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ORIGINAL INVESTIGATION

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Effects of early handling on amphetamine-induced locomotor activation and conditioned place preference in the adult rat

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Abstract *Rationale*: Altered hormonal stress responsiveness has been implicated in psychostimulant responsivity, and early handling represents a mild environmental manipulation which alters the hormonal profile following stress exposure. *Objective*: The present experiments examined whether early handling in rats would alter locomotor effects of amphetamine, as well as cross-sensitization of locomotor responsiveness after chronic stress. Conditioned place preference (CPP) for amphetamine was also measured. *Methods*: Handling consisted of daily 15-min isolation periods from days 1–12 postnatally. Novelty- and amphetamine (0, 1.5 mg/kg)-induced locomotion were examined using circular corridors in adult rats that were either restrained repeatedly over 8 days or not disturbed prior to testing. The effects of handling on amphetamine (0, 1, 2, 5 mg/kg) conditioned place preference (CPP) were also examined following 3 days of drug-compartment pairings. *Results*: Early handling produced a more rapid post-stress recovery in corticosterone levels. Handled animals also exhibited a significant attenuation in amphetamine-induced CPP compared to non-handled controls. Locomotor responsiveness to novelty and amphetamine was not altered by early handling. Although no cross-sensitization was observed, evidence for stress sensitization was seen, but was unaffected by early handling. *Conclusions*: Handled animals showed an attenuated CPP for amphetamine, data suggesting that sensitivity to the reward value of drugs of abuse in adulthood may be susceptible to relatively minor environmental manipulations early in life. This effect of handling on CPP does not seem to reflect differences in locomotor sensitivity to amphetamine.

Key words Early handling · CPP · Reward · Stress · Sensitization · Locomotion

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Introduction

Isolating rat pups from the dam for short periods (e.g., 3–15 min or more) daily during early postnatal life is an environmental manipulation called "handling" that is known to exert long-term effects on the behavioral and hormonal stress responsivity of offspring. The most robust outcome evident in adulthood following this early experience is an attenuation of the plasma corticosterone response to stressors, including restraint (Meaney et al. 1989) and foot shock (Levine 1962). While baseline corticosterone levels generally are unaffected, handled animals typically show more rapid recovery to prestress corticosterone levels (e.g., Meaney et al. 1985) and sometimes show lower peak plasma corticosterone levels following a stressor (Meaney et al. 1989) than non-handled controls. Although early handling has been shown to delay aging-related neural and cognitive deficits (Meaney et al. 1988), behavioral ramifications of these robust alterations in the hormonal response to stress following early handling remain to be fully characterized in pre-senescent animals. While there are often cited reports that early handling reduces "emotionality" in adulthood as indexed by greater locomotion and fewer boli upon exposure to a novel open field arena (e.g., Denenberg and Whimbey 1963; Meaney et al. 1985), some recent research has failed to confirm these findings (Costela et al. 1995; Vallee et al. 1997).

Behavioral and hormonal responsivity to stressors has recently been shown to be related to several parameters implicated in the reward value of psychostimulants (Piazza et al. 1989, 1991). For instance, animals displaying high levels of locomotor activity when exposed to a novel environment (high responders) display prolonged elevations in corticosterone post-stress (Piazza et al. 1991), along with heightened amphetamine activation, greater amphetamine sensitization, and an increased likelihood of self-administering low doses of amphetamine (Piazza et al. 1989). Corticosterone may play a role in these effects, given that adrenalectomy or inhibition of corticosterone synthesis diminishes both locomotor stim-

ulation and acquisition of self-administration of psychostimulants (Piazza et al. 1994; Goeders and Guerin 1996).

A number of perinatal environmental manipulations that influence hypothalamo-pituitary-adrenal (HPA) responsivity have been shown to alter sensitization and acquisition of psychomotor stimulant self-administration. For instance, prenatal stress delays corticosterone recovery from stress in adult offspring (Henry et al. 1994), while also increasing locomotor responses to both novelty and an amphetamine challenge (Deminiere et al. 1992), facilitating amphetamine-induced sensitization (Henry et al. 1995), and elevating rates of self-administration of a low dose (30 µg) of intravenous *d*-amphetamine (Deminiere et al. 1992). Isolation during the preweaning period for relatively long intervals (e.g., 3 or more hours on multiple days) has been reported to both increase hormonal responses to stressors in adulthood (Plotsky and Meaney 1993), as well as attenuate locomotor responses to a novel environment and reduce responsiveness to alterations in the magnitude of sucrose reinforcement, as measured with both positive and negative contrast (Matthews et al. 1996).

Effects of postnatal handling on sensitivity to psychomotor stimulants and their sensitization have yet to be explored. Given the apparent importance of HPA activation in psychostimulant sensitivity, sensitization and self-administration (e.g., Goeders and Guerin 1996), the handling-related attenuation in later corticosterone responsivity to stressors would be expected to produce an animal that is less behaviorally sensitive to stressors as well as to both the locomotor activation and rewarding effects of psychomotor stimulants. These possibilities were explored in the current study by examining effects of early handling on locomotor activation in a circular corridor in response to novelty and amphetamine as well as the sensitization of these responses following chronic restraint stress; in addition, reward value of amphetamine, as indexed using a conditioned place preference (CPP) paradigm, was assessed. Effects of early handling were examined in both sexes, given evidence that females exhibit higher stress-induced increases in corticosterone (Kitay 1961), greater novelty- (Koos Slob et al. 1986) and amphetamine- (Savageau and Beatty 1981) induced locomotion, as well as increased break points on a progressive ratio schedule for intravenous cocaine self-administration (Roberts et al. 1989) when compared with males.

General methods

Offspring were derived from Sprague-Dawley breeding pairs. Animals were maintained on a 14/10 h light/dark cycle (lights on at 0700 hours), with ad libitum access to food and water. Cages were checked for births daily between 1100 and 1400 hours, with the day of birth designated postnatal day 0 (P0). On P1 litters were culled to eight to ten pups, and the handling procedure commenced and continued daily until P12. This treatment interval was chosen because handling has the strongest effect when administered during the first week of life, with minimal effect when pups are handled after the first 2 postnatal weeks (Meaney and Aitken 1985).

Entire litters were assigned to either the handling or no handling condition. At the onset of each handling session, the parents were removed from the home cage and the pups were placed individually for 15 min in cubicles lined with 5 cm of fresh pine shavings. Pups were then returned to the home cage, followed by return of the parents. The home cage shavings were replaced every 3 days during the handling period. Control litters were not manipulated other than the changing of bedding every 3 days and replenishing food and water as needed. On P21, the litters were weaned and housed in pairs of same-sex littermates in hanging cages. No more than one subject/litter was placed into any given test condition, and experimenters were blind to treatment at time of testing. All procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the university's Institutional Animal Care and Use Committee.

Analyses

Each data set was subjected to a Cochran test prior to conduct of analyses of variance (ANOVAs). In cases where data violated the assumption of homogeneity of variance, the dependent measure to be analyzed was subjected to $\log_{10}$ and square root transformations, with the transformation most effective at reducing the mean-variance correlation being used for analysis of that data set. All significant ANOVA results are mentioned in the text and were followed by analyses of simple effects and Newman-Keuls post hoc tests where appropriate. A P value of <0.05 was accepted as significant for all analyses.

Experiment I: recovery of corticosterone following acute restraint

This study was conducted to ensure that the early handling parameters employed in these experiments were effective in producing a faster return of corticosterone to basal levels after exposure to an acute stressor.

Materials and methods

The design of this experiment was a 2 (Handling Condition) × 2 (Gender) × 5 (Time of sample) factorial, with all variables between subject. Six to eight adult (P98–112) animals were tested in each experimental group, with a total sample size of 136 animals.

All animals were killed between 1330 and 1630 hours. To determine basal corticosterone levels, animals were removed from the home cage, rapidly transported a short distance to an isolated room, and decapitated within 30 s from the time of first being disturbed. All other animals were restrained via placement in half-cylinders (6 cm diameter, 18 cm long) for 30 min, with samples collected at 30, 60, 90, and 120 min after the onset of restraint. Animals in the 30-min (peak) group were killed immediately upon removal from restraint, while animals in the latter three groups recovered in isolation in hanging cages until time of death. Trunk blood was collected in heparinized tubes and held on ice until centrifugation at 3000 rpm for 20 min at 4°C. Plasma was then stored at –80°C until time of assay. Plasma corticosterone concentrations were determined in duplicate samples by radioimmunoassay (RIA) using assay kits supplied by ICN Pharmaceuticals (Costa Mesa, Calif., USA).

Results and discussion

A 2 (Handling) × 2 (Gender) × 5 (Time) ANOVA of the plasma corticosterone data revealed significant main ef-

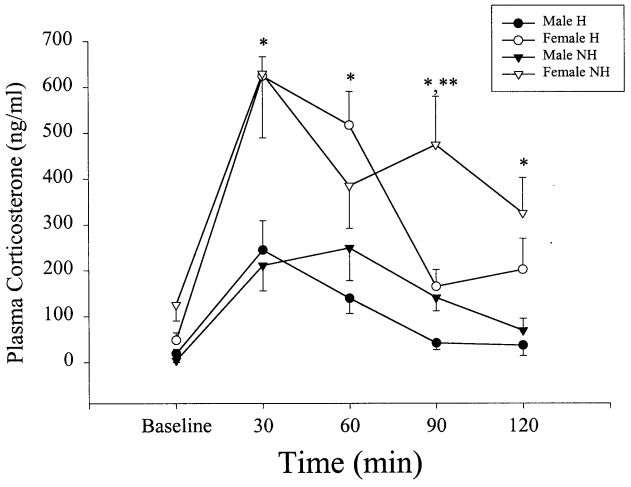

Fig. 1 Effects of handling and gender on recovery of corticosterone after restraint stress. Mean plasma corticosterone (ng/ml) for handled (*H, circles*) and non-handled (*NH, triangles*) male (*black symbols*) and female (*clear symbols*) animals (n=6–8/group) prior to (baseline), immediately upon removal from (peak), and at half-hour intervals following termination of a half-hour restraint stress. Error bars represent SEMs. *Indicates significant group differences between males and females in post-hoc analyses conducted on data collapsed over handling condition (P<0.05). **Indicates significant group differences between handled and non-handled animals in post-hoc analyses conducted on data collapsed across gender (P<0.05)

fects of Handling, Gender and Time tempered by significant interactions of Gender×Time [$F(4,116)=4.05$, $P<0.05$] and Handling×Time [$F(4,116)=2.50$, $P<0.05$]. Post-hoc analyses conducted on the data collapsed across gender to examine the Handling×Time interaction revealed that handled animals exhibited significantly lower corticosterone levels than non-handled controls at the 90-min interval (see Fig. 1). While corticosterone levels of the handled group were no longer significantly elevated above basal at 90 and 120 min after restraint onset, levels in non-handled animals remained elevated until they were killed. Post hoc analyses of the data collapsed across handling condition to explore the Gender×Time interaction revealed that females had higher plasma corticosterone levels compared to males at all points other than baseline. Corticosterone levels in males returned to baseline by 90 min, whereas levels in females remained elevated throughout. Similar gender differences in corticosterone responses to stress have been reported by others (e.g., Kitay 1961).

The results of this experiment document the effectiveness of the early handling procedure for producing a more rapid post-stress recovery in corticosterone levels. While the magnitude of this handling-related effect was similar to that observed by some others (e.g., Weinberg et al. 1995), more robust handling-induced decreases in post-stress corticosterone levels have been reported, such as those seen by Meaney and colleagues (1989). Given the importance of maternal-pup interactions in production of handling effects (e.g., Liu et al. 1997; Sapolsky 1997), one prominent methodological difference that may have contributed to the differing magnitude of handling effects between Meaney et al. (1989) and the present experiment may have been our use of a rearing environment consisting of both parents, in contrast to the maternal rearing situation typically used in handling studies.

Experiment II: initial drug/stress sensitivity and cross-sensitization

This experiment was designed to test whether early handling would affect locomotor responsivity to novelty or amphetamine, as well as development of cross-sensitization between prior chronic restraint stress and amphetamine. Response to novelty and stress/amphetamine cross-sensitization of stimulant-induced locomotion were of interest because both have recently been found to be related to an animal's corticosterone response to stress, and to the propensity of animals to self-administer psychostimulants (e.g., Piazza et al. 1989, 1991).

Materials and methods

The design used for this study was a 2 (Handling) × 2 (Chronic stress) × 2 (Drug challenge) × 2 (Gender) factorial. Seven to eight adult (P90–100) animals were placed into each of the 16 experimental groups, with a total of 131 animals tested.

The apparatus, test parameters and procedures were modeled after similar work done by Piazza and colleagues (1989). The apparatus consisted of circular corridors 12 cm wide with an internal diameter of 54 cm and inner and outer walls 48 cm in height. Locomotion was detected by eight photocell beams located 2.5 cm above the floor and spaced equally (i.e., every 45°) around the donut-shaped apparatus. A computer interfaced with the corridors recorded the number of beam breaks for an animal.

The chronic stressor used was repeated episodes of restraint occurring on a total of 5 days within an 8-day period. On each of these days, animals received two 30-min restraint sessions separated by 4 h. Based on the work of Deroche and coworkers (1992), intervals between stress days were varied to minimize the possibility of habituation to the stressor, with animals exposed to the stressor on treatment days 1, 2, 4, 7, and 8. The time of day of restraint was also varied, with the morning session being conducted between 0900 and 1200 hours, and the afternoon session 4 h later. Testing was conducted between 0900 and 1330 hours, 4 days after the last restraint session; non-stressed control animals were not manipulated until the test day.

On the test day, animals were weighed and then exposed to the circular corridor for 1 h to test for responsivity to novelty. Animals were then immediately injected intraperitoneally (IP) with *d*-amphetamine (1.5 mg/kg per ml) (Sigma Chemical Co., St Louis, Mo., USA) or an equal volume of 0.9% saline and returned to the circular corridor for an additional hour. Number of photocell interruptions during the four successive 15-min time bins of each hour-long test session was recorded.

Results and discussion

Response to novelty

A 2 (Handling) × 2 (Stress) × 2 (Gender) × 4 (Time bin) mixed factorial ANOVA of the square root transformed

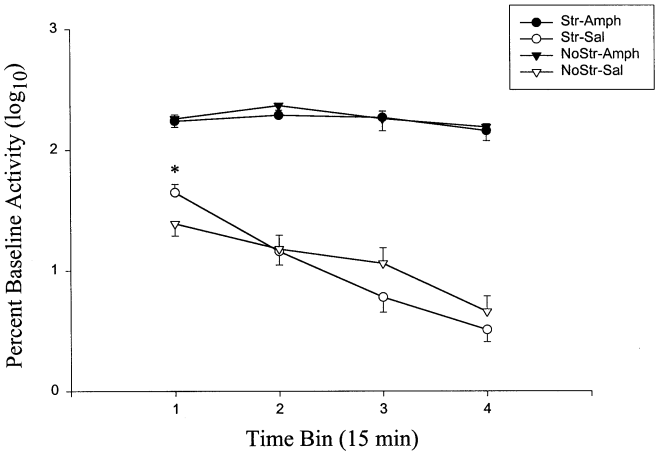

Fig. 2 Locomotor activity of chronically restrained (*Str, circles*) and non-stressed (*NoStr, triangles*) animals during second hour in circular corridor. Animals were given 1.5 mg/kg amphetamine (IP) (*Amph, dark symbols*) or saline (*Sal, clear symbols*) immediately prior to testing. Locomotor activity was calculated for each animal as a percentage of photocell interruptions during the initial hour followed by a $\log_{10}$ transformation. Data are collapsed across handling condition and gender. Error bars represent SEMs. *Indicates significant differences between stressed and non-stressed animals treated with saline on test day ($P<0.05$)

activity data revealed a significant main effect of Stress [$F(1,123)=12.18$, $P<0.05$], with previously restrained animals locomoting more (9.05±0.20) than non-restrained controls (7.96±0.23). There was also a significant interaction between Gender and Bin [$F(3,369)=3.69$, $P<0.05$], with females being more active than males, especially during the latter bins (data not shown). No main effects or interactions involving handling were observed.

Stress sensitization and cross-sensitization

Post-injection locomotor activation of each animal was expressed as a percentage of that animal's average activity during the preceding novelty exposure (see Piazza et al. 1989). A 2 (Handling) × 2 (Stress) × 2 (Drug) × 2 (Gender) × 4 (Time Bin) mixed factorial ANOVA of the log transformed data revealed significant main effects of Gender, Drug, and Bin as well as interactions involving Gender×Bin and Drug×Bin, with all of these effects tempered by two higher-order interactions.

Post-hoc analyses exploring the significant three-way interaction of Gender×Handling×Bin [$F(3,345)=3.25$, $P<0.05$] revealed that while handling did not alter activity in animals of either sex, females were more active than males at all time bins in handled animals, and during the last three time bins in the non-handled group (data not shown). The significant three-way interaction of Stress×Drug×Bin [$F(3,345)=2.98$, $P<0.05$] reflected that amphetamine-treated animals were consistently more active than animals injected with saline, with previously stressed animals given saline exhibiting significantly higher activity levels than non-stressed controls during the first time bin (see Fig. 2).

Thus, previously stressed animals were found to be more active in a novel environment and initially more responsive to saline injection than animals not exposed to chronic stress, suggesting stress sensitization. No evidence for cross-sensitization was seen, nor did early handling exert any effect on stress sensitization or the locomotor response to novelty or amphetamine.

Experiment III: amphetamine-induced conditioned place preference

This experiment was designed to determine whether early handling alters the reward value of amphetamine as indexed using CPP (see Carr et al. 1989 for review). While *d*-amphetamine has been shown to support CPP (Swerdlow and Koob 1984; Mackey and van der Kooy 1985), the effect of handling on such conditioning has not been previously explored.

Materials and methods

The design of the study was a 2 (Handling) × 4 (Dose) × 2 (Drug Side) × 2 (Gender) factorial, with all variables between-subject. Four to five adult animals (P62 at the start of training) were tested in each of the 32 experimental groups, with a total of 139 animals used. The variable Drug side refers to the side of the CPP chamber (white or black) paired with the drug injection; such counterbalancing has been shown to be important to the interpretation of CPP results (Heinrichs and Martinez 1986).

Conditioning and testing were conducted in wooden chambers divided into three compartments by guillotine doors. The two outer compartments were of equal size (25×22×30 cm), and each had a photocell beam located 5 cm into the compartment from the center compartment and 2.5 cm above the floor. One outer compartment had white walls and a metal rod floor over cedar shavings, while the other had black walls and a wire mesh floor over pine shavings. The center compartment (13×22×30 cm) had gray walls with a solid wooden floor and a photocell beam located midway in the chamber 2.5 cm above the floor.

Each animal was given 3 days of training, with two trials given each day. In the morning (approximately 1000 hours), each animal was given an IP saline injection (1 ml/kg) immediately prior to being placed in one of the two distinct outer compartments of the chamber for 30 min. Five hours after the morning trial, animals were given a second training trial consisting of an IP *d*-amphetamine injection (0, 1, 2, or 5 mg/kg per ml), immediately followed by confinement to the other outer compartment for 30 min. The test session was conducted on day 4, at a time of day midway between the morning and afternoon sessions of the previous days. Each animal was placed in the central gray compartment and the guillotine doors removed, allowing the animal free access to all three compartments for a 15-min test session. Time spent in each compartment was detected by the photocell beams and recorded by a computer interfaced with the photocells. Percentage of time spent in the drug-paired compartment relative to the combined time spent in the two outer chambers as well as relative to the total test time were used for analysis of CPP; analogous findings were obtained with both ways of calculating CPP, and hence for brevity only the former analyses are presented. Number of photocell interruptions was used as an estimate of locomotor activity during the preference test.

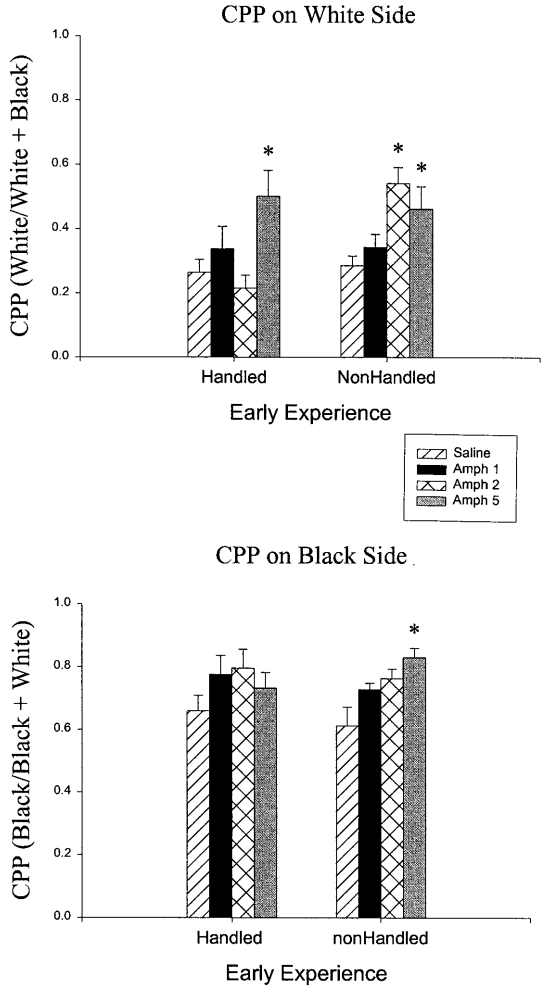

Fig. 3 Mean CPP ratio (time in drug-paired chamber/time in both conditioning chambers) for white and black chambers as a function of conditioning dose and whether animals experienced early handling. Data are collapsed across gender. Error bars represent SEMs. *Indicates significant increase in CPP ratio compared to similarly treated saline group

Results and discussion

A 2 (Handling) × 2 (Drug side) × 4 (Dose) × 2 (Gender) between-subjects ANOVA on the time spent in the drug-paired chamber expressed as a percentage of time spent in the two conditioning chambers revealed a significant Handling×Drug side×Dose interaction [$F(3,107)=3.65$, $P<0.05$] (see Fig. 3). Handled animals given only the highest dose of amphetamine in the white chamber spent a greater percentage of time in that chamber relative to animals given saline. In contrast, CPP in non-handled animals reached asymptote at a moderate dose of amphetamine, with significant CPP evident following pairings of this chamber with both moderate (2 mg/kg) and high (5 mg/kg) doses of the drug. Similar asymptotic performance in amphetamine-induced CPP despite further dose augmentation is frequently observed (e.g., Spyraki et al. 1982). When drug exposure was paired with the black compartment, non-handled animals given the high dose of amphetamine developed a preference for the black compartment, while handled animals failed to show a preference for the black compartment at any dose. Thus, regardless of which side was paired with amphetamine, handled animals exhibited an apparent decrease in the reward value of amphetamine as indexed in terms of CPP.

The ANOVA conducted on the number of photocell beam breaks as a measure of activity during the CPP test revealed only that females (155.0±4.4) were more active than males (138.2±4.5) [$F(1,107)=4.09$, $P<0.05$]. Consequently, handling-associated alterations in CPP do not appear to be related to any handling-induced alteration in locomotion during the preference test.

General discussion

Behavioral alterations were evident in adult animals subjected to an early handling procedure that was effective in producing a faster post-stress restoration of basal corticosterone levels in adulthood. Handled animals exhibited attenuated CPP for amphetamine when compared with non-handled controls, whereas no handling effects were evident in terms of locomotion in response to novelty or amphetamine, or in the development of stress sensitization in the circular corridor.

Early handling did not influence activity of adults tested in the circular corridor, although early handling is often associated with increased exploration in novel situations (e.g., Meaney et al. 1985). Nevertheless, similar negative findings (Costela et al. 1995; Vallee et al. 1997) and even decreases in open field locomotion (Ogawa et al. 1994) have been recently reported in adult animals exposed early in life to maternal separation procedures that also were effective in producing faster post-stress recovery of corticosterone in adulthood. The particular testing situation used seems to influence the nature of the behavioral alterations observed (Vallee et al. 1997).

While no handling effects on locomotion were evident, chronic stress increased activity in response to initial exposure to the circular corridor as well as to the presumably mild stress of saline injection. Although not previously reported in work using circular corridors (Deroche et al. 1992), this apparent stress sensitization is reminiscent of other reports of chronic stress-induced sensitization to subsequent stressors evident using other behavioral measures, including latency to drop from a hanging wire (Ottenweller et al. 1992) and acoustic startle response (Groves and Thompson 1970; Servatius et al. 1994). In contrast to the evidence for stress sensitization, attempts to induce cross-sensitization were largely unsuccessful. Only one dose of amphetamine was chosen for examination, and it is possible that this dose resulted in maximal locomotor stimulation in the circular corridors, thereby masking any potential expression of cross-sensitization. While the dose of amphetamine used in this experiment was the same as that used by Piazza and colleagues (1989) in demonstrating cross-sensitization,

our animals were activated by the drug throughout the entire post-injection hour, while the animals of Piazza's group (1989) although initially activated by amphetamine, returned to near baseline by the end of the hour.

The lack of any observed effects of early handling on stress sensitization is interesting, given the altered corticosterone response of handled animals after exposure to restraint stress (Meaney et al. 1989; present study) and the reported importance of this hormonal response to stress for the development of psychostimulant sensitization (Cador et al. 1993; Deroche et al. 1995). However, the current experiments did not directly assess the hormonal response of handled animals to the circular corridors. As with the effects of perinatal stress models on later behavioral responses to novelty (Vallee et al. 1997), the hormonal alterations seen in these animals may be apparatus-specific.

In contrast to the lack of impact of early handling on locomotor responses to stress and novelty in the circular corridor, handling was observed to decrease the apparent reward value of amphetamine as indexed in terms of amphetamine-induced CPP. This pattern of results is particularly interesting given apparent similarities in the neural substrates of drug-induced locomotion and reward (Wise and Bozarth 1987). Yet, analogous dissociations have been observed between the effects of various manipulations on reward value and locomotor activation in other testing situations, including ethanol-induced CPP in selectively bred murine lines (Cunningham et al. 1992) and acquisition of cocaine self-administration in rats after an environmental rearing manipulation (Phillips et al. 1994).

The finding of an apparent decrease in the reward value of amphetamine as indexed by CPP in handled animals is, to our knowledge, the first report of a possible alteration in the reward value of any drug of abuse after early handling. Alternatively, the differences seen in the current data could also possibly reflect an effect of early handling on responsiveness to multiple injections of amphetamine. Given that this early handling procedure also produced an enhanced post-stress recovery of corticosterone (see expt 1), together these findings are reminiscent of previous data showing a positive relationship between sensitivity to the reward value of amphetamine and the duration of elevated corticosterone following stress exposure (Piazza et al. 1991). The effect of handling on CPP was equally apparent in both genders, confirming previous work showing a lack of gender differences in CPP for cocaine in mice (Laviola and Dell'Omo 1997). The handling effect was also apparent following the pairing of amphetamine injection with either side of the conditioning/test apparatus, although a higher dose of amphetamine was required to support CPP when drug was paired with the black chamber. The effect of side of conditioning was probably related to the natural preference of these animals for the black compartment, with this elevated baseline making expression of a further CPP after drug experience in the black chamber more difficult to detect. Of course, CPP is only one paradigm used to examine the reward value of drugs of abuse. As with all approaches, it has advantages and disadvantages (e.g., see Carr et al. 1989; Bardo 1998 for review). Hence conclusions derived using this approach should ultimately be confirmed using procedures such as drug self-administration, work that is currently ongoing in our laboratory.

The neuronal mechanism(s) through which corticosterone affects addictive potential is unclear to date. One exciting connection between corticosterone and drug-seeking behavior is the presence of glucocorticoid (GC) receptors on the dopamine-containing neurons of the ventral tegmental area (Harfstrand et al. 1986), which project to the nucleus accumbens. These GC receptors are capable of modulating release of dopamine from the mesolimbic pathway (Rothschild et al. 1985), a neural system known to be important for the reward value of stimulants (Roberts et al. 1980; Roberts and Koob 1982). Given the well characterized alterations in corticosterone levels following early handling (e.g., see Meaney et al. 1985), the current finding that this early manipulation is effective in altering the later reward value of amphetamine suggests that early handling may provide an exciting model with which to explore further the relationship between stress hormone profiles and propensity to seek out drugs of abuse.

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