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Sensitization of the Locomotor Response to Psychostimulants after Repeated Opiate Exposure: Role of the Nucleus Accumbens

S.T. Cunningham, Ph.D., Marianne Finn, B.A., and Ann E. Kelley, Ph.D.

The following experiments were performed to ascertain the role of the nucleus accumbens in opiate–dopamine interactions using measures of locomotor activity. Three separate experiments were carried out. In Experiment 1, rats received systemic morphine (10 mg/kg IP) or saline (1 ml/kg IP) every other day for 5 days, followed by systemic amphetamine (1.5 mg/kg) 48 hours following the fifth injection. Animals in the morphine pretreatment group exhibited a sensitized locomotor response to amphetamine. In Experiment 2, animals received the same systemic pretreatment and were subsequently given intraaccumbens saline, amphetamine (2.5 μg/0.5 μl) or cocaine (7 μg/0.5 μl), each separated by 48 hours. Morphine-pretreated animals showed enhanced motor activity in response to intraaccumbens microinfusion of the psychostimulant drugs. Finally, in Experiment 3, multiple microinjections of morphine (0.5 μg/0.5 μl) directly into the nucleus accumbens resulted in a potentiated locomotor response to intraaccumbens amphetamine (2.5 μg/0.5 μl). These data indicate that the nucleus accumbens may contribute to both the development and expression of opiate-stimulant cross-sensitization. The neural basis of this sensitization is hypothesized to be a common intracellular pathway affected by both classes of drugs, such as the cyclic adenosine monophosphate (AMP) system. **© 1997 American College of Neuropsychopharmacology**
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KEY WORDS: *Locomotor activity; Nucleus accumbens; Morphine; d-Amphetamine; Cocaine; Sensitization*

Opiate–dopamine interactions have been studied in a number of behavioral paradigms. For example, there is ample evidence in the literature that preexposure to opiates results in an augmented locomotor response to subsequent treatment with stimulants such as cocaine or amphetamine (Kalivas 1985; DuMars et al. 1988; Vezina et al. 1989; Vezina and Stewart 1990). In addition, researchers also have shown that prior treatment with opiates potentiates stimulant-induced responses in reward-related paradigms, such as place preference and conditioned reinforcement (Lett 1989; Bilsky et al. 1992; Cunningham and Kelley 1992).

Much behavioral evidence implicates the ventral tegmental area (VTA) as a substrate for opiate-dopamine cross-sensitization. For example, repeated microinjection of enkephalin or opiates into the VTA causes a progressive increase in the locomotor response and also results in enhanced activation following systemic psychostimulant challenge (Kalivas et al. 1983, 1985; Vezina et al. 1987; DuMars et al. 1988). It is likely that the nucleus accumbens may also be involved in opiate–dopamine cross-sensitization, although few behavioral studies have addressed this question. Anatomical studies indicate that endoge-

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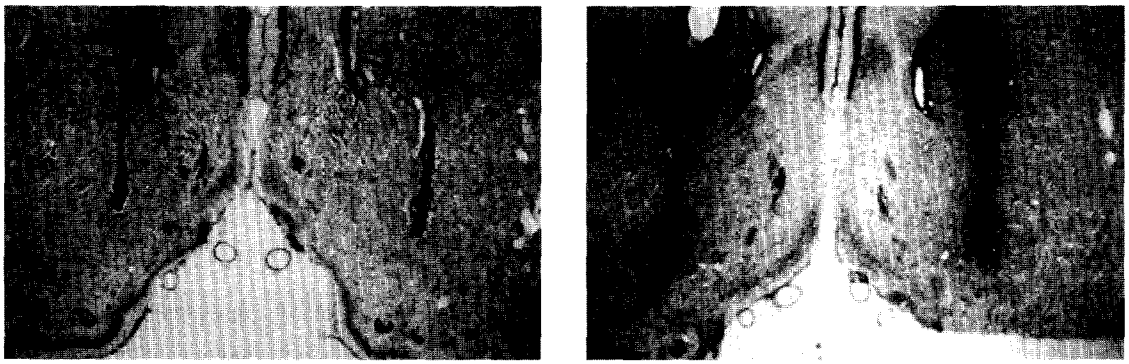

Figure 1. Cannula and injection track location in the nucleus accumbens. (**A**) Animal from Experiment 2. (**B**) Animal from Experiment 3. As noted the stereotaxic coordinates were not aimed specifically at "core" or "shell" subregions in these experiments. Most placements were localized approximately at the core–shell border or in the core.

nous enkephalins and their receptors are localized in association with the mesolimbic dopamine system, suggesting a modulatory role for opiates in dopaminergic function (Goodman et al. 1980; Johnson et al. 1980; Pickel et al. 1980; Bouyer et al. 1984; Mansour et al. 1987). Moreover, alterations in striatal dopamine neurotransmission, metabolite production and G protein–second messenger activity have been reported following opiate manipulations (Kalivas et al. 1983; Di Chiara and Imperato 1988; Pentney and Gratton 1991; Terwilliger et al. 1991; Nestler 1994). In particular, changes in dopamine turnover within the nucleus accumbens have been demonstrated in parallel with sensitized locomotor effects of morphine treatment (Kalivas et al. 1983; Kalivas and Duffy 1988; see Kalivas and Stewart 1991 for review). Therefore, as neurochemical changes are observed within the nucleus accumbens, it is possible that this region may be involved in the expression, and perhaps the development, of behavioral sensitization.

Several studies have suggested that the nucleus accumbens participates in the expression of sensitization; for example, behavioral sensitization to intraaccumbens amphetamine has been described 21 days following a chronic systemic regimen with amphetamine (Paulson and Robinson 1991) and several days following repeated intra-VTA amphetamine injections (Cador et al. 1995). Although the latter study clearly demonstrated the lack of involvement of the accumbens in the induction of amphetamine sensitization, our previous work has suggested that sensitization may be induced by multiple intraaccumbens opiate injections. In an investigation of opiate–dopamine cross-sensitization, we reported that intraaccumbens pretreatment with morphine resulted in potentiated amphetamine-induced responding for conditioned reward (Cunningham and Kelley 1992). The present study was designed to further investigate the direct involvement of the nucleus accumbens in the development of opiate–dopamine cross-sensitization in a locomotor activity paradigm.

MATERIALS AND METHODS

Animals and Surgery

A total of 42 male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) was used for the following experiments. Food and water were available ad libitum, and the animals were housed in pairs on a 12-hour light–dark cycle. All behavioral testing was carried out between 0900 and 1700 h.

A few days after arrival, animals were anesthetized with sodium pentobarbital (50 mg/kg IP) and given atropine (0.54 mg/kg SC) for surgical procedures. Animals were placed in a Kopf stereotaxis for implantation of stainless 23-gauge steel cannula guides. Based on the atlas of Pellegrino and Cushman (1967) with incisor bar 5 mm above interaural zero, the coordinates were (in mm): anteroposterior +3.5 from bregma; mediolateral ±1.7 from midline; and dorsoventral −5.7 from the skull surface. The cannulae (10 mm) were aimed at the nucleus accumbens and affixed to skull screws with liquid acrylic and light-curable dental resin (Dental Supply Co. of New England, Boston, MA). At the end of surgery, wire stylets were placed in the cannulae to prevent occlusion, and animals were allowed a minimum recovery period of 2 to 3 days.

Drugs and Microinfusion

Morphine sulfate (Penick Corp., Lyndhurst, NJ) *d*-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO), and cocaine hydrochloride (Sigma) were dissolved in 0.9% isotonic sterile saline. Systemic injections were given IP. For microinjections, stainless 30-gauge steel injector needles 2.5 mm longer than indwelling cannulae, were used to infuse the drugs bilaterally. A microdrive pump (Harvard Apparatus), connected to the injectors via polyethylene tubing (PE-10, Clay Adams), delivered the drugs over 1 minute and 33 seconds with a 1-minute diffusion

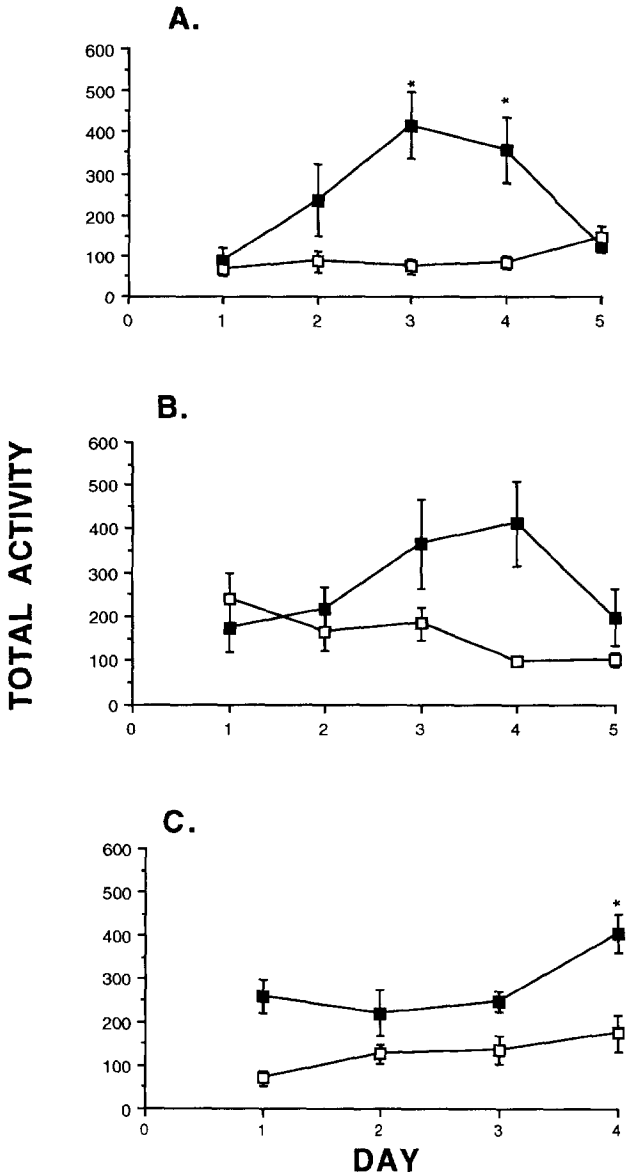

Figure 2. Pattern of motor activity for saline and morphine pretreatment days. Each symbol represents mean activity per group for a 2-hour session. (**A**) Locomotor response to five systemic morphine (n = 6, solid squares; 10 mg/kg IP) or saline (n = 7, open squares) injections in Experiment 1. *$p < .05$, **$p < .01$ compared to Day 1; also significantly different from saline group. (**B**) Repeated systemic morphine (n = 9, solid squares, 10 mg/kg IP) or saline (n = 5, open squares) activation effects for five intermittent pretreatment days in Experiment 2. *$p < .05$, relative to Days 1 and 5; also significantly different from saline. (**C**) Effects of multiple intermittent intraaccumbens morphine (n = 9, solid squares, 0.5 μg/0.5 μl) or saline (n = 6, open squares) on motor response (Experiment 3). **$p < .01$, relative to Days 1–3 and to saline control.

time. A preliminary saline infusion was given to animals implanted with cannulae to familiarize them with the procedure. For all microinjections, a volume of 0.5 μl (per side) was infused.

Behavioral Apparatus

Fifteen plastic cages with wire grid floors were used to measure locomotor activity. A total of six infrared photocells were situated along each cage; two photocells along the horizontal axis recorded locomotor activity, and four photocells placed at the top of the cage recorded rearing. All photocells were interfaced to a microprocessor (Stimtek, Arlington, MA) that recorded the total number of photobeam breaks every 10 minutes. Animals were habituated to these activity cages for 2 hours (postoperatively), and for 1 hour before each test procedure.

Experimental Design

All doses and drug regimens for the current experiments were chosen based on preliminary data and the existing literature. Dose–response curves were assessed for both the induction and the expression of the behavioral effect. Following all pretreatment regimens and subsequent stimulant challenges, animals were placed in the test apparatus for 2 hours.

Experiment 1

Thirteen rats were pretreated with five intermittent (every 48 hours) morphine (n = 6, 10 mg/kg) or saline (n = 7) systemic injections. Forty-eight hours after the final morphine or saline injection, animals were administered amphetamine (1.5 mg/kg IP), following the same behavioral procedure. The choice of "withdrawal" period (i.e., the time between the end of repeated treatment and the sensitization test) was based on evidence that behavioral sensitization can be observed 2 days after the end of chronic treatment (Stewart and Vezina 1989; Vezina and Stewart 1989). However, it should be noted that maximal sensitization, as well as more robust neuronal changes, may be observed 2 to 3 weeks following treatment (Paulson and Robinson 1995; Pierce and Kalivas 1995; Pilotte et al. 1996).

Experiment 2

In this experiment, a total of 14 rats were given five intermittent peripheral treatments with morphine (n = 9) (10 mg/kg) or saline (n = 5) every 48 hours. Forty-eight hours following the last IP injection, animals were given intraaccumbens microinfusions of saline (0.5 μl), amphetamine (2.5 μg/0.5 μl) and cocaine (7 μg/0.5 μl), each separated by 48 hours. These were given in a counterbalanced order over the test days.

Experiment 3

For this experiment, a total of 15 rats were used. Nine rats received four morphine injections (0.5 μg/0.5 μl) in

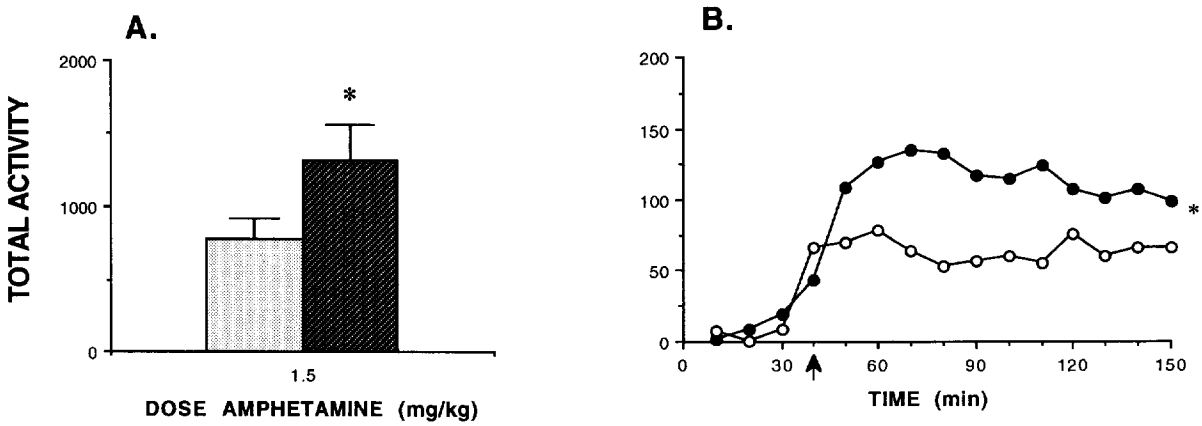

Figure 3. Locomotor response to systemic amphetamine challenge in animals pretreated with IP saline ($n = 7$) or IP morphine ($n = 6$, 10 mg/kg). (**A**) Total motor response to amphetamine (1.5 mg/kg IP) over a 2-hour period. Bars represent mean activation per group ± SEM. *Grey bar*, saline pretreatment. *Cross-hatched bar*, morphine pretreatment. *$p < .05$, between-groups effect. (**B**) Time course of motor-activating effects of systemic amphetamine. *$p < .05$, group-by-time interaction. Each circle represents mean horizontal activity for that time point. The first three time points indicate the last 30 minutes of habituation prior to amphetamine challenge (arrow indicates first 10-minute period following amphetamine). *Open circles*, saline. *Closed circle*, morphine.

the nucleus accumbens, and six rats received four intraaccumbens saline infusion. Two days following the end of pretreatment, a localized injection of amphetamine (2.5 μg/0.5 μl) was given directly into the nucleus accumbens of all animals.

Data Analysis

All data analyses were done with the aid of an IBM-compatible statistical program (Crunch Interactive Statistical Package). Following a within-subjects analysis of variance of the pretreatment data, means comparisons (orthogonal contrasts) were used to compare differences between pretreatment days within a group. The Student's *t*-test was used to compare between-group means (morphine- and saline-treated groups) on the different pretreatment days. A two-factor (group and time, with repeated measures for time), between-subjects analysis of variance (ANOVA) was performed to analyze locomotor differences between groups on challenge day(s). If any violation of the FMAX test of homogeneity of variance was found, a square root transformation of the data was performed (Bruning and Kintz 1987).

Histology

To verify cannulae locations, subjects were given an overdose of pentobarbital (75-80 mg/kg IP) and perfused transcardially by 10% formalin. Following in situ fixation, the brains were then placed in formalin (minimum 3 days), and coronal cross-sections (60 μm) were made and stored on slides. Hand-drawn reconstructions or photomicrographs of these sections were made. Two representative photographs of Nissl-stained sections through the accumbens are shown in Figure 1. The studies described below were not designed with the aim of distinguishing between "core" and "shell" subdivisions of the accumbens; the majority of placements should be considered to be in the core or on the core–shell border.

RESULTS

All data for locomotor (horizontal) activity are reported in the following, and only those data for vertical activity (rearing) that reached statistical significance are included.

Experiment 1: Effect of Systemic Morphine Pretreatment on Amphetamine-Induced Motor Activation

Repeated peripheral administration of morphine resulted in progressively greater activation over the first few days followed by a diminution in motor response on subsequent days. An ANOVA of the morphine pretreatment data revealed a significant effect of day ($F[4,28] = 6.09$, $p < .01$). Post hoc analysis indicated that the locomotor response in the morphine group was significantly greater on Days 3 and 4 as compared to Days 1 or 5 [Day 1 vs. 3, $p < .01$; Day 1 vs. 4, $p < .05$; Day 3 vs. 5, $p < .01$; Day 4 vs. 5, $p < .05$ (Figure 2A)]. No significant differences were observed across saline pretreatments. Comparison of the mean total activity between pretreatment groups indicated that morphine-treated rats had significantly higher activity counts than the saline group on Day 3 [$t(13) = 3.82$, $p < .01$, and Day 4 $t(13) = 3.10$, $p < .01$)].

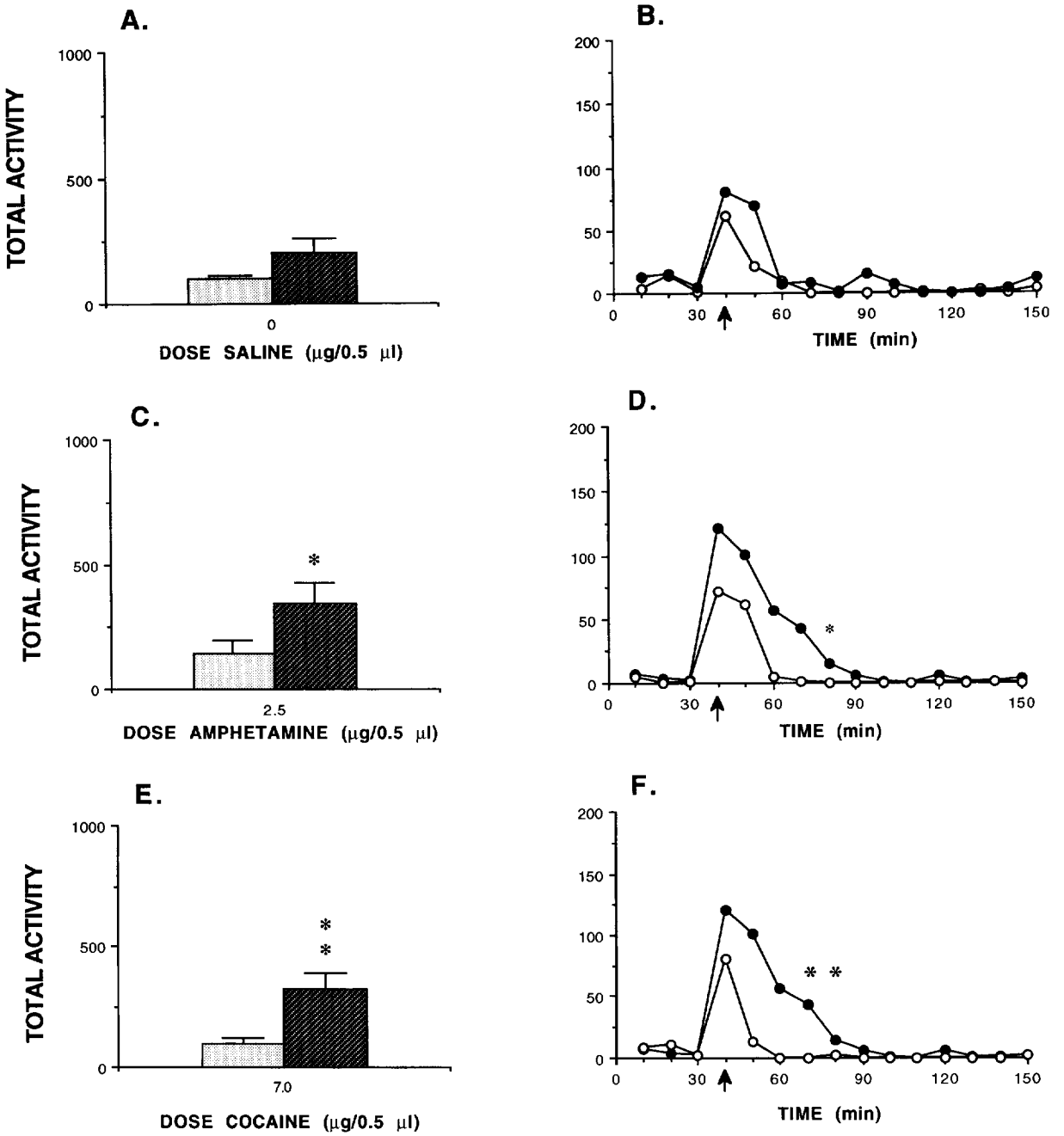

Figure 4. Effects of intraaccumbens drug treatment on motor activity in rats preexposed to systemic pretreatment with saline ($n = 5$) or morphine ($n = 9$). (**A**) Average locomotor response to saline challenge in animals. *Grey bar*, saline pretreatment. *Cross-hatched bar*, morphine pretreatment (10 mg/kg IP). (**B**) Time course of activity during habituation and following saline (*arrow*) infusion. *Open circles*, saline pretreatment. *Solid circles*, morphine pretreatment (10 mg/kg IP). (**C**) Mean of total activity (2 hours) for animals given intraaccumbens amphetamine (2.5 μg/0.5 μl). *Grey bar*, saline pretreatment. *Cross-hatched bar*, morphine pretreatment (10 mg/kg IP). $^{*}p < .05$, pretreatment group effect. (**D**) Time course for amphetamine-induced hyperactivity, following habituation (10–30 minutes). *Open circles*, saline pretreatment. *Solid circles*, morphine pretreatment (10 mg/kg IP). $^{*}p < .05$, group-by-time interaction. (**E**) Mean response levels for cocaine-injected (7.0 μg/0.5 μl) rats. *Grey bar*, saline pretreatment. *Cross-hatched bar*, morphine pretreatment (10 mg/kg IP). $^{**}p < .01$ group effect. (**F**) Activity pattern over time for cocaine microinfusion into the accumbens (*arrow*), which followed a habituation period. *Open circles*, saline pretreatment. *Solid circles*, morphine pretreatment (10 mg/kg IP). $^{**}p < .01$, group-by-time interaction.

Following the morphine pretreatment regimen, IP treatment with amphetamine resulted in higher motor activity in the morphine-treated rats than in the saline-treated rats (Figure 3A). ANOVA indicated an overall effect of group [$F(1,112) = 4.374$, $p < .05$, as well as a group-by-time interaction, $F(11,132) = 2.325$, $p < .01$]. This potentiating motor response lasted throughout the test period (Figure 3B). Moreover, as can be noted from Figure 2B, baseline activity was not different between the two pretreatment groups.

Experiment 2: Effect of Systemic Morphine Pretreatment on Locomotor Activity Elicited by Intraaccumbens Amphetamine and Cocaine

As in the first experiment, animals in Experiment 2 showed progressively enhanced motor activity over the first four morphine treatment days, which subsided on Day 5 (Figure 2B). ANOVA of the daily morphine-elicited motor effect revealed a significant effect of day [$F(4,32) = 4.51$, $p < .01$], which was due to Day 4 activity counts relative to Days 1 and 5 ($p < .05$). A significant difference across saline pretreatment days was also obtained [$F(4,16) = 4.26$, $p < .05$], indicating that the activity level on Day 1 was greater than on Days 4 and 5 ($p < .05$). A comparison of the mean total activity across pretreatments revealed that morphine-induced locomotion was significantly greater than that elicited by saline on Day 4 [$t(12) = 2.34$, $p < .05$]. In other words, activity gradually diminished over days with saline treatment, while the response to morphine first tended to increase over days, then returned to control levels.

Systemic morphine preexposure did not significantly alter activity to intraaccumbens saline (Figure 4A–B) or augment the behavioral response to intraaccumbens amphetamine and cocaine administration (Figure 4C–F). For the amphetamine data, a significant between-groups effect was obtained [$F(1,112) = 4.83$, $p < 0.05$; Figure 4C–D]. Similar results were obtained following cocaine challenge; an overall significant between-groups effect [$F(1,111) = 11.44$, $p < 0.001$] and group-by-time interaction [$F(11,121) = 7.6$, $p < .001$] were found (Figure 4E–F). In addition, cocaine microinfusion also significantly elevated vertical activity (rearing) in animals previously exposed to morphine (data not shown). A between-groups effect [$F(1,112) = 5.24$, $p < .05$] and a group-by-time interaction for rearing [$F(11,132) = 2.31$, $p < 0.01$] were obtained.

Experiment 3: Effect of Intraaccumbens Morphine Pretreatment on Locomotor Response Following Amphetamine in the Nucleus Accumbens

The motor-activating effect of multiple microinfusions of morphine into the nucleus accumbens remained stable over the first 3 days and was increased on the fourth pretreatment day (Figure 2C). The ANOVA for the morphine data indicated a significant effect of day [$F(3,24) = 5.10$, $p < .01$]. Post hoc analysis indicated that Day 4 was different from all other treatment days (Day 1 vs. Day 4, $p < .01$; Day 2 vs. Day 4, $p < .01$; Day 3 vs. Day 4, $p < .05$). No significant differences were found across saline treatments. Comparisons of the daily treatments in the saline and morphine groups indicated that the groups differed on Days 1, 3, and 4. The unpaired Student's t-test indicated significant differences on Day 1 [$t(13) = 3.45$, $p < .01$; Day 3 $t(13) = 2.80$, $p < .05$; and on Day 4 $t(13) = 3.67$, $p < .01$].

Twenty-four hours following the termination of morphine or saline pretreatment, animals received an intraaccumbens infusion of amphetamine. Although the temporal pattern was somewhat erratic, Figure 5A–B shows that animals preexposed to morphine had a

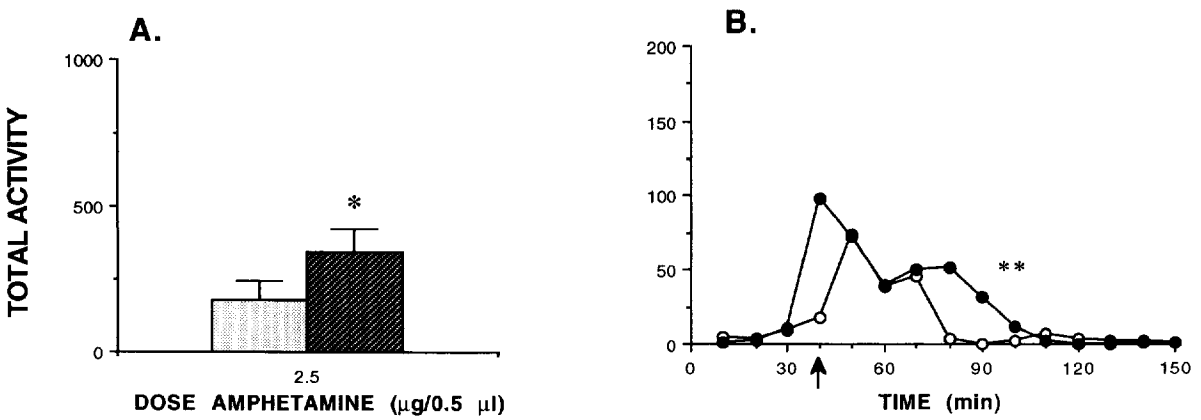

Figure 5. Total locomotor activity of rats administered intraaccumbens amphetamine (2.5 µg/0.5 µl) following multiple saline ($n = 6$) or morphine ($n = 9$) (0.5 µg/0.5 µl IC) microinfusion into the accumbens. (**A**) Average activity levels for 2 hours following amphetamine challenge. *Grey bar*, saline pretreatment. *Cross-hatched bar*, morphine pretreatment. *$p < .05$, pretreatment group effect. (**B**) Locomotor profile following nucleus accumbens infusion of amphetamine. *Open circles*, saline pretreatment. *Solid circles*, morphine pretreatment. **$p < .01$, group-by-time interaction.

greater magnitude of activation following microinfusion of amphetamine. ANOVA revealed a significant between-groups effect [$F(1,112) = 5.832$, $p < .05$, as well as a group-by-time interaction, $F(11,132) = 2.820$, $p < .01$].

DISCUSSION

The present results demonstrate that prior exposure to morphine sensitizes animals to amphetamine or cocaine and that the nucleus accumbens is a neural substrate involved in the induction of this phenomenon. The findings in Experiment 1, that repeated systemic administration of morphine results in higher behavioral response to amphetamine, are in agreement with previous reports (Kalivas 1985; DuMars et al. 1988; Vezina et al. 1989). In Experiments 2 and 3, we report novel findings regarding the role of the nucleus accumbens in this behavioral phenomenon. Following intermittent systemic morphine exposure, local injection of amphetamine or cocaine into the nucleus accumbens resulted in a potentiated locomotor response. This finding indicates that the reactivity of the accumbens to drugs that augment synaptic DA has been altered by preexposure to systemic morphine. Although environment-specific conditioning may have contributed to the potentiation, a conditioned response is not solely responsible for the observed sensitized locomotor response, as vehicle challenge did not result in significantly potentiated locomotion. However, the tendency toward conditioned activity is apparent in Figure 4B.

In regimens that have employed systemic injections of opiates or stimulants, it has been clearly shown that alterations take place at the level of dopamine cell bodies, in the ventral tegmental area (Vezina et al. 1987; DuMars et al. 1988; Stewart and Vezina 1989). In consideration of the present findings, it is possible that multiple systemic morphine injections also induce intrinsic alterations in the nucleus accumbens. One possible underlying mechanism is an enhancement of morphine-induced dopamine release. Opiates increase dopamine release acutely (Di Chiara and Imperato 1988; Pentney and Gratton 1991), and several studies have reported higher dopamine release following repeated opiate treatment (Kalivas and Duffy 1988, 1990). However, at the level of the accumbens, opiate behavioral effects are thought to be primarily dopamine-independent (Pert and Sivit 1977; Kalivas et al. 1983; Stinus et al. 1985; Vaccarino et al. 1986). Therefore, alteration in dopamine release probably does not entirely explain morphine-elicited facilitation of the stimulant locomotor response, although it could be a contributing factor.

A second possible component of opiate–dopamine interactions in the nucleus accumbens may involve intraneuronal signal transduction mechanisms, as both opiates and psychostimulants exert their effects through the cyclic adenosine manophasphate (AMP) second-messenger system (Nestler 1994). Early theories of opiate addiction and withdrawal implicated the cyclic adenosine monophosphate (AMP) system (Collier and Roy 1974; Law et al. 1981). For example, it was initially observed that acute morphine exposure downregulated cyclic AMP. More recent biochemical data show that chronic exposure to opiates and psychostimulants induces alterations in the cyclic AMP second-messenger system (Tirone et al. 1988; Johnson and Fleming 1989; Guitart and Nestler 1989; Nestler et al. 1990; De Vries et al. 1991; Terwilliger et al. 1991; Van Vliet et al. 1992). Moreover, direct upregulation of the cyclic AMP system in the mesolimbic dopamine system, via treatment with selective bacterial toxins, has been demonstrated to potentiate the motor response to stimulants (Steketee and Kalivas 1991; Cunningham and Kelley 1993). Further evidence that the reinforcing effects of both opiates and stimulants depend on common intracellular pathways is provided by the finding that pertussis-toxin–induced inactivation of inhibitory G proteins in the accumbens reduces self-administration of these drugs (Self et al. 1994). Thus, the enhanced response observed in the present experiments could be due to an altered regulation of these signaling pathways.

The observation in Experiment 2, that prior systemic exposure to morphine results in a facilitation of intraaccumbens amphetamine-induced motility, further implicates the nucleus accumbens in the *expression* of behavioral sensitization. Moreover, we propose a direct involvement of this region in the *development* of this phenomenon as well. In experiment 3, intermittent localized injections of morphine into the nucleus accumbens also resulted in a small, yet significant, increase in amphetamine-induced locomotion. It is noteworthy that the magnitude of elevation was smaller than that observed in either Experiments 1 or 2, in which morphine was administered systemically. It is probable, therefore, that the nucleus accumbens may only contribute to the development of sensitization, in conjunction with the ventral tegmental area and perhaps other forebrain sites. In summary, intracellular mechanisms in the nucleus accumbens may play a role in both the development and expression of opiate–dopamine cross-sensitization. Further work is needed to address more precisely what specific molecular changes underlie these behavioral observations, their duration, and their relation to long-term phenomena such as relapse to drug use.

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