home-restricted rats injected with 30 mg/kg cocaine on the pretreatment day exhibited a sensitized response on the test day (see Figure 3). It is unclear why a greater dose of cocaine (40 mg/kg) did not induce a stronger or at least a statistically significant sensitized response, especially since there was no evidence that stereotypy was elevated in rats pretreated with 40 mg/kg cocaine (data not shown). Second, the sensitized responding of home-restricted rats was weaker than when rats were injected with saline in the novel chamber and cocaine in the home cage (the cocaine-home groups). This conclusion is based on the finding that the cocaine-home groups pretreated with 20, 30, or 40 mg/kg cocaine exhibited behavioral sensitization; whereas, rats in the home-restricted groups only showed a sensitized response when pretreated with 30 mg/kg cocaine. Pert et al. (1990) state that “conditioning would not be expected to occur in a paradigm in which animals were injected in their home environment (p. 215),” because the “entire stimulus complex” (i.e., the environmental context, injection procedure, transportation to the testing room, interoceptive cues, etc.) is less discriminable than when rats are conditioned in a novel environment. In the present study, transporting preweanling rats from the colony room and placing them in a novel chamber (regardless of whether it was the environment they were ultimately tested in) seemed to promote stronger behavioral sensitization. One possibility is that a more robust sensitized response was evident on the test day because additional salient cues were incorporated into the “entire stimulus complex” on the pretreatment day.

Alternatively, stress may have been responsible for the different patterns of responding exhibited by the cocaine-home and home-restricted groups. In adult rats, stress is known to both enhance responsivity to psychostimulants and induce behavioral sensitization (Anisman,

Hahn, Hoffman, & Zacharko, 1985; de Jong, Wasilewski, van der Vegt, Buwalda, & Koolhaas, 2005; Prasad, Sorg, Ulibarri, & Kalivas, 1995). Similarly, rats postnatally exposed to repeated isolation stress show a sensitized response when challenged with a psychostimulant drug during early ontogeny (PD 10) or in adulthood (Kehoe, Shoemaker, Arons, Triano, & Suresh, 1998; Kehoe, Shoemaker, Triano, Callahan, & Rappolt, 1998; Kikusui, Faccidomo, & Miczek, 2005). In the present study, therefore, the stress due to extended removal (30 min) from the home cage, transport, and placement in a novel environment may have contributed to the strength of the sensitized response. Of course, this explanation assumes that stress interacted with cocaine to affect performance, otherwise stress-induced sensitization should have been observed in the saline-pretreated groups as well.

Although environmental context does not appear to determine whether one-trial behavioral sensitization will be expressed by preweanling rats, the importance of other cues (e.g., injection and interoceptive cues) had not been previously assessed in young rats. In adult rats, the “entire stimulus complex” impacts the induction and ultimate expression of behavioral sensitization. In an illustrative set of studies, a modest sensitized response was evident if adult rats were injected intraperitoneally with amphetamine in the home environment (Badiani, Anagnostaras, & Robinson, 1995; Badiani, Browman, & Robinson, 1995); however, behavioral sensitization did not occur if injection and handling cues were eliminated by administering amphetamine via an indwelling catheter (Crombag et al., 1996; Fraioli, Crombag, Badiani, & Robinson, 1999). Anesthetizing adult rats with pentobarbital or a ketamine/xylazine mixture prior to daily cocaine treatments also eliminated the expression of context-independent behavioral sensitization (Torres, Rivier, & Weiss, 1994), thus suggesting that interoceptive cues may be an important component of the stimulus complex modulating behavioral sensitization. In contrast, Wang and Hsiao (2003) reported that adult rats had a normal sensitized response on the test day even if they had been anesthetized with chloral hydrate prior to daily amphetamine administration. Various procedural differences could be responsible for these inconsistent results (e.g., the psychostimulant used, rat strain, number of pretreatment days, etc.), but of greatest relevance may be the unique actions of each anesthetic agent on neurotransmitter system functioning (e.g., ketamine is a noncompetitive NMDA receptor antagonist; for a discussion, see Torres et al., 1994).

In the present study, we attempted to minimize the impact of interoceptive and injection cues by anesthetizing preweanling rats with isoflurane during either the injection procedure (approximately 5 min) or for the duration of the pretreatment session (approximately 35 min). Consistent with the results reported by Wang and Hsiao (2003), preweanling rats exhibited a sensitized locomotor response on the test day (PD 20) even if anesthesia had been administered on the pretreatment day (PD 19). Thus, it appears that eliminating injection cues and reducing interoceptive cues (i.e., anesthesia was only administered for 35 min) does not abolish the context-independent behavioral sensitization of preweanling rats. Isoflurane was used in the present study because an inhalable anesthetic avoids the injection process entirely (i.e., ketamine, pentobarbital, and chloral hydrate are injectables) and it does not antagonize NMDA receptors. Isoflurane has its own limitations, however, because dopamine synthesis and release are altered after prolonged exposure (Adachi, Yamada, Satomoto, Higuchi, Watanabe, & Kazama, 2005). Even so, isoflurane has only minimal impact on cocaine-induced Fos expression in the caudate-putamen and nucleus accumbens of adult rats (Kufahl, Pentkowski, Heintzelman, & Neisewander, 2009).

In a further attempt to dissociate the one-trial context-specific and context-independent sensitization of preweanling rats, we pretreated rats with various locomotor-enhancing compounds (MK-801, U50,488, or methylphenidate) in activity or anesthesia chambers on PD 19. Interpretation of this experiment is somewhat limited because only one dose of each compound was tested (due to constraints caused by litter size). Nonetheless, cross-sensitization

between cocaine and either MK-801 or U50,488 (both nonpsychostimulants) was not evident on PD 20, thus showing that merely elevating locomotor activity on the pretreatment day was not sufficient to induce an augmented locomotor response on the test day. Interestingly, methylphenidate (a psychostimulant) and cocaine cross-sensitized, but only in the context-specific situation. The ability of drugs to cross-sensitize is often interpreted to mean that a common neural substrate underlies the sensitization process (Aizenstein, Segal, & Kuczenski, 1990; Cadoni, Valentini, & Di Chiara, 2008). In the present circumstance, however, the lack of cross-sensitization in the context-independent situation should not be taken as evidence that the neural mechanisms mediating context-specific and context-independent sensitization are separate and discrete (see Anagnostaras & Robinson, 1996; Anagnostaras et al., 2002). Instead, it is possible that associative/perceptual processes might be responsible for the lack of cross-sensitization in the context-independent situation (this explanation is discussed below).

Interestingly, young and adult animals appear to perceive stimuli differently, with rats and humans showing an age-dependent decline in stimulus generalization across ontogeny (Chotro & Alonso, 1999; Gibson, 1969; Spear & McKenzie, 1994). For example, adult rats treat multiple CSs as discrete and often competitive events (Spear & McKenzie, 1994), whereas preweanling rats treat two distinguishable stimuli as if they were equivalent (i.e., components of a single event or object) as long as both stimuli were paired with the same US (Kraemer, Kraemer, Smoller, & Spear, 1989; Lariviere, Chen, & Spear, 1990; Molina, Hoffmann, Serwatka, & Spear, 1991; Spear, Kraemer, Molina, & Smoller, 1988). This process is referred to as “unitization” and may explain why preweanling rats showed context-independent sensitization to cocaine, yet did not exhibit context-independent cross-sensitization after methylphenidate pretreatment. In the former case, preweanling rats may have shown context-independent behavioral sensitization because the different environmental contexts (e.g., the activity chamber, anesthesia chamber, and home cage), although discriminable, were treated as equivalent units. In other words, the two environments where cocaine was experienced (e.g., the anesthesia chamber and the activity chamber) may have been organized as a single integrated event (i.e., components of a single CS or occasion-setter). If unitization occurred, rats would be expected to show a sensitized response regardless of the location where cocaine was initially administered.

Spear and colleagues have shown that the unitization process will not occur if separate CSs are paired with either qualitatively different unconditioned stimuli (US) or with a single US that differs in intensity (Molina et al., 1991; Spear et al., 1988). Assuming that preweanling rats did not treat cocaine and methylphenidate as a common US, unitization may explain the results from the cross-sensitization experiment. More specifically, if cocaine and methylphenidate were sufficiently discriminable (e.g., as a result of pharmacokinetic differences or differential activity at the serotonin transporter) then rats should have perceived the anesthesia and activity chambers as separate and isolated events. In this situation, cross-sensitization would not be evident because the pretreatment and testing chambers would be recognized as different environments. Although the potential relationship between unitization and one-trial sensitization is still speculative, it is possible that this phenomenon may explain why preweanling rats, but not adults, show context-independent behavioral sensitization when using the one-trial procedure.

In conclusion, the sensitized responding of rodents is characterized by a number of changes across ontogeny (for a review, see Tirelli, Laviola, & Adriani, 2003), not the least important of which is the ability of preweanling rats to show one-trial context-independent behavioral sensitization. An obvious possibility is that these various ontogenetic differences are due to the immaturity of neural systems underlying the nonassociative components of behavioral sensitization (e.g., the mesocorticolimbic dopamine system and glutamatergic systems). Available evidence suggests otherwise, however, because dopamine (D1 and D2) and

glutamate (NMDA and nonNMDA) receptor levels, and other indices of dopaminergic and glutamatergic functioning (e.g., coupling with G proteins and adenylyl cyclase, etc.), have reached nearly adult values by PD 15 (Broaddus & Bennett, 1990; Gelbard, Teicher, Faedda, & Baldessarini, 1989; Insel, Miller, & Gelhard, 1990; Jung & Bennett, 1996; Miller, Johnson, Gelhard, & Insel, 1990; Nansen, Jokel, Lobo, Micevych, Ariano, & Levine, 2000; Rao, Molinoff, & Joyce, 1991; Sales, Martes, Bouthenet, & Schwartz, 1991). Moreover, NMDA receptor antagonists modulate the development of psychostimulant-induced sensitization in a similar manner in preweanling and adult rats (Duke, O'Neal, et al., 1997). Instead, ontogenetic differences in behavioral sensitization may be due to age-dependent changes in associative learning. An obvious possibility is that associative processes are incapable of modulating the neural (nonassociative) mechanisms responsible for mediating the one-trial behavioral sensitization of preweanling rats. Another possibility is that the associative/perceptual process of unitization, which is largely restricted to early development, allows preweanling rats to perceive the different cocaine-paired environments as an integrated event or object. If preweanling rats do, in fact, treat the different chambers as equivalent, then sensitized responding should occur independent of environmental context.

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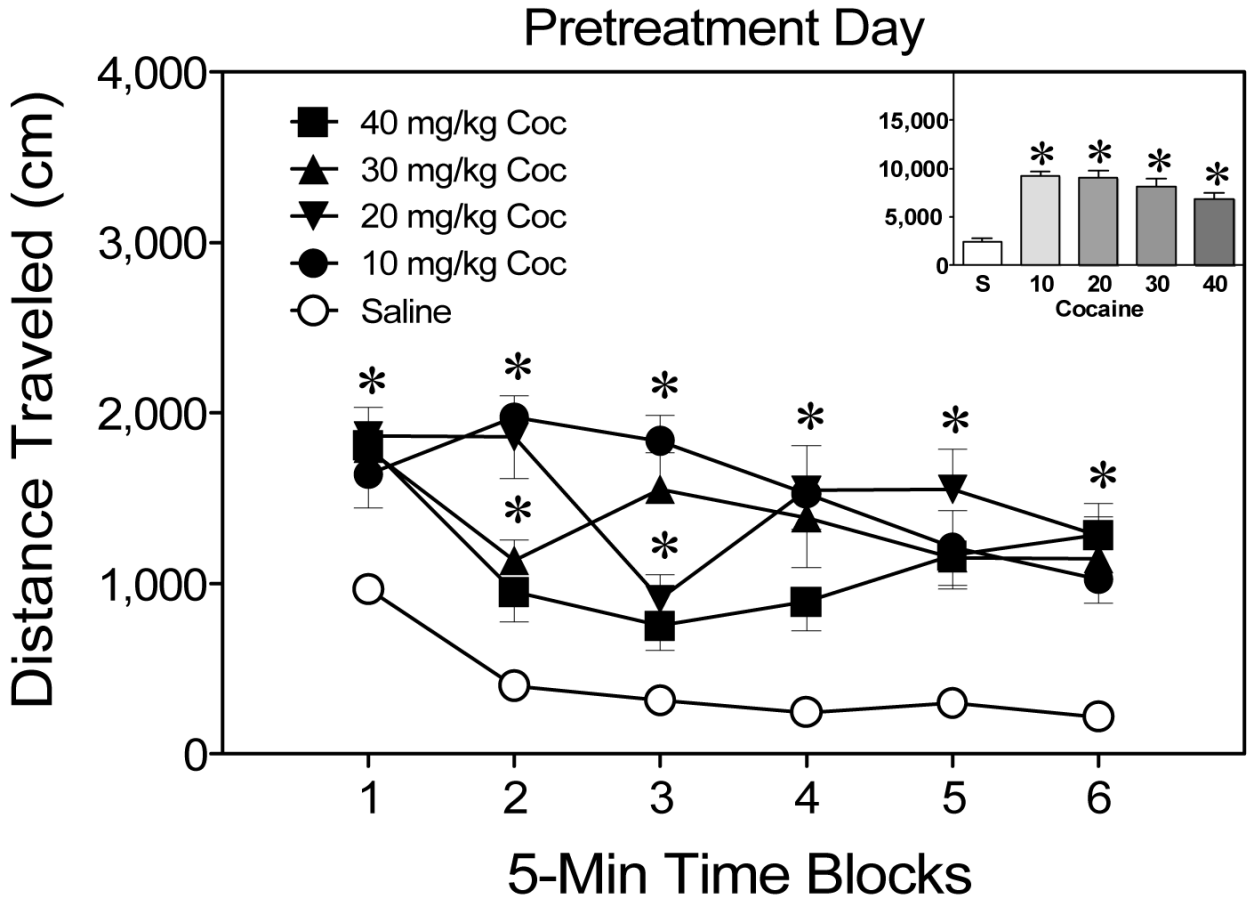

Figure 1.
Mean distance traveled scores (+*SEM*) of preweanling rats injected with cocaine (0, 10, 20, 30, or 40 mg/kg, ip) and placed in activity chambers on the pretreatment day (i.e., PD 19). The inset shows mean distance traveled collapsed across time blocks 1–6. *Significantly different from the saline group ($p < .05$).

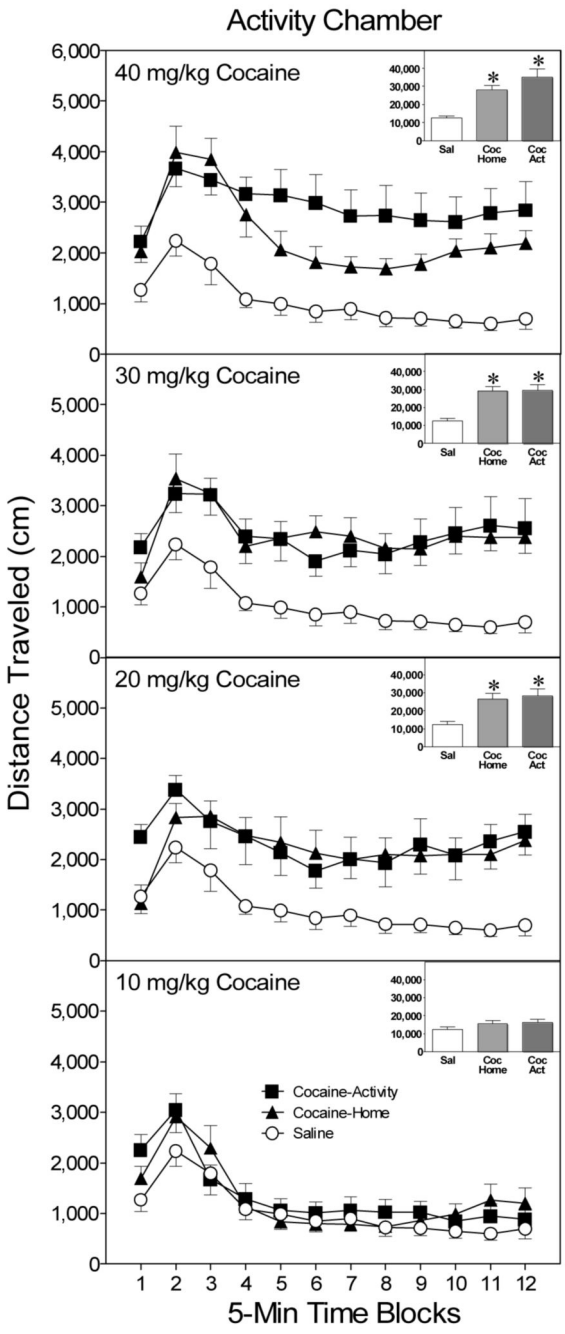

Figure 2.

Mean distance traveled scores (+*SEM*) of preweanling rats (*n* = 8 per group) given a challenge injection of cocaine (20 mg/kg, ip) prior to placement in activity chambers on PD 20. Rats in the cocaine-activity groups (*filled squares*) had been pretreated with cocaine (10–40 mg/kg, ip) before being placed in the activity chamber on PD 19, while rats in the cocaine-home groups (*filled triangles*) had been injected with cocaine 30 min after being returned to the home cage. The saline group (*open circles*) was injected with saline at both time points. The inset shows mean distance traveled collapsed across time blocks 1–12. *Significantly different from the saline group ($p < .05$).

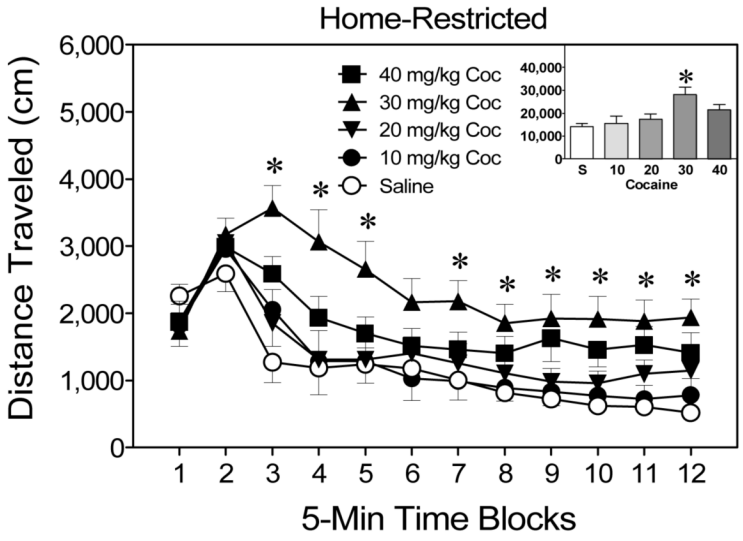

Figure 3.

Mean distance traveled scores (+*SEM*) of preweanling rats (*n* = 8 per group) given a challenge injection of cocaine (20 mg/kg, ip) prior to placement in activity chambers on PD 20. Rats were pretreated with cocaine (0–40 mg/kg, ip) while being maintained in the home cage on PD 19. The inset shows mean distance traveled collapsed across time blocks 1–12. *Significantly different from the 0 mg/kg group ($p < .05$).

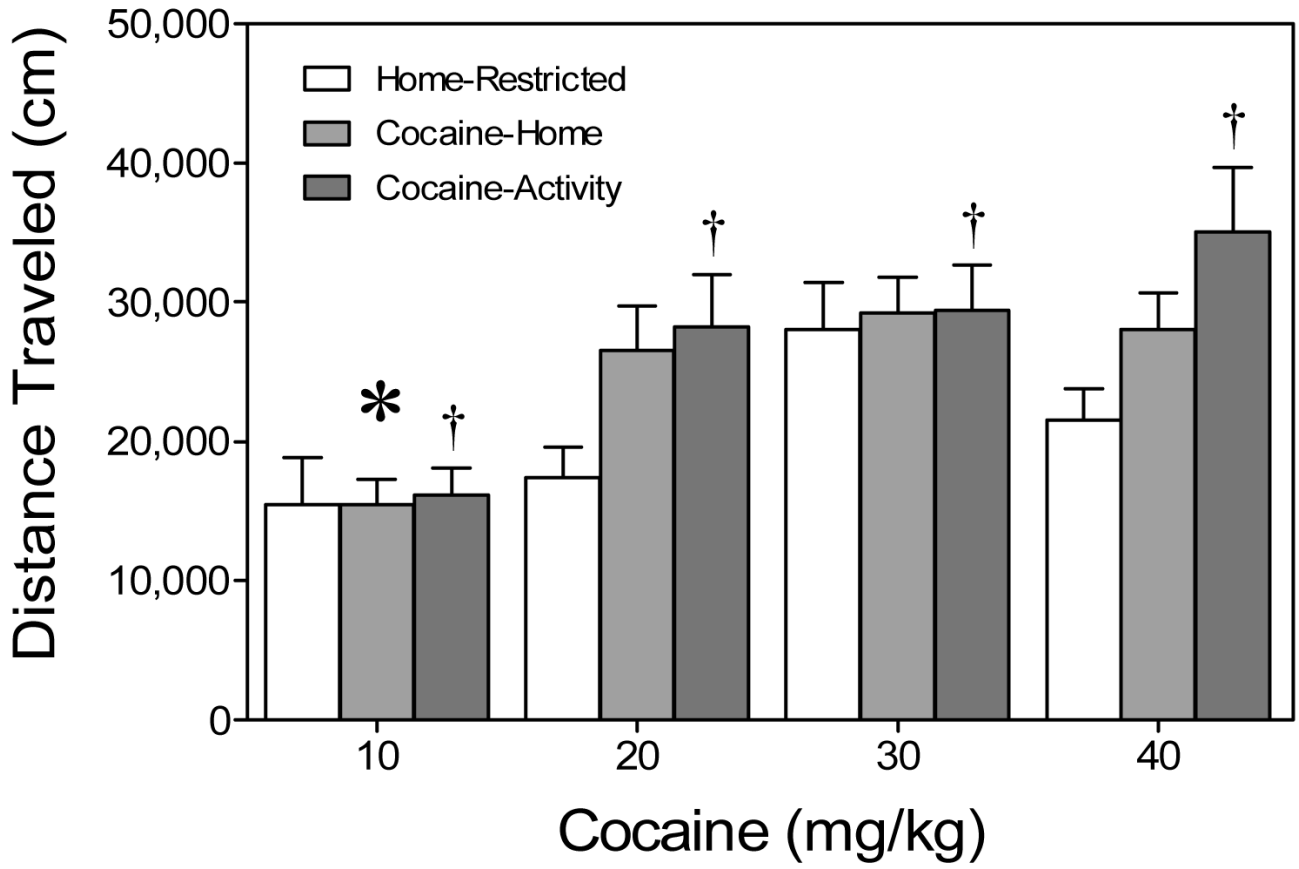

Figure 4.

Mean total distance traveled scores (+*SEM*) of preweanling rats (*n* = 8 per group) given a challenge injection of cocaine (20 mg/kg, ip) prior to placement in activity chambers on PD 20. These are the same rats as described in Figures 2 and 3. The cocaine-activity groups (*dark gray bars*) were pretreated with cocaine (10–40 mg/kg, ip) before being placed in the activity chamber on PD 19, while the cocaine-home groups (*light gray bars*) were injected with cocaine 30 min after being returned to the home cage. The home-restricted groups (*open bars*) were pretreated with cocaine (10–40 mg/kg, ip) while being maintained in the home cage on PD 19. *Significantly different from the other cocaine groups (Drug Dose main effect, $p < .05$). †Significantly different from the home-restricted condition (Condition main effect, $p < .05$).

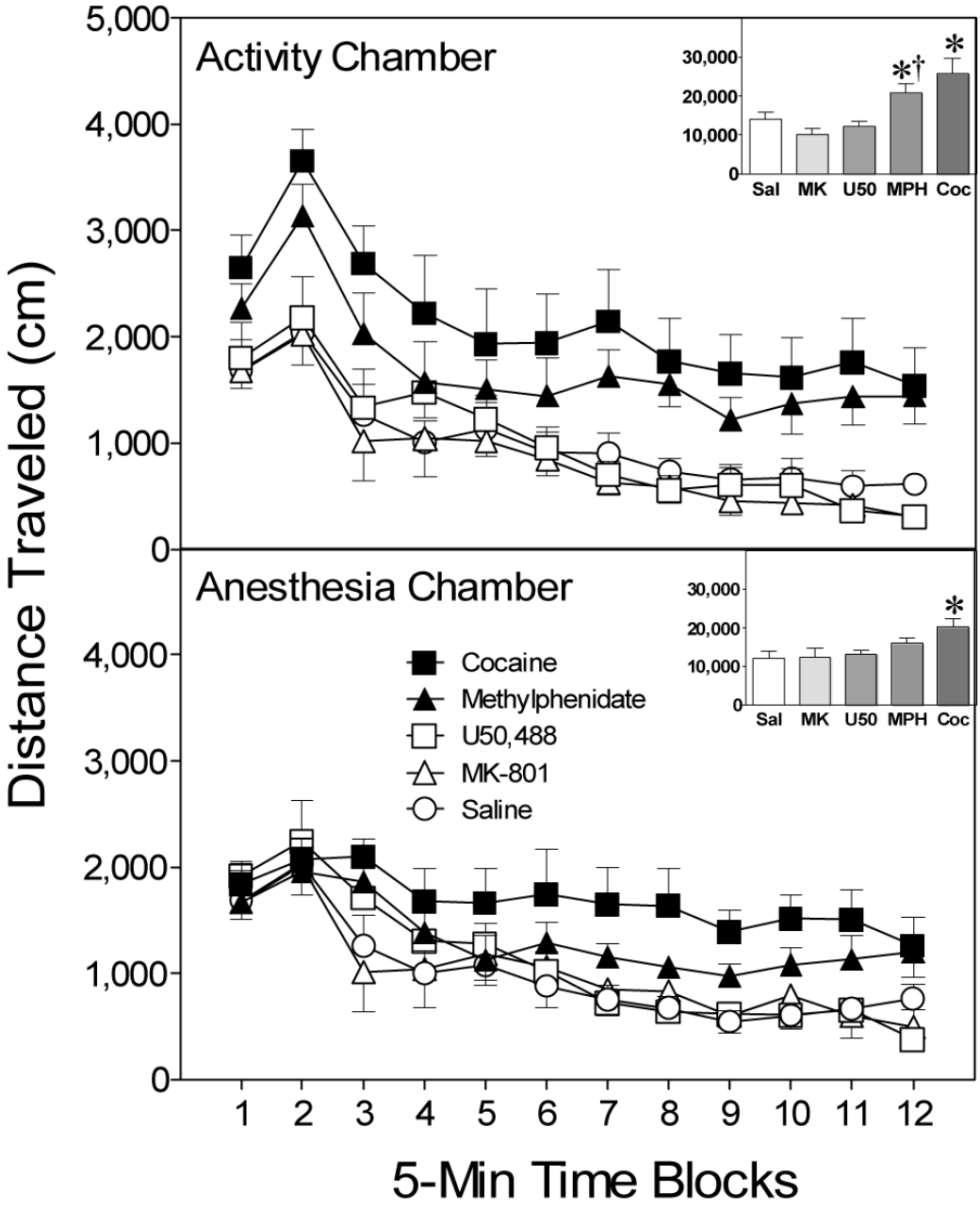

Figure 5.

Mean distance traveled scores (+*SEM*) of preweanling rats ($n = 8$ per group) given a challenge injection of cocaine (20 mg/kg, ip) prior to placement in activity chambers on PD 20. Rats had been pretreated with saline, MK-801 (0.3 mg/kg, ip), U50,488 (5 mg/kg, ip), methylphenidate (10 mg/kg, ip), or cocaine (30 mg/kg, ip) before being placed in activity chambers or anesthesia chambers on PD 19. The inset shows mean distance traveled collapsed across time blocks 1–12. *Significantly different from the saline group from the same chamber ($p < .05$). †Significantly different from the methylphenidate group from the anesthesia chamber ($p < .05$).

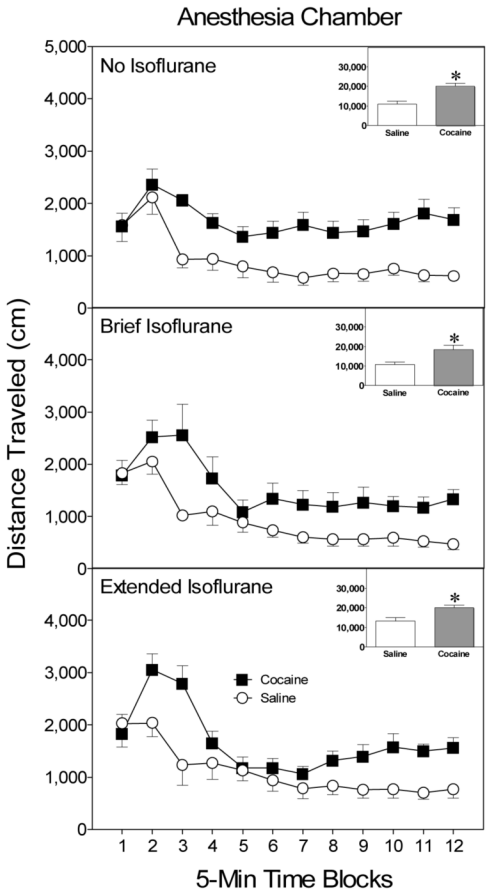

Figure 6.

Mean distance traveled scores (+*SEM*) of preweanling rats (*n* = 8 per group) given a challenge injection of cocaine (20 mg/kg, ip) prior to placement in activity chambers on PD 20. Rats in the various isoflurane conditions had been pretreated with saline or cocaine (30 mg/kg, ip) before being placed in the anesthesia chambers on PD 19. The inset shows mean distance traveled collapsed across time blocks 1–12. *Significantly different from the saline group ($p < .05$).