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Intraaccumbens Administration of NMDA Receptor Antagonist (±)-CPP Prevents Locomotor Activation Conditioned by Morphine and Amphetamine in Rats

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BESPALOV, A. YU. AND E. E. ZVARTAU. *Intraaccumbens administration of NMDA receptor antagonist (±)-CPP prevents locomotor activation conditioned by morphine and amphetamine in rats.* PHARMACOL BIOCHEM BEHAV **55**(2) 203–207, 1996.—In the present experiments the influence of NMDA receptor antagonist (±)-CPP on morphine- and amphetamine-conditioned activation of locomotor activity was studied in rats chronically implanted with bilateral cannulas in the nucleus accumbens septi. Animals were conditioned by pairing subcutaneous injections of morphine (3.0 mg/kg), amphetamine (1.5 mg/kg), or saline with a distinctive environment. Following the five drug-environment pairings, rats displayed significant increase in locomotion when exposed to the drug-paired environment. The expression of this conditioned response was completely prevented by the bilateral intraaccumbens pretreatment with (±)-CPP (1.0, but not 0.1 or 0.3 μg/μl/side). These findings suggest that the locomotor hyperactivity conditioned by morphine and amphetamine involves the activation of NMDA receptors within the nucleus accumbens. **Copyright © 1996 Elsevier Science Inc.**

Morphine Amphetamine NMDA receptor antagonist Nucleus accumbens Locomotor activity Conditioning Rats

THE classical conditioning of psychomotor stimulant responses can be shown by placing the experimental animals into the environment in which they have received a repeated psychostimulant drug treatment (11,27,31). These conditioned psychomotor effects have been demonstrated for classical psychostimulants (e.g., amphetamine, cocaine) and other drugs, like morphine (29,42).

Given the fact that drugs of abuse stimulate dopamine metabolism in mesolimbic system (6), it could be hypothesized that drug-conditioned stimuli may also produce increases in dopaminergic transmission. Support for this hypothesis comes from studies that have demonstrated that dopamine receptor antagonists have blocked expression of the conditioned responses (12,19,28,29,33). However, there is also evidence suggesting that expression of the conditioned effects of psychostimulants is mediated, at least in part, by nondopaminergic mechanisms (7,11,27). For example, apomorphine-conditioned contralateral rotation in rats with 6-OHDA–lesioned substantia nigra was not affected by dopamine receptors blockade (7). Interestingly, both increase (16,24) and no changes in the mesolimbic dopaminergic activity (4,15) were reported following conditioning with cocaine.

Several studies have revealed that the mesolimbic system, including nucleus accumbens septi, receives excitatory projections from prefrontal cortex, amygdala, and hippocampus. These areas are known to participate in different aspects of learning and memory (14,18,35), and their outputs to the region of nucleus accumbens utilizes excitatory amino acids as its neurotransmitters (17,21,22,23,36).

Recent studies have demonstrated that glutamate receptor antagonists affect both acquisition and expression of drug-conditioned place preference in rats (2,3,9,40). Previously, systemic administration of the noncompetitive NMDA receptor antagonist MK-801 has been shown to block the development of amphetamine- and apomorphine-conditioned hyperactivity (13,38,39). The NMDA receptor blockade in the nucleus accumbens septi (NAC) has also prevented unconditioned locomotor stimulation produced by heroin and cocaine (34), as well

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as the amphetamine-potentiated responding with conditioned food reinforcement (5).

The present study sought to test whether intraaccumbens administration of the NMDA receptor antagonist (±)-CPP affects the expression of morphine- and amphetamine-conditioned locomotion in rats.

METHOD

Animals

Adult male Wistar rats (250–300 g; State Breeding Farm "Rappolovo," St. Petersburg, Russia) were used. Animals were housed individually with food and water available ad lib. All experiments were conducted during the light period of a 12 L:12 D cycle (0800–2000 h).

Drugs

Morphine hydrochloride and *d*-amphetamine hydrochloride were purchased from commercial sources, (±)-CPP [(±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid] from RBI (Natick, MA). All drugs were dissolved in phosphate-buffered saline (pH = 7.4) and injected subcutaneously in a volume of 1 ml/kg (morphine and amphetamine) or bilaterally into the nucleus accumbens in a volume of 1 μl/side over a period of 1 min/μl [(±)-CPP].

Surgery

For intraaccumbens injections, each animal was anesthetized with Nembutal (60 mg/kg, IP) and stainless steel guide cannulae of 0.68 mm thickness were stereotaxically implanted using a David Kopf Micromanipulator. Cannulae were lowered either into the nucleus accumbens septi (coordinates: AP: +2.5 mm from bregma, L: 2.7 mm from the midline, V: 6.2 mm from a flat skull, angle: 12°, incisor bar at the level of interaural line), or into the dorsal striatum (coordinates: AP: +2.5 mm from bregma, L: 2.7 mm from the midline, V: 4.3 mm from a flat skull, angle: 12°). Four stainless steel jeweller screws and dental cement were used to anchor the cannula assembly to the skull.

Procedure

Locomotor activity was measured in three identical boxes (50 × 30 × 30 cm) with transparent Plexiglas walls and a nontransparent plastic floor. Boxes were equipped with eight photocell beams (5 cm off the floor) for measuring horizontal activity and six beams (14 cm off the floor) for vertical component of locomotor activity. The total number of photocell interruptions during the 15-min test was used as a measure of locomotor activity.

The experiment consisted of two periods: a conditioning period (5 consecutive days) and a postconditioning test (two days after the last conditioning session). All animals were habituated to handling for 2 days prior to the start of conditioning.

Conditioning Period. Rats were randomly assigned to one of three treatment conditions (paired, unpaired, and saline). Unpaired groups received daily injections of saline (1 ml/kg, SC) immediately before being placed into the experimental boxes. One hour later rats were removed from the experimental boxes and returned to their home cages. Animals were then injected with either morphine (3.0 mg/kg, SC, group pairedM) or amphetamine (1.5 mg/kg, SC, group pairedA) and placed back into the home cage so that interinjection intervals were no less than 2 h.

Paired groups were first given saline (1 ml/kg, SC) and placed back into the home cages. Two hours later these animals were pretreated with either morphine (3.0 mg/kg, SC, group unpairedM) or amphetamine (1.5 mg/kg, SC, group unpairedA) just prior to placement in the experimental boxes for 1 h.

Saline groups were always given saline injections irrespective of the placement into the experimental boxes or home cages.

In an attempt to prepare animals for intra-NAC infusions, rats were exposed to a dummy bilateral intra-NAC administration procedure (no actual volume delivery) that preceded each SC injection.

Postconditioning Test. All animals were first pretreated with a bilateral intra-NAC injection of (±)-CPP (0.1, 0.3, or 1.0 μg/μl/side) or its vehicle (VEH). Subsequently, animals were injected with saline subcutaneously and immediately placed into the experimental boxes for 15 min observations.

An additional experiment was designed to test the effects of (±)-CPP delivered into the dorsal striatum instead of the nucleus accumbens. The conditioning period was conducted as described above with the exception that prior to the postconditioning test pairedM, pairedA, unpairedM, unpairedA, and saline groups received an intrastriatal injection of (±)-CPP (1.5 μg/μl/side) and its vehicle.

Histology

After completion of the experiments, rats were decapitated with the brains quickly removed and stored in 10% formalin. The cannula tip placement was examined for each experimental animal under a light microscope in a cresyl violet stained sections of 50 μm thickness. The atlas of rat brain stereotaxic coordinates (30) was used to verify cannula tip placement.

Statistics

Data obtained from experiments with intraaccumbens administration of (±)-CPP were subjected to three-way analysis of variance (ANOVA) with treatment as the first factor (three levels: morphine, amphetamine, and saline), type of conditioning as the second factor (two levels: paired and unpaired), and dose of (±)-CPP as a third factor (four levels: 0, 0.1, 0.3, and 1.0 μg). One-way ANOVA was used to process data from experiments with intrastriatal drug administration. ANOVA was followed by post hoc Student–Newman–Keuls' test. The null hypothesis was rejected at $p < 0.05$ level. Statistical analysis was conducted using SAS-STAT software version 6.10 (SAS Institute, Cary, NC).

RESULTS

Animals with injector tip placements outside the targeted area were excluded from the statistical analysis. Figure 1 schematically represents the localization of the injector tips within the nucleus accumbens (A) and the dorsal striatum (B).

The results of the experiments with intraaccumbens administration of (±)-CPP are displayed in Fig. 2. When data were subjected to ANOVA, overall effects of conditioning, dose of (±)-CPP, and their interaction were found to be significant, $F(1, 155) = 76.53$, $p < 0.001$; $F(3, 155) = 15.22$, $p < 0.001$; $F(3, 155) = 7.86$, $p < 0.01$, respectively. Student–Newman–Keuls' test revealed significantly lower locomotor activity score in unpaired vs. paired groups and following administra-

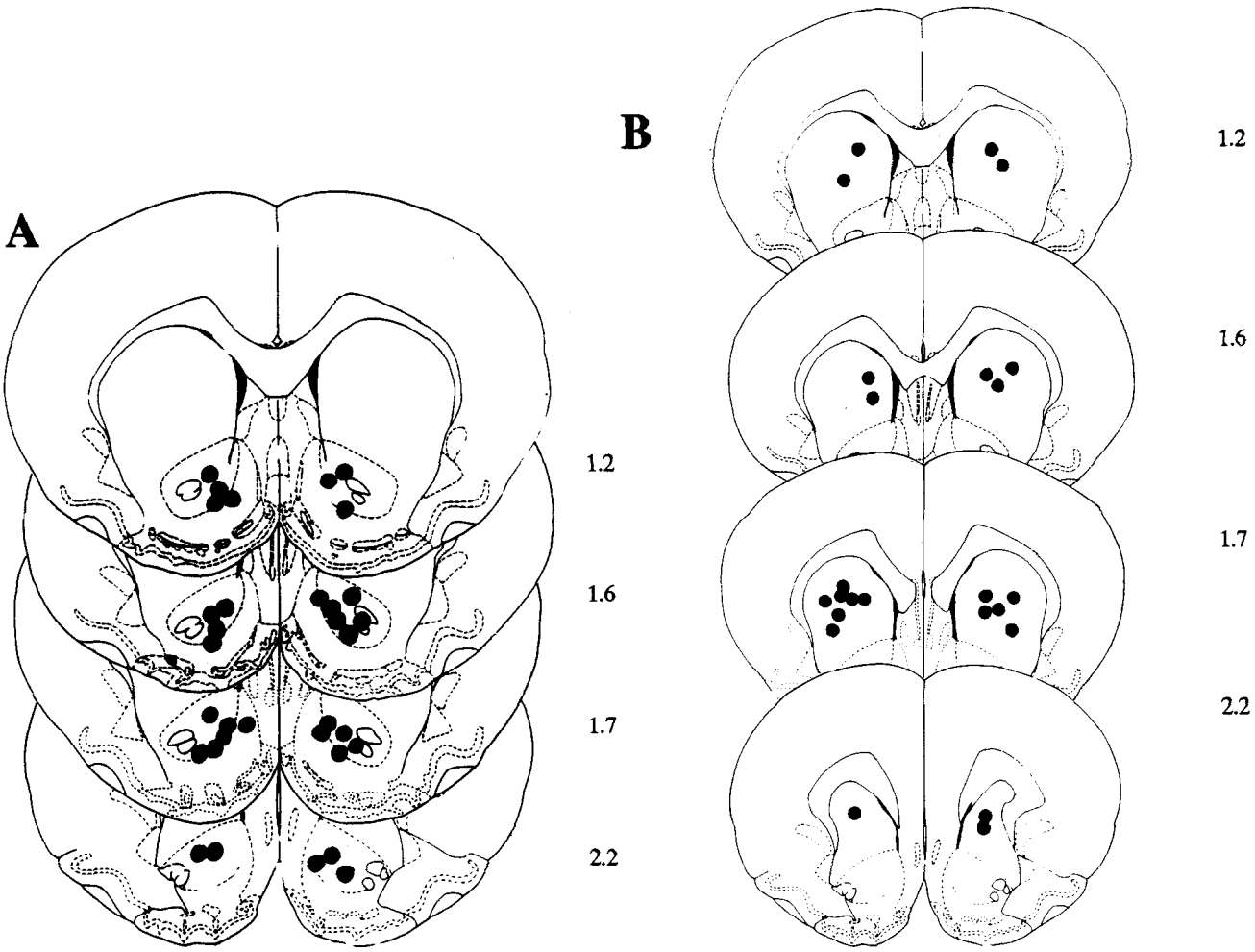

FIG. 1. Serial sections showing the localization of injector tips within the nucleus accumbens (A) and striatum (B) as seen on light microscopy and transferred to diagrams from (30). The locations are shown from the representative animals treated with (±)-CPP or its vehicle. Distance anterior from bregma (mm) is indicated.

tion of 1.0 μg/μl/side of (±)-CPP compared to the rest of drug doses ($p < 0.05$).

Further analysis treated each test condition [vehicle and (±)-CPP] separately. Significant differences in the total locomotor activity were found among the groups received an intra-accumbens vehicle injection prior to the test, $F(4, 44) = 11.57$, $p < 0.01$. Similar results were obtained in groups treated prior to the test with intrastriatal vehicle instead of (±)-CPP [Fig. 3, $F(4, 27) = 4.92$, $p < 0.01$].

Animals that repeatedly experienced either morphine (pairedM) or amphetamine (pairedA) in the experimental boxes showed significantly higher locomotor activity than control animals (unpairedM and unpairedA, i.e., saline injections before placement into the experimental boxes) (Figs. 2 and 3, VEH-bars).

Pretreatment with bilateral intraaccumbens (±)-CPP (1.0, but not 0.1 or 0.3 μg/μl/side; Fig. 2) instead of vehicle abolished the differences between groups, $F(4, 46) = 0.55$, $p > 0.05$. This effect was not observed when (±)-CPP (1.5 μg/μl/side) was administered into the dorsal striatum, $F(4, 25) = 7.96$, $p < 0.01$; Fig. 3.

The administration of (±)-CPP did not affect spontaneous locomotor activity because there were no differences between saline groups pretreated with vehicle and (±)-CPP ($p > 0.05$) (Figs. 2 and 3).

DISCUSSION

The major finding of this study is that NMDA receptor antagonist (±)-CPP when administered locally into the nucleus accumbens septi blocks the expression of the classical conditioning of morphine's and amphetamine's locomotor effects. This effect was demonstrated to be dose dependent for (±)-CPP and was not observed when the drug was delivered into the dorsal striatum. Previous studies have demonstrated that nucleus accumbens and striatum respond differentially to the drugs of abuse that share the ability to facilitate dopamine turnover in the ventral areas (nucleus accumbens) but less in the dorsal striatum (6). Local injections of psychostimulants and opiates into the ventral striatum are known to be rewarding as demonstrated by self-administration, conditioned place preference, and electrical self-stimulation techniques (8,32,41,44).

The present study explored the effects of intrastriatal administration of a single dose of (±)-CPP. Higher dose of the

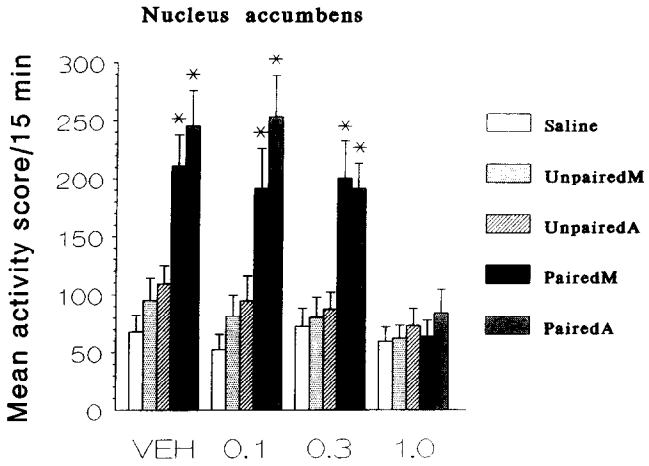

FIG. 2. Effect of intraaccumbens (±)-CPP on the locomotor activity conditioned with morphine or amphetamine. During the conditioning period rats received injections of morphine (PairedM), amphetamine (PairedA), or saline (Saline, UnpairedM, and UnpairedA) prior to the placement into the experiment boxes, and second daily injection of morphine (UnpairedM), amphetamine (UnpairedA), or saline (Saline, PairedM, and PairedA) was paired with placement back into the home cages. Data represents group mean 15-min activity scores (± SEM) on day 3 of postconditioning period for animals pretreated with bilateral intraaccumbens vehicle (VEH, phosphate-buffered saline, pH = 7.4) or (±)-CPP (0.1, 0.3, or 1.0 g) 2 min prior to testing (n = 8–11 per group). *$p < 0.05$ with respect to Saline group (Student–Newman–Keuls' tests).

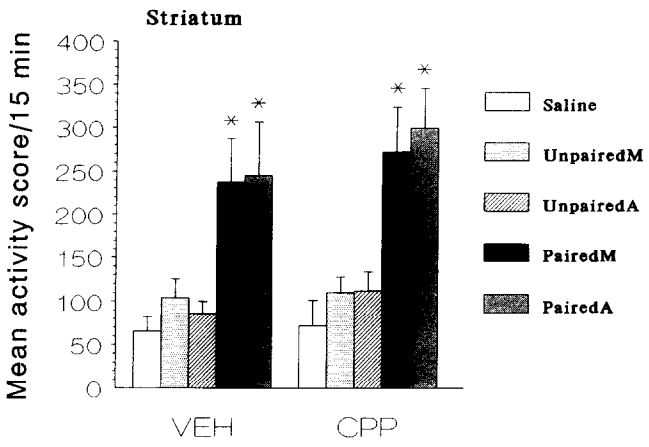

FIG. 3. Effect of intrastriatal (±)-CPP on the locomotor activity conditioned with morphine or amphetamine. During the conditioning period rats received injections of morphine (PairedM), amphetamine (PairedA), or saline (Saline, UnpairedM, and UnpairedA) prior to the placement into the experiment boxes, and second daily injection of morphine (UnpairedM), amphetamine (UnpairedA), or saline (Saline, PairedM, and PairedA) was paired with placement back into the home cages. Data represents group mean 15-min activity scores (± SEM) on day 3 of postconditioning period for animals pretreated with bilateral intrastriatal vehicle (VEH, phosphate-buffered saline, pH = 7.4) or (±)-CPP (1.5 g) 2 min prior to testing (n = 8–11 per group). *$p < 0.05$ with respect to saline group (Student–Newman–Keuls' tests).

drug (3 μg/μl/side) caused significant elevation in spontaneous locomotion (data are not shown) and was not employed in conditioning studies. Therefore, evidence obtained in the present experiments is insufficient to suggest different involvement of nucleus accumbens and striatum in the expression of drug-conditioned responses.

An understanding of the role of NMDA receptors in the expression of drug-conditioned hyperactivity may be derived from the studies of the effects of NMDA antagonists on attention-processing functions. Noncompetitive antagonists of NMDA receptors were demonstrated to impair attention to exteroceptive stimuli in the modified open field (with a stimulus object) (10) and prepulse inhibition of the acoustic startle paradigms (26,43). Therefore, it is possible that (±)-CPP decreased the drug-conditioned hyperactivity by interfering with the processing of the exteroceptive conditioned stimuli.

Although systemic administration of the competitive antagonists of NMDA receptors failed to disrupt prepulse inhibition (26,43), intracerebral injections could be disruptive. Excitotoxic lesions of the ventral striatum reduce prepulse inhibition (25), suggesting the role of this brain area in sensorimotor gating of acoustic startle and, perhaps, in processing of relevant sensory information. Because NMDA receptors are vastly represented in the nucleus accumbens [(1); for references on glutamatergic projections to the nucleus accumbens see Introduction], local infusions of NMDA ligands can modulate arousal function of this structure.

Repeated administration of various drugs (e.g., amphetamine, cocaine, morphine) leads to the increased behavioral sensitivity to the acute challenge with the drug. The development of the phenomenon of behavioral sensitization to various psychoactive drugs is prevented by cotreatment with NMDA receptor antagonists (21,38,45). Classical conditioning contributes to the development of sensitization (31). Because the NMDA receptor antagonist was able to prevent the expression of conditioned locomotor response in the present study, it is possible that these drugs would affect the expression of the behavioral sensitization to opiates or stimulants. However, it has been reported that NMDA receptor antagonists failed to prevent the expression of behavioral sensitization to morphine and amphetamine [(20,21), but see (37)]. Classical conditioning is certainly one of a variety of processes that underlie the development of behavioral sensitization.

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