THE EFFECTS OF PERINATAL CADMIUM EXPOSURE ON BEHAVIORAL SENSITIZATION TO MORPHINE

A Senior Honors Thesis

By

KELLY RANAE SMITH

Submitted to the Office of Honors Programs
& Academic Scholarships
Texas A&M University
In partial fulfillment of the requirements of the

UNIVERSITY UNDERGRADUATE
RESEARCH FELLOWS

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Group: Psychology

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Approved as to style and content by:

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(Executive Director)

April 2000

ABSTRACT

The Effects of Perinatal Cadmium Exposure on

Behavioral Sensitization

to Morphine. (April 2000)

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This study examined the effects of developmental cadmium exposure on morphine-induced locomotor activity. Adult female rats were exposed to 0 ppm, 25 ppm and 50 ppm cadmium via an adulterated food source for 30 days prior to breeding. This exposure continued throughout gestation and for the initial 15 days of lactation. Male pups of the dams were then administered 10 mg/kg morphine or vehicle injections at PND 60 and locomotor activity was monitored. Days 1,7, and 14 produced no separation of exposure groups. On Day 21 attenuation of morphine-induced behavioral sensitization was evident among animals in the 25 ppm and 50 ppm exposure groups. Administration of dopamine D1 receptor-type antagonist SCH 23390 produced a dose-related decrease in locomotor activity across all groups. D2 receptor-type antagonist eticlopride showed no significant separation of responding among exposure groups. Context effects were not found to play a role in these findings.

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INTRODUCTION

The societal implications of drug abuse are incalculable. Given the magnitude of the problem, it is not surprising that vast amounts of research have been conducted in an attempt to elucidate the various physiological dynamics of drug use and addiction, and adjunctive factors that might alter these dynamics. Yet, one area of research that has largely been ignored is the possible influence of environmental pollutants on drug seeking and drug taking behaviors. Heavy metals, such as cadmium and lead, have been shown to alter the effects of cocaine and morphine in adult rats. Self administration of cocaine increases with adult cadmium exposure (Nation, Livermore, Bratton & Schenk, 1996), while the discriminitive properties of cocaine are reduced in animals exposed to cadmium, as demonstrated by drug discrimination studies (Nation & Miller, 1999). Elsewhere it has been shown that adult cadmium exposure also produces an attenuation of behavioral sensitization, a heightened sensitivity to a chronically administered drug, induced by chronic morphine administration (Nation, Miller, & Livermore, 1997). Increases in ethanol consumption also have been observed after adult cadmium exposure. (Nation, Pugh, Von Schultz, Bratton & Clark, 1989). In a like manner to cadmium, lead exposure has been shown to produce effects similar to those described above, altering behavioral sensitization to cocaine (Nation, Livermore, & Burkey, 1996; Grover, Nation & Bratton, 1993) as well as the effects of ethanol consumption. (Burkey, Nation & Bratton, 1994).

With respect to exposure vectors of heavy metals, it is of particular interest here that cadmium has been shown to accumulate in tobacco leaves (Yue, 1992), which poses a particular risk for cadmium toxicity for smokers. This route of exposure and the extraordinarily long half-life of cadmium (approximately 30 years; Berman, 1980) can result in an accumulation of the

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This thesis follows the style and format of *Experimental and Clinical Psychopharmacology*.

metal in the body after repeated exposure. In fact, it has been shown that tobacco users have elevated blood cadmium levels relative to non-smokers and those who smoke approximately two pack of cigarettes per day have twice the blood cadmium levels as non-smokers (Piascik et al., 1985; Wu et al., 1995). Non-tobacco users also have been shown to be at risk as a result of exposure to second-hand (passive) cigarette smoke (Shaham et al., 1996). And, smoking has been found to be prevalent among those who abuse drugs, with opiate-dependent individuals having an extremely high prevalence of tobacco use (Frosch, Nahom, Shoptaw & Jarvik, 2000). Because of this demonstrated relation between tobacco use and drug use, it would seem reasonable to explore linkages between cadmium and opiates.

Of the studies that have examined metal and drug interactions, some of the more compelling findings have come from behavioral sensitization studies. Behavioral sensitization refers to an increase in locomotor activity that is evident following chronic drug administration. This increase in locomotor activity is thought to be the result of a supersensitivity to the drug that occurs with repeated administration. Of special relevance to this project, is the notion that the phenomenon may serve as an animal model for drug seeking and drug taking behaviors. It is thought that sensitization in humans could contribute to the development of drug dependence and addiction (Laviola, Wood, Kuhn, Francis & Spear, 1995). Given the above discussion, it must be considered that cadmium exposure could lead to an alteration in the use and abuse of morphine.

The development of behavioral sensitization is believed to occur through mechanisms of the nucleus accumbens (NA) and ventral tegmental area (VTA) of the brain. These areas have been implicated in the drug reward pathway, and it is thought that behavioral sensitization is also the result of altered neurotransmitter levels in this area of the brain, though the role of the VTA in this pathway is still debated (Jeziorski & White, 1995). Opiates bind to μ-opioid receptors presumably at γ-aminobutyric acid (GABA) neurons of the VTA. These neurons play an inhibitory role in regulating dopamine (DA) firing rates in the VTA, ultimately limiting the

amount of dopamine release in the NA. Morphine and other opiate derivatives competitively bind to the opioid receptor, thereby reducing GABA inhibitory action. As this loss of inhibition occurs, dopaminergic transmission in the VTA, and consequently dopamine availability in the NA ,is largely uninhibited resulting in an increase in dopamine present in the NA (Julien, 1998).

The use of dopamine antagonists lends support to the proposed role of dopamine in behavioral sensitization, although studies investigating the effects of the administration of dopamine antagonists on behavioral sensitization have not been definitive. One study found that administration of the D1 receptor-type antagonist SCH 23390 resulted in an increase in ambulation in mice, thereby indicating an increase in the sensitivity seen with behavioral sensitization (Kuribara, 1995). Others, however, have shown that administration of SCH 23390 and a D2 antagonist eticlopride result in a decrease in the heightened locomotor activity induced by behavioral sensitization to morphine (Jeziorski & White, 1995). Also of interest is that although the administration of dopamine antagonists such as SCH 23390 and eticlopride block the expression of behavioral sensitization, they do not block its development. Because behavioral sensitization is observed after dopamine antagonist treatment is terminated, even if morphine has never been administered in the absence of the antagonist, it appears that the development of behavioral sensitization is dependent on μ-opioid receptor stimulation. Yet, treatment with dopamine antagonists concurrently with morphine does not result in apparent increases in locomotor activity induced by behavioral sensitization. This suggests that stimulation of dopamine receptors is necessary for the expression of behavioral sensitization, but not for its development (Jeziorski & White, 1995). Within this context, it would be of interest to determine if cadmium results in differential sensitivity to dopamine antagonists SCH 23390 and eticlopride, indicating that the dopamine dependent pathway that results in the expression of increased locomotor activity due to behavioral sensitization to morphine, has somehow been altered by cadmium exposure.

Although several studies have investigated the interactions of cadmium and drugs like cocaine and morphine in adult rats, no studies to date have examined the possible effects of developmental cadmium exposure on drug behaviors later in life. Considering the aforementioned parallels suggested between behavioral sensitization as a laboratory phenomenon and drug taking and seeking behaviors, careful inspection of such possible interactions would seem warranted. The importance of understanding possible consequences of developmental cadmium exposure is underscored by the fact that 20.4% of American women smoke during pregnancy (National Institute of Health, 1996). Because cadmium is readily transferred from the mother to the fetus and cadmium levels are elevated in women who smoke, the fetus of a woman who smokes during pregnancy is at risk for high levels of cadmium exposure. Because cadmium alters behavioral responses to morphine and because a neonate can be exposed to high levels of cadmium in utero and while nursing, it is possible that perinatal cadmium exposure (exposure during gestation and lactation), could result in an alteration in drug responsiveness later in life. Accordingly, this study was designed to investigate the effects of perinatal cadmium exposure on behavioral sensitization to morphine. Additionally, antagonists SCH 23390, a D1 antagonist, and eticlopride, a D2 antagonist, were used to test for differential sensitivity to dopamine antagonism.

Method

Animals and Exposure Regimen

All aspects of the research reported here were approved by the University Laboratory Animal Care Committee. Adult female Sprague-Dawley female rats (Charles River) were matched on initial body weight across groups. Each female rat was exposed to cadmium via an adulterated food supply. Following 30 days of exposure to their respective cadmium doses,

females were bred to nonexposed males. Males were removed from the home cage once females tested positive for copulatory plugs. Females continued to receive their daily doses of cadmium throughout the gestational period and for the first 15 days of lactation (see below). Tap water was available ad libitum in the home cage.

Litters were culled to 8 pups seven days after parturition rather than earlier to permit a more reliable sex determination of pups via visual inspection of genital spacing. Sixteen male pups from 10 dams exposed daily to 0 ppm cadmium, 13 male pups from 3 dams exposed to 25 ppm cadmium, and 9 male pups from 1 dam exposed to 50 ppm cadmium, were included in the investigation. The remaining pups were used in other research projects. During the first 15 days of lactation, except for the day of parturition, dams continued to be exposed to their respective diets. The resulting procedure permitted perinatal cadmium exposure within an experimental framework wherein pups were unable to gain access to lead postnatally via routes other than the maternal milk supply. Dams were placed on standard rat chow at PND 15 to ensure that pups did not begin feeding on cadmium supplemented rat chow.

On PND 21, pups were weaned and for the remainder of the study placed on ad libitum standard rat chow diets, and they had continuous access to a tap water supply that contained no added cadmium. All animals were individually housed from PND 21 until the study was completed. Prior to weaning, food intake and body weight readings were recorded weekly for dams and pups, and postweaning pup food intake and weight measures were recorded daily for the remainder of the study.

Apparatus

The test apparatus involved an automated Digiscan-16 system. (Omnitech Electronics, Inc., Columbus, OH). Activity monitors and cages were located in a sound-proof room with a 40 dB [SPL] white noise generator operating continuously. A multiplexor-analyzer in an adjacent room monitored beam breaks from the optical beam activity monitors and tracked the

simultaneous interruption of beams. The multiplexor-analyzer updated the animal's position in the acrylic cage (40 X 40 X 30.5 cm) every 10 ms using a 100% real-time conversion system. Computerized integration of the data obtained from the monitor afforded the recording of general activity using total distance (in cm) as the dependent measure.

Procedure

The selection of cadmium doses was made on the basis of pilot investigations that yielded blood cadmium levels falling within a clinically relevant range (≈35 μg/dl or less).
Male pups from each of the three exposure conditions (0, 25 and 50 ppm cadmium) were stratified according to body weight. Within given weight ranges, pups were randomly assigned receive either saline or morphine injections .

All efforts were made to place male pups from the same litter in different test conditions to control for possible litter effects. (cf. Holson & Pearce, 1992) Animals began activity testing on PND 60 and were randomly assigned to one of six test groups created by interacting cadmium-exposure condition (0, 25, 50 ppm) and type of injection (vehicle, morphine). Thus, the 6 groups used in this study were 0-Vehicle, 0-Morphine, 25-Vehicle, 25-Morphine, 50-Vehicle, and 50-Morphine. Animals receiving morphine were administered daily ip injections of 10 mg/kg morphine sulfate expressed as the salt, while vehicle controls received saline (1.0 ml/kg volume). In this initial phase of the project, animals were tested during 80 minute sessions each day for 21 successive days, in squads of four, counterbalancing by group. The animal was placed in the chamber immediately following the injection, at which time the room lights were turned off. This procedure was employed in order to increase the discriminatory properties of the injections. Previous cocaine investigations (e.g., Post et al., 1981) have shown that contextual cues contribute to augmented responding associated with repeated drug administration. Insofar as administering the injections, placement in the test chambers, turning off the test room lights and other pre-injection correlates serve in a feed-forward capacity, (as CSs), it is reasonable to assume

that reinstatement of such events could play an additive role in behavioral sensitization. We tested such a possibility by administering a vehicle only (0 mg/kg morphine) injection following initial sensitization testing (see procedures for Day 22 of testing). In all tests conducted in this study, total distance traveled (cm) was recorded post-injection across successive 5-min intervals for 80 minutes.

On Days 22-24, all animals within each of the three morphine-treated groups (0-Morphine, 25-Morphine, 50-Morphine) received successive daily injections of 0, 10, and 20 mg/kg morphine. This range of morphine doses has been shown to be sufficient to characterize the complete dose-effect function produced by increasing doses of the drug (Nation, Miller, & Livermore, 1997). Groups given vehicle injections (0-vehicle, 25-vehicle and 50-vehicle) continued to receive vehicle injections during this period.

Following one day of interpolated morphine or vehicle exposure (Day 25), antagonist doses were administered in random order beginning on Day 26. All animals in all 6 groups received an injection of the antagonist (SCH 23390 or eticlopride) 30 minutes prior to administration of 10 mg/kg morphine or vehicle and were placed in the activity chamber immediately after the morphine or vehicle injection. Antagonist injections were given in the home cage. SCH 23390 was administered on Days 26, 28 and 30. The doses administered were .01 mg/kg, .056 mg/kg and .1 mg/kg. Eticlopride was administered on Days 33, 35 and 37, with doses corresponding to those of SCH 23390. On the day following each dose of the antagonist, animals received only 10 mg/kg morphine or vehicle in order to reestablish baseline responding. During this period, at least one day of a vehicle (saline) pre-injection was administered in an effort to control for the possible development of cueing properties associated with the injection of the antagonist. Only with the administration of SCH 23390 was two days of morphine and vehicle exposure with a vehicle pre-injection required.

Analysis of variance (ANOVA) tests were performed on the behavioral data. In all cases throughout this report, Neuman-Keuls procedure for examining significant mean differences was employed as the post hoc test.

Results

Body Weight and Food Intake

A two-way repeated measures analysis of variance (ANOVA) Exposure Condition (0, 25. 50 ppm) x 6 Weeks (1-6) was performed to analyze possible differences in body weight and food intake among groups. A significant main effect of Exposure Group was found ($F(2,227)=268.48$, $p<.001$). The main effect for Week also revealed an acceptable level for statistical significance ($F(5,227)=1482.41, p<.001$). Also, body weights across all Exposure Conditions were significantly different from one another for all 6 Weeks ($p<.001$). An interaction of Exposure Condition x Week was also found ($F(10,227)=31.50$, $p<.001$). Subsequent post hoc analyses reveal that 25 ppm and 50 ppm cadmium exposed animals have significantly lower body weights than animals exposed to 0 ppm cadmium ($p<.001$) for all Weeks except for Week 1. The body weights of animals exposed to 25 ppm cadmium and 50 ppm cadmium were not found to be significantly different, except on Week 5 and Week 6 ($p<.05$),where it was observed that 50 ppm animals had lower body weights than 25 ppm animals.

An identical ANOVA performed on food intake found a significant main effect of Exposure Condition ($F(2,227)=23.36, p<.001$). Also, a significant main effect of Week was found ($F(5,227)= 83.00, p<.001$). The results of interaction tests showed a statistically significant interaction of Exposure Condition x Week ($F(10,227)=83.00, p<.001$). Post Hoc analyses determined that food intake was significantly lower for the 25 ppm cadmium Exposure Condition (mean=177 g/week) and the 50 ppm cadmium Exposure Condition (mean=149 g/week) than for the 0 ppm cadmium Exposure Group (mean=194 g/week) ($p<.05$). It was found that almost all

cadmium Exposure Group (mean=194 g/week) ($p<.05$). It was found that almost all weekly food intake values were significantly different from one another, with the exception of Week 5 and Week 6.

Behavioral Data

Figure 1 shows the mean total distance traveled for each exposure group across Days 1, 7, 14 and 21. Figure 1 profiles behavioral sensitization in each of the morphine-exposure groups, with locomotor activity being reduced for all groups on Day 1, but gradually increasing across Days 7, 14 and 21. This sensitization effect was attenuated for those animals exposed to 25 and 50 ppm cadmium.

Statistical confirmation of the group separation apparent in Figure 1, was provided by the results of separate 2-way (Exposure Condition x Type of Injection) analysis of variance (ANOVA) tests performed on the data for Days 1, 7, 14 and 21. These analyses revealed no significant main effects or interactions on Days 1, 7, and 14. However, on Day 21 a significant interaction effect of Exposure Condition x Type of Injection was found. ($F(2,32)= 4.85$, $p<.05$). Post hoc tests revealed that animals treated with morphine and exposed to 50 ppm cadmium showed significantly less locomotor activity than morphine treated controls ($p<.05$). Marginal differences in the same direction were shown for the comparison of group 0-morphine and group 25-morphine ($p=0.051$).

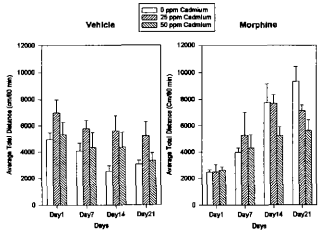

Figure 1 Morphine Sensitization at Days 1, 7, 14, and 21. Mean (± SEM) total distance traveled per daily session for 0 ppm, 25 ppm and 50 ppm cadmium groups on days 1,7, 14 and 21 of morphine behavioral sensitization testing.

The results of the dose effect test (Days 22-24) across exposure groups are seen in Figure 2. Administration of 0 mg/kg morphine (Day 22) resulted in no difference in locomotor activity across morphine-exposed groups or vehicle only groups. A dose effect was apparent, with locomotor activity being reduced relative to 10 mg/kg performances for all groups receiving an injection of 20 mg/kg morphine ($F(2,64)= 3.95, p<.05$). While there appears to be a trend for the 0-Morphine group to show higher mean total distance traveled than the 25- Morphine and 50-Morphine group; results of a three-way ANOVA revealed no main effects or interactions across the three doses of morphine administered that might indicate a separation of the 0-Morphine Exposure Condition and the 25-Morphine and 50-Morphine groups. .

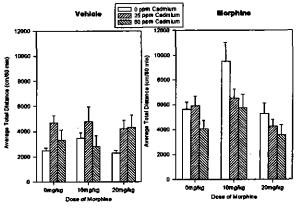

Figure 2 Dose Effect Data on Days 22-24. Mean (± SEM) total distance traveled (cm) per daily session for vehicle and morphine-treated groups at 0 mg/kg morphine, 10 mg/kg morphine and 20 mg/kg morphine. Note: Vehicle-treated animals did not receive morphine during dose effect testing.

Figure 3 depicts the average total distance traveled on those days during which the antagonist SCH 23390 was administered. Visual inspection of mean total distances of groups reveals that animals in both the vehicle and morphine groups that were exposed to 50 ppm cadmium consistently averaged lower total distance than those for the 0 ppm and 25 ppm conditions. Also, increasing doses of SCH 23390 effectively reduced locomotor activity for all animals across all groups. Statistical confirmations of these differences were provided in part by the finding of a marginally significant main effect for Exposure Condition ($F(2,32)= 2.58, p < .10$) Because of the absence of significant interactions between Exposure Condition and Type of Injection, it would seem that this effect resulted from decreased locomotor responding across both vehicle and morphine groups exposed to dams receiving 50 ppm cadmium.

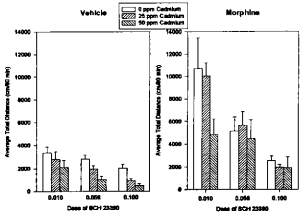

Figure 3 Doses of SCH 23390. Mean (± SEM) distance traveled (cm) for each group for entire daily session after administration of SCH 23390. All groups experienced a decrease in locomotor activity as a result of the administration of SCH 23390.

Administration of increasing doses of eticlopride reduced locomotor activity for 25-Morphine and 50-Morphine Exposure groups (See Figure 4). 0-Morphine groups showed anomalous responding to the highest dose of antagonist, .1 mg/kg, i.e., an unexpected rebound effect was observed at this highest dose. Examination of figure 4 reveals no apparent differential sensitivity to doses of eticlopride among the 25- Morphine and 50-Morphine Exposure Groups.

A three-way ANOVA revealed a significant interaction effect (Dose x Exposure Condition x Type of Injection) for eticlopride administration ($F(4,64)=4.88$, $p< .05$). Post Hoc analyses indicated that the dose of eticlopride resulted in differential locomotor activity depending on the level of cadmium exposure and type of injection. As with SCH 23390, a marginal main effect of Exposure Condition was found ($F(2,32)=2.67$, $p<.1$), suggesting that across both vehicle and morphine groups exposed to dams receiving 50 ppm cadmium. However, unlike the case for SCH 23390, the eticlopride data were not reliable across the range of doses tested here.

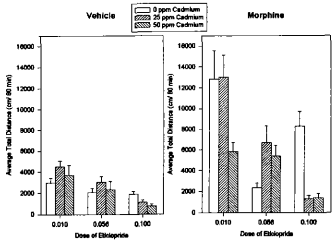

Figure 4 Doses of Eticlopride. Mean (± SEM) distance traveled (cm) for each group for entire daily session after administration of eticlopride.

Discussion

The findings from this study revealed that perinatal exposure to cadmium results in an attenuation of behavioral sensitization to morphine. This attenuation was observed as a decrease in mean locomotor activity across an 80 minute interval, and the cadmium-based antagonism of the locomotor-stimulating effects of morphine was most prominently expressed on Day 21 by animals born to dams exposed to 50 ppm cadmium. Marginal differences were observed for

group 25-Morphine on Day 21 as well. The finding of significantly lower locomotor activity among 50-Morphine animals indicates that behavioral sensitization was attenuated for this group.

These data, as well as results from the SCH 23390 test, reveal a possible alteration in the neurotransmitter systems previously implicated in the development and expression of behavioral sensitization as a result of developmental cadmium exposure. Such an alteration could be the result of a decrease in DA receptor viability or function. Insofar as dopaminergic activity is integral to the expression of morphine sensitization (Jeziorski & White, 1995) and given that cadmium is an established dopamine antagonist (Olivier, Guibert & Liviel, 1995), the observed attenuation of cadmium is not altogether surprising. What is noteworthy is that this effect was observed during the adult cycle, long after the exposure regiment was discontinued. Also, results from administration of SCH 23390 are instructive. Compromised DA levels resulting from a lack of dopamine receptors, or decreased receptor functionality, could explain the increased sensitivity of 50-Morphine animals to low doses of SCH 23390. That is, if functional DA receptors are reduced in these animals, any antagonistic effects exerted by SCH 23390, even at very low doses, would be amplified. Such effects could also explain the decreased locomotor activity of 50-Vehicle animals seen with the administration of SCH 23390, in comparison to 0-Vehicle and 25-Vehicle animals. For vehicle-treated animals, as well as morphine-treated animals, a decrease in functional receptors would result in more pronounced attenuation of locomotor activity at lower doses of SCH 23390 compared to animals exposed to 0 ppm cadmium.

Eticlopride data revealed significant interactions between the dose of eticlopride and cadmium pre-treatment. The unusual response of the 0-Morphine animals across .056 mg/kg and .1 mg/kg doses of eticlopride, i.e., an increase or rebound effect, points to the complexity of the differences in locomotor activity between the 0-Morphine groups and the 25-Morphine and 50-Morphine groups. Unlike the case for the control animals, the trend for 25-Morphine and 50-Morphine groups was a decrease in locomotor activity with an increase in eticlopride dose. This

trend among metal-exposed animals, which was not apparent among the controls, is compatible with previous research indicating that eticlopride administration results in a decrease in the locomotor effects of behavioral sensitization (Jeziorski & White, 1995).

Along with the novel finding of the attenuation of behavioral sensitization to morphine for the 50-Morphine group, more general patterns of responsiveness to morphine administration were observed and these patterns are in agreement with previous findings. For instance, sedative properties of morphine were observed, followed by a gradual development of the stimulatory properties of morphine (Jeziorski et al., 1994). One difference in the pattern of development of behavioral sensitization to morphine seen in all groups of developmental animals was a later onset of the stimulatory properties of morphine, relative to adult cases of cadmium exposure. In prior studies examining the effects of adult cadmium exposure to behavioral sensitization to morphine, behavioral sensitization was clearly established before Day 14 (Nation, Miller & Livermore, 1997). In developmental studies, such as this one, behavioral sensitization was not clearly evident until Day 21. This delayed establishment of behavioral sensitization was evident in all animals including 0-Vehicle animals, indicating that this was not an idiosyncratic effect associated with cadmium exposure.

Elsewhere, the dose effect data were consistent with previous findings (Nation, Miller & Livermore, 1997). In this regard it is worth noting that responding to 0 mg/kg morphine was similar for cadmium-exposed and control animals. At this dose, it was also evident that contextual stimuli were not a factor in the increases in morphine-induced locomotor activity (test Day 22). At 10 mg/kg morphine, increased locomotor activity patterns were again evident, as seen with previous exposure to this dose of morphine. Here, there appears to be a tendency for both cadmium exposed groups to show attenuation of this increased locomotion, but statistical analyses yielded no significant main effects or interactions. Locomotor activity was decreased for all animals that received a morphine injection at the dose of 20 mg/kg.

The finding of significant differences between the locomotor activity of animals exposed to cadmium indicates that the toxicant can alter pathways in the brain that are responsible for behavioral sensitization. The mechanism of this alteration is unclear and further research is necessary to explore the possibility of altered receptor viability or function. Investigation into how cadmium might alter the self administration of morphine is also of interest, as this would indicate an alteration in reward pathways thought to be responsible for drug taking and addictive behaviors. The levels of dopamine in the area of the NA are believed to be associated with the reinforcing effects of drug intake and previous research has shown that administration of antagonists lead to increased self-administration. (Nation, Livermore, Bratton & Schenk, 1996). Therefore, the antagonistic effects of cadmium could result in an increase in opiate use. This could prove to be of particular significance to portions of the population who smoke, resulting in increased health risks for smokers, and increased risks for the development of addictive behaviors. Regarding the implications of the present findings, it must be considered that developmental cadmium exposure, perhaps via mothers who smoke, could impact drug responsiveness of their progeny, possibly resulting in increased opiate use later in life.

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