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Hyperactivity Induced by N-Methyl-d-Aspartate Injections Into Nucleus Accumbens: Lack of Evidence for Mediation by Dopaminergic Neurons

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O'NEILL, K. A., R. M. CARELLI, M. F. JARVIS AND J. M. LIEBMAN. *Hyperactivity induced by N-methyl-d-aspartate injections into nucleus accumbens: Lack of evidence for mediation by dopaminergic neurons.* PHARMACOL BIOCHEM BEHAV **34**(4) 739–745, 1989.—To test the hypothesis that the motor hyperactivity associated with intra-accumbens injections of N-methyl-d-aspartate (NMDA) results from stimulation (direct or indirect) of nucleus accumbens dopaminergic mechanisms, the behavioral effects of intra-accumbens and intraventricular NMDA were compared to those of the prototypic dopaminergic releasing agent, amphetamine, and the competitive NMDA receptor antagonist, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP). Drugs were injected into the right lateral ventricle, or bilaterally into the nucleus accumbens of rats. Locomotor activity was monitored electronically and by direct observation for 40 min prior to, and 1 hour after, drug treatment. Intra-accumbens injections of NMDA (0.4, 1.2 and 2.0 μg/side) produced dose-related increases in distance traveled, but had no significant effect on movement time or vertical movements. The NMDA-induced increase in distance traveled was temporally correlated with convulsive wild running, but not with exploratory behavior, suggesting that this increase may have been secondary to seizure-like activity. Intra-accumbens injections of amphetamine (10, 20 and 40 μg) or CPP (0.1 μg) produced dose-related increases in all three measures. By the intraventricular route, the effects of NMDA were similar to those of intra-accumbens administration, whereas intraventricularly administered d-amphetamine had no effect. The behavioral effects of intra-accumbens NMDA cannot be explained by an NMDA receptor-mediated facilitation of dopaminergic neurotransmission; rather, this type of facilitation may be associated with competitive NMDA receptor antagonism.

NMDA Amphetamine Locomotion Nucleus accumbens NMDA receptor antagonist CPP

A large body of evidence supports the hypothesis that certain endogenous amino acids function as excitatory neurotransmitters within the central nervous system (5). Electrophysiological and pharmacological data indicate that glutamate and its analogs exert their effects through several subtypes of excitatory amino acid (EAA) receptors. Characterized on the basis of their sensitivity to particular ligands, at least three subtypes have been identified: those preferring N-methyl-d-aspartate (NMDA), kainate and quisqualate, respectively (12).

The excitatory amino acids (EAAs) and their analogs have been shown to exert a variety of behavioral effects upon intracerebral injection into various sites. Of particular interest is the locomotor hyperactivity associated with injections of N-methyl-d-aspartate (NMDA) or its racemate, N-methyl-d,l-aspartate, into the nucleus accumbens (3,4). Recent evidence indicates that the nucleus accumbens receives glutamatergic projections from hippocampus and frontal cortex, and also contains EAA interneurons (5,7). The release of [^{3}H]dopamine from nucleus accumbens slices is enhanced by incubation with l-glutamate (18). These observations, and the ability of intra-accumbens fluphenazine to attenuate the effects of NMDA (3), have suggested that the hyperactivity reported to result from microinjection of EAAs into the nucleus accumbens may result from enhancement of dopamine release (3). Because the nucleus accumbens is thought to be an interface between cortical and limbic systems (13) and has been hypothesized to mediate, in part, the therapeutic effects of antipsychotic medications (1), these effects of EAAs may be of considerable significance.

The present experiments were designed to assess the hypothesis that the behavioral excitation induced by intra-accumbens

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stimulation of NMDA receptors is mediated by the same pathway(s) as those activated by synaptically released dopamine. It was postulated that if this is the case, then the resulting behavioral profile should resemble that induced by intra-accumbens d-amphetamine in rats. Using a computerized movement analysis system in conjunction with periodic visual observations, the present experiments characterized this behavioral profile in detail. Further, it was hypothesized that NMDA would be more potent in increasing motor activity when microinjected directly into the nucleus accumbens than into the lateral ventricle. Finally, it was predicted that a competitive NMDA receptor antagonist, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) (11), should have an effect opposite to that of NMDA.

METHOD

Male Sprague-Dawley rats [Mbf:(SD); Marland Farms, Hewitt, NJ] served as subjects. Rats weighed approximately 250–300 g at the time of surgery, and after surgery were housed individually, with free access to food and water.

At least one week prior to experimentation, rats were anesthetized with a combination of ketamine (100 mg/kg) and acepromazine (1 mg/kg) given IM, and stainless steel cannulae (Plastic Products, Richmond, VA) were stereotaxically implanted bilaterally into the lateral ventricle or nucleus accumbens. Coordinates (from bregma) for lateral ventricle placements were: AP −0.8, L 1.3 and 4.7 mm ventral from the skull surface. To avoid puncturing the lateral ventricle in animals to be treated with NMDA or d-amphetamine, intra-accumbens cannulae were implanted at a 10 degree angle from the sagittal plane. In these animals, cannulae were 1.7 mm anterior and 2.7 lateral to bregma and 6.5 mm ventral to the skull surface. Because CPP has been shown to have minimal effects on motor activity when injected intraventricularly at the doses used in the present experiments (14), cannulae were not angled in animals that subsequently received CPP. Rats were allowed a 7–10 day recovery period prior to experiments.

All drugs used were dissolved in physiological saline. Drugs and sources were: N-methyl-d-aspartate (NMDA) (Sigma Chemical Co., St. Louis, MO), 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) (synthesized by Dr. Josef Schneider, CIBA-GEIGY, Summit, NJ) and d-amphetamine sulfate (Smith, Kline and French, Philadelphia, PA). Doses of d-amphetamine were expressed as the salt.

Motor activity was recorded by Digiscan animal activity analyzers (Omnitech, Columbus, OH), each of which consisted of a horizontal movement sensor and a vertical movement sensor located just outside a large clear plastic chamber (39 × 39 × 30 cm high). The horizontal sensor was located 2.5 cm above the floor, and the vertical sensor was mounted at a height of 13 cm. Each sensor consisted of an 8-beam array of infrared movement detectors. The central processing unit of the Digiscan system provided several measures of motor activity patterns. Distance traveled was the distance actually traversed by the experimental animal, independently of the path taken; movement time was the number of one-second intervals during which the animal moved across at least one photocell beam; and vertical movements represented the number of interruptions detected by the vertical sensor. In some experiments, direct behavioral observations were also performed at 20-min intervals, during which qualitative assessments of motor activity were conducted.

All experiments involving NMDA or d-amphetamine were conducted using a Latin square design, in which each rat received all drug doses and vehicle over the course of testing. Because previous studies of CPP microinjections into frontal cortex had indicated possible carry-over effects at a 1.0 μg dose of CPP (14), the experiments involving intra-accumbens CPP were designed so that no animal received more than one treatment. At least 48 hours elapsed between test sessions. At the beginning of each test session, animals were placed in the motor activity monitors for a 40-min habituation period (60 min for CPP). Rats were then individually removed, and hand-held during injections into the nucleus accumbens (0.5 μl) or the lateral ventricle (5 μl). Injections of either drugs or vehicle took place over a 1-min period, using a microburette. Injection needles remained in place for 10 sec after injection. Rats were then returned to the locomotor activity boxes and activity was recorded at 20 min intervals, for a total period of 60 min posttreatment (80 min for CPP).

Nucleus accumbens placements were verified by examination of fresh brain tissue sections following sacrifice of rats by decapitation. Intraventricular cannulae placements were verified by cannula injection of Evans blue dye (0.5 μl) in anesthetized rats, followed by removal of the brain and visual examination of dye localization. Data from rats with faulty cannulae placements were excluded from the analysis. Locomotor activity measures were analyzed by repeated measures analysis of variance (ANOVA), followed by Tukey tests (20).

RESULTS

Intra-Accumbens Drug Administration

Intra-accumbens injections of NMDA produced dose-related increases in distance traveled but only a slight effect on movement time and no effect on vertical movements (Fig. 1). A significant overall drug effect was found for distance traveled, $F(3,18) = 19.19$, $p<0.001$, as well as a significant drug by time interaction, $F(12,84) = 2.38$, $p<0.05$. Further analysis showed that at the highest dose tested (2 μg), NMDA significantly increased distance traveled in the first 20 min after administration ($p<0.05$, Tukey test). The overall effects of drug on movement time and vertical movements were not statistically significant. At all doses tested, NMDA induced convulsive fits, with greater than a 50% incidence at the highest dose tested (Table 1). These fits occurred 3 to 6 min after injection, and were characterized by wild running around the perimeter of the locomotor activity chambers, sometimes (but not always) preceded by tonic-clonic convulsions. Between episodes of wild running, rats appeared slightly ataxic and showed relatively little locomotion.

Nucleus accumbens injections of d-amphetamine significantly increased distance traveled [$F(3,24) = 3.53$, $p<0.05$, for treatment effect], movement time, $F(3,24) = 3.50$, $p<0.05$, and vertical movements, $F(3,32) = 2.97$, $p<0.05$ (Fig. 2). At 40 μg, amphetamine significantly increased distance traveled for 40 min after injection ($p<0.05$, Tukey test). Movement time was significantly increased by doses of either 10 or 40 μg of amphetamine over the second and third 20-min periods after injection ($p<0.05$, Tukey test). Vertical movements, which appeared to reflect rearing behavior, were significantly increased by 10 or 40 μg doses of amphetamine, and these effects were seen during the first 40 min after drug treatment ($p<0.05$, Tukey test). At no time were wild running fits or convulsive behaviors observed in animals which received d-amphetamine. Instead, the d-amphetamine-treated animals appeared to be exploring the environment actively.

No significant effect was found for the order of treatment (NMDA or amphetamine), indicating that given drug treatments did not affect subsequent responses to other doses of the same drug or to saline.

Nucleus accumbens injections of CPP (0.1 μg) markedly increased distance traveled [$F(1,12) = 36$, $p<0.0001$ for treatment effect], movement time, $F(1,12) = 45$, $p<0.0001$, and vertical

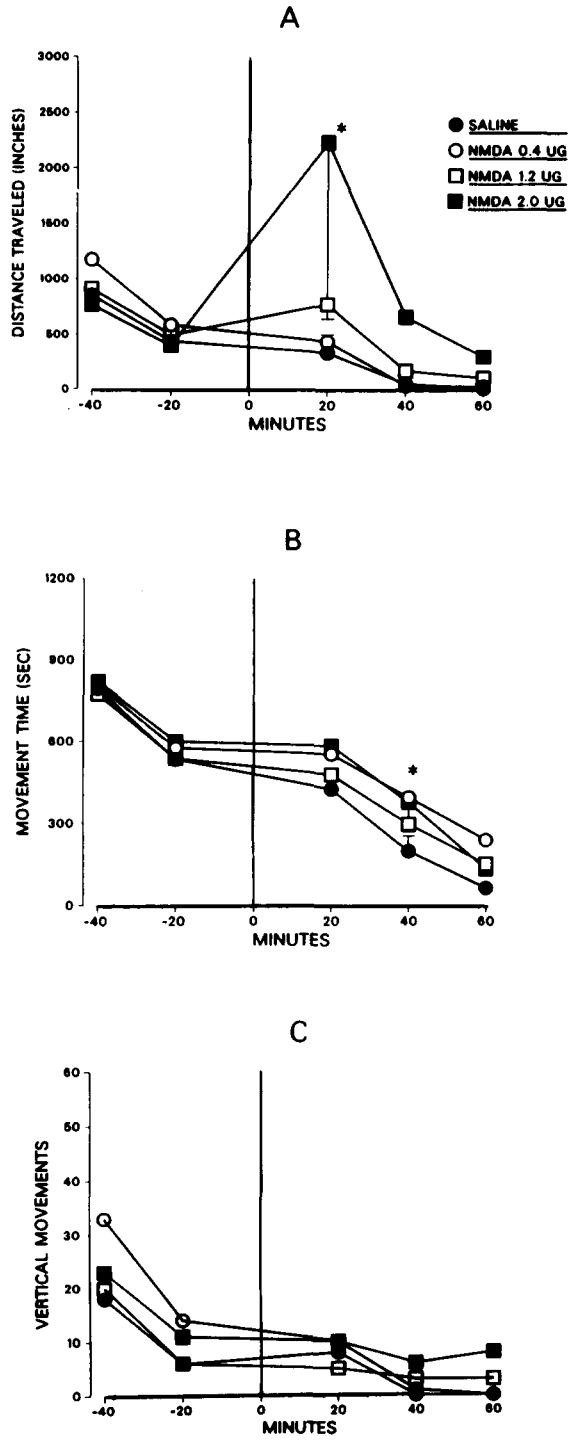

FIG. 1. Effects of intra-accumbens NMDA on distance traveled, movement time and vertical movements. *Significantly different from saline control at that time point, $p<0.05$, Tukey test. N = 10.

movements, $F(1,12)=21$, $p<0.0001$ (Fig. 3). The difference between vehicle and CPP was significant at all postdrug time intervals ($p<0.05$, t-test). At this dose, gross motor coordination appeared normal in all rats, and active exploration was noted. In 50% of the rats, occasional rapid, hopping (darting) movements were noted. These movements differed from NMDA-elicited wild

TABLE 1

OBSERVED EFFECTS OF INTRA-ACCUMBENS NMDA AND CPP ON BEHAVIOR OF RATS (PERCENT RATS SHOWING EFFECTS)

Treatment	Convulsions	Perimeter Running	Ataxia
Vehicle	0	0	0
NMDA 0.4 μg	28	40	20
1.2 μg	28	60	20
2.0 μg	55	60	20
Latency (min)	3–6	5–15	10–20

running in that they were brief (2–4 sec), were marked by hopping rather than continuous rapid running and were preceded and followed by normal behaviors including grooming. They resembled those elicited by intra-frontal cortex microinjections of CPP in rats (14). Higher doses (0.3 and 1.0 μg) also increased motor activity markedly, but muscle relaxation was also apparent at these doses and markedly altered the pattern of locomotion, complicating the interpretation of the results (data not shown; not included in statistical analyses). At no time after administration of any dose of CPP (0.1, 0.3 or 1.0 μg) were wild running episodes or clonic convulsions observed.

Intraventricular Drug Administration

Intraventricular injection of NMDA produced several behavioral effects. Analysis of variance showed a significant overall drug effect on distance traveled, $F(3,12)=5.88$, $p<0.05$, but no drug effect on movement time or vertical movement. Further analysis indicated that at the highest dose (2 μg), NMDA significantly increased distance traveled, but only during the first 20 min after administration ($p<0.05$, Tukey test, Fig. 4). This dose of NMDA produced convulsive fits in 3 of the 8 subjects tested (Table 2). These fits occurred immediately upon injection, and resembled those following nucleus accumbens microinjections of NMDA. They were best characterized as tonic-clonic convulsions followed by wild running episodes. The wild running lasted for about 20 min postinjection, correlating with the time course of significant increases in distance traveled. As with the nucleus accumbens injections, no evidence of enhanced exploratory activity was apparent upon direct observation.

Minimal effects on locomotion were observed after intraventricular injection of amphetamine (Fig. 5). There was, however, a significant interaction of time by drug effects on movement time, $F(12,91)=1.90$, $p<0.05$, and vertical movements, $F(12,81)=1.95$, $p<0.05$. Further analysis showed a delayed effect of amphetamine (40 μg) in that at 40–60 min postdrug, movement time and vertical movements were increased. Neither tonic-clonic convulsions nor wild running were observed in amphetamine-treated rats.

As in the experiments involving nucleus accumbens microinjections, no significant order effects were seen.

DISCUSSION

The present results are at variance with the suggestion that nucleus accumbens dopamine terminals may mediate the stimulation of locomotor behavior by microinjected NMDA (3,8). First, the hyperactivity induced by nucleus accumbens injections of NMDA is linked to convulsive fits and has little anatomical specificity. Second, this hyperactivity does not mimic the pattern

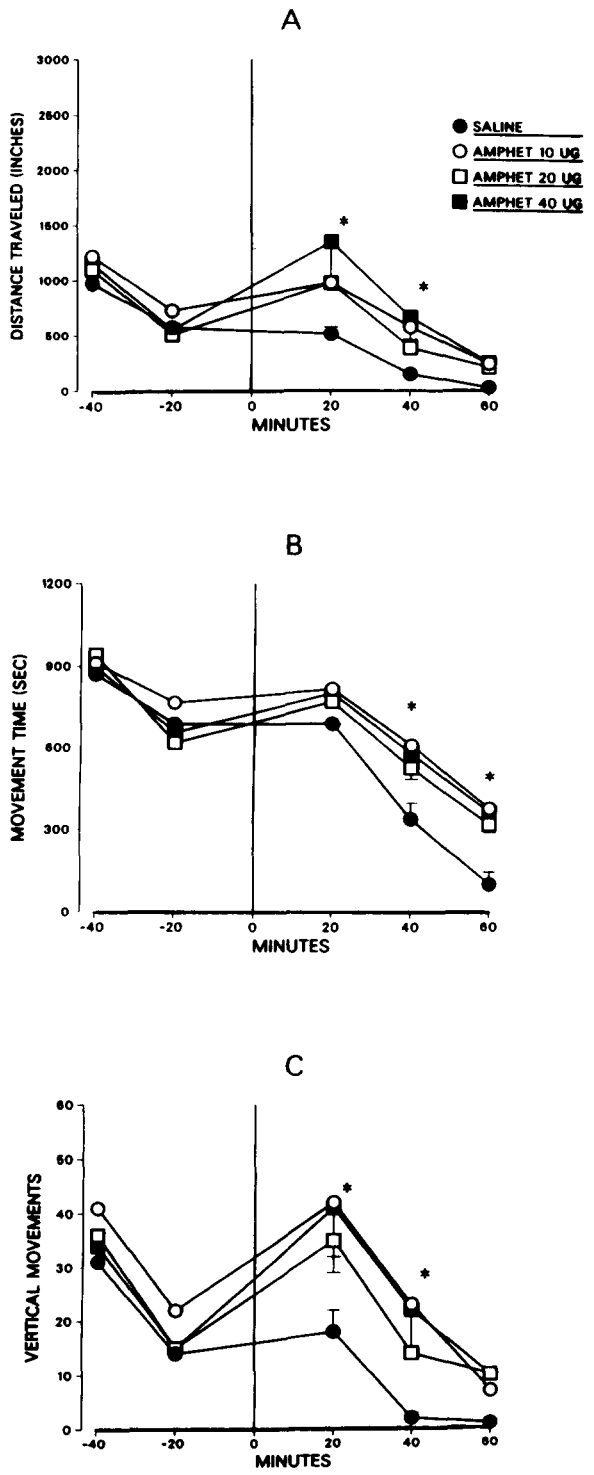

FIG. 2. Effects of intra-accumbens amphetamine on distance traveled, movement time and vertical movements. *Significantly different from saline control at that time point, $p<0.05$, Tukey test. N = 12.

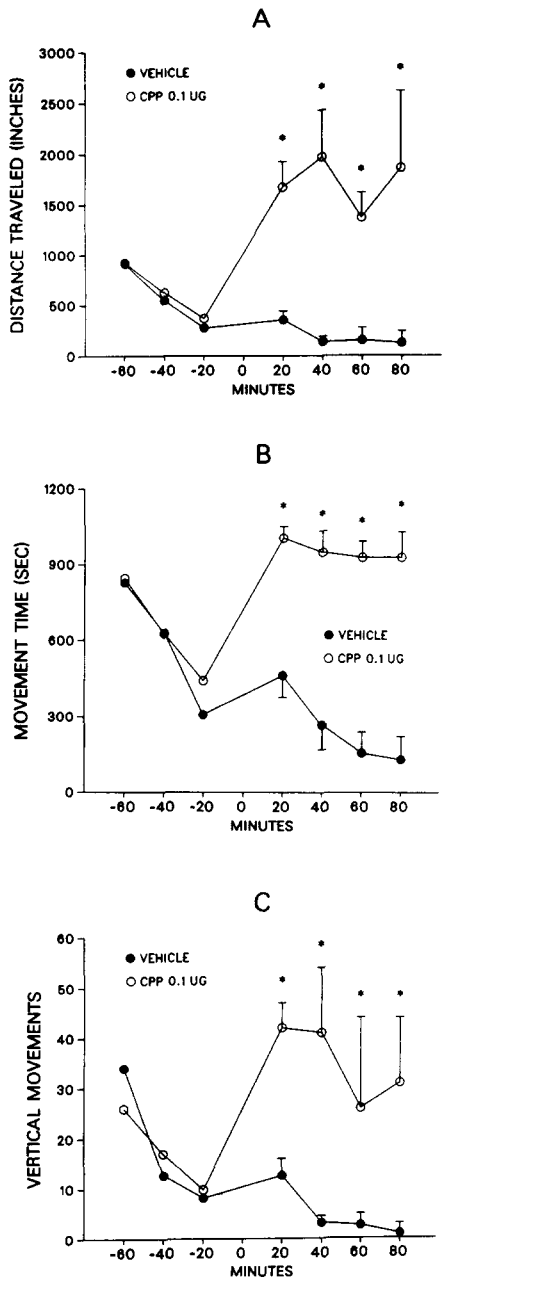

FIG. 3. Effects of intra-accumbens CPP on distance traveled, movement time and vertical movements. *Significantly different from saline control at that time point, $p<0.05$, Tukey test. N = 7.

of motor hyperactivity associated with intra-accumbens d-amphetamine, which appears to act by releasing dopamine from presynaptic terminals in nucleus accumbens. Finally, at least one competitive NMDA receptor antagonist, CPP, does not decrease motor activity upon microinjection into nucleus accumbens, but instead increases it.

The "hyperactivity" induced by intra-accumbens NMDA did not resemble that induced by intra-accumbens d-amphetamine. Instead, NMDA produced clonic convulsions and wild running behavior in a dose-related fashion when injected into either the nucleus accumbens or lateral ventricle of unanesthetized rats. The dose-related effects on distance traveled appeared to be secondary to wild running behavior, and both effects ceased after 20 min. The minimal effects on movement time (in contrast to the increase

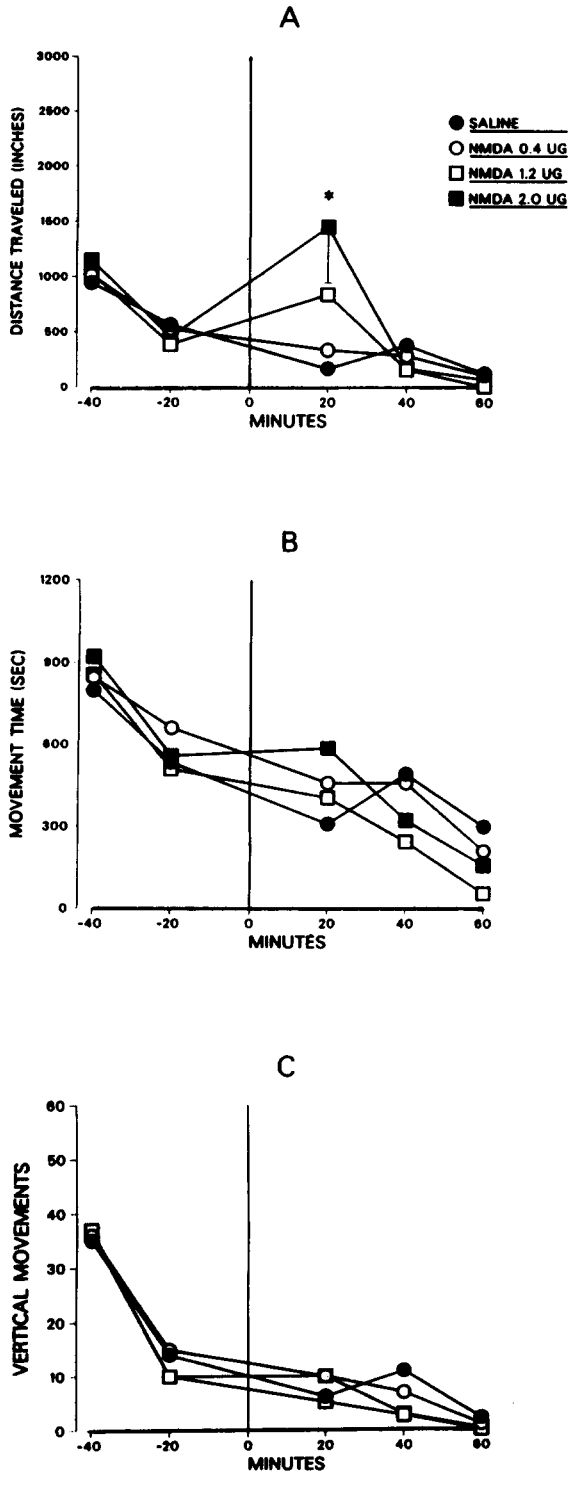

FIG. 4. Effect of intraventricular NMDA on distance traveled, movement time and vertical movements. *Significantly different from saline control at that time point, $p<0.05$, Tukey test. N = 8.

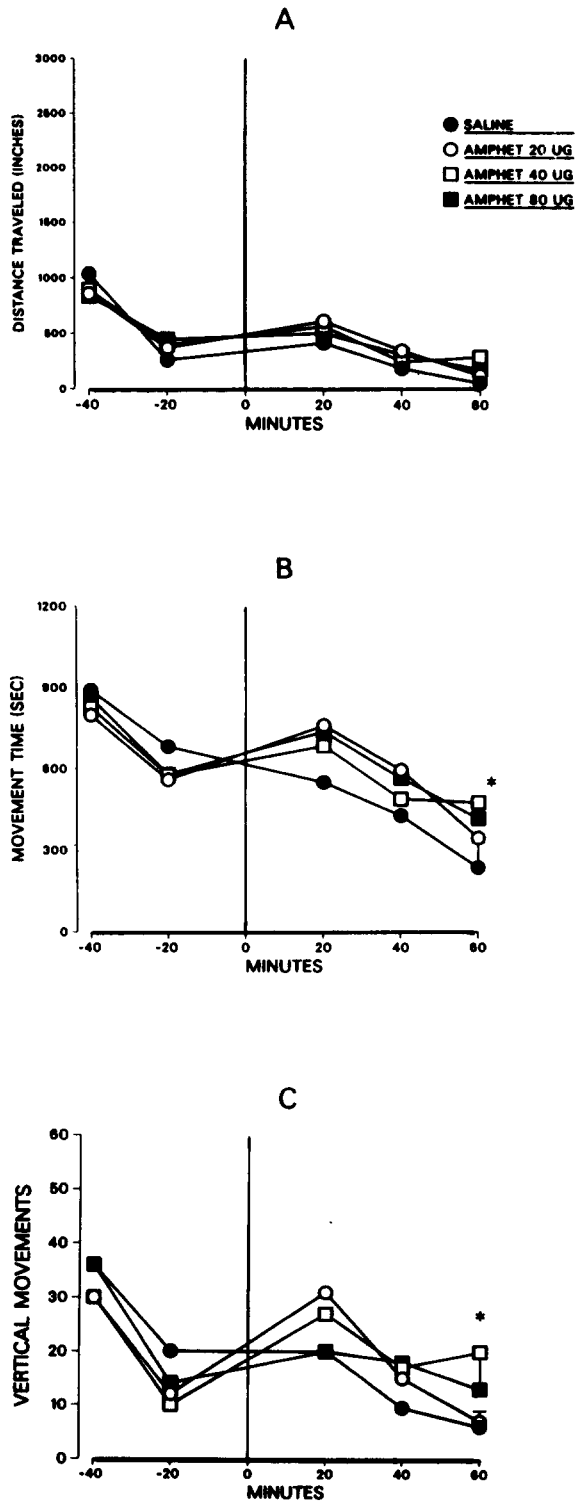

FIG. 5. Effect of intraventricular amphetamine on distance traveled, movement time and vertical movements. *Significantly different from saline control at that time point, $p<0.05$, Tukey test. N = 9.

in distance traveled) appeared to reflect periods of quiescence intervening between wild running episodes, the latter of which were characterized by rapid increases in total distance traveled. The absence of increases in vertical movements correlated well with the observed lack of rearing behavior in these animals.

In contrast, intra-accumbens amphetamine significantly in-

TABLE 2

OBSERVED EFFECTS OF INTRAVENTRICULAR NMDA ON BEHAVIOR OF RATS (PERCENT RATS SHOWING EFFECTS)

Treatment	Convulsions	Perimeter Running	Ataxia
Vehicle	0	0	0
NMDA 0.4 μg	0	0	0
NMDA 1.2 μg	13	25	0
NMDA 2.0 μg	38	63	38
Latency (min)	0	5–20	10–40

creased all three measures of activity. The increases in distance traveled and movement time appeared to reflect the enhancement of continuous exploratory motor activity that is characteristic of d-amphetamine. The increase in vertical movements was consistent with the well-known ability of d-amphetamine to enhance rearing behavior (6). These effects of amphetamine are generally considered to be mediated by dopamine release within the n. accumbens, since 6-OHDA lesions of the accumbens attenuate amphetamine-induced locomotor activity (9) and since directly acting dopamine agonists injected into the accumbens produce the same behavioral pattern, including an increase in rearing behavior [(16); unpublished observations by ourselves].

The results also failed to uphold the original hypothesis in that NMDA was equipotent when injected into lateral ventricle or nucleus accumbens. The specificity of its effects on NMDA receptors was confirmed by the ability of 2-amino-7-phosphonoheptanoic acid to antagonize the effects of intraventricular NMDA (unpublished observations). The effects of NMDA at either injection site could be distinguished only on the basis of latency to seizures. Intraventricular injection induced immediate seizures, while intra-accumbens injections induced seizures with a 3 to 6 min latency. In contrast, d-amphetamine was considerably more effective in the nucleus accumbens. A late onset of motor hyperactivity was noted when d-amphetamine was injected intraventricularly, possibly reflecting diffusion to active brain sites including the nucleus accumbens.

Other studies have indicated that microinjections of high NMDA doses in the frontal cortex or hippocampus may produce lesions (2,21) and it could be argued that perhaps NMDA-induced neurotoxicity altered the responsiveness of the animals to subsequent injections of vehicle or other injections of NMDA, since a repeated treatment design was used. This does not appear to have been the case. Statistical analysis of the data using the latin square design showed no significant order effect, indicating that given injections did not alter the subsequent responsiveness of the animals. In addition, histological evaluations of four brains were performed in animals treated with 2 μg NMDA in the nucleus accumbens (unpublished observations). No lesions nor any other gross tissue pathology could be seen in corresponding brain sections from these animals, unlike previous reports of NMDA-induced neuronal destruction (2,21), which used considerably higher doses of NMDA (≥15 μg).

One major difference between previous investigations and the present results was that neither Hamilton *et al.* (8) nor Donzanti and Uretsky (3) reported any characterization of the pattern of motor activity increases produced by NMDA or other excitatory amino acid agonists. It is, therefore, possible that the motor activity increases they reported were also attributable to wild running fits, rather than to facilitation of exploratory behavior such as is produced by stimulation of nucleus accumbens dopaminergic mechanisms. Donzanti and Uretsky (3) reported convulsions at 5.0 μg of N-methyl-D,L-aspartate, the pharmacological equivalent of 2.5 μg of NMDA, and Hamilton *et al.* (8) reported convulsions at doses exceeding 5 μg of N-methyl-D,L-aspartate. These investigators anesthetized rats with halothane (3) or ether (8) during nucleus accumbens injections, which may have masked the immediate emergence of convulsions. Upon recovery from anesthetic, wild running-type hyperactivity, rather than exploratory behavior, may have emerged.

An association of wild running fits with NMDA injections into nucleus accumbens would be consistent with previous studies of injections into other extrapyramidal brain regions. For example, injections of kainate and NMDA into globus pallidus of rats also induce dose-related stimulation of motor activity as well as dyskinesia and wild running fits (10). Wild running fits have also been observed after bilateral injections of NMDA or kainate into the ventral tegmentum or the pars compacta of the substantia nigra (17). Possible common brain sites mediating these actions include the hippocampus and the prepyriform cortex since seizures are induced by injections of low NMDA doses into these sites (15,21).

The injection of a selective NMDA receptor antagonist (CPP) into the nucleus accumbens did not reduce motor activity at doses of 0.1 to 1.0 μg. By contast, within the first 30 min after injection of 0.1 μg, significant increases in motor activity were evident. These included a marked increase in vertical movements, in contrast to the lack of effect of NMDA on this measure. The present experiments appear to constitute the first report that a competitive NMDA receptor antagonist may cause locomotor hyperactivity from nucleus accumbens, a brain region closely associated with dopamine-mediated hyperactivity. It is of interest that NMDA receptor antagonists may produce stereotyped sniffing when injected into the striatum (19) and may also produce motor hyperactivity including the observed episodic hopping (darting) behavior when injected into frontal cortex (14). The muscle relaxation (manifest as ataxia) that was seen after high intra-accumbens doses of CPP is also associated with systemic (11) and intraventricular (14) administration of CPP.

The present findings do not rule out the possibility that NMDA receptors may modulate the synaptic effects of nucleus accumbens dopamine. For example, the finding that intra-accumbens fluphenazine reduces the effects of NMDA, albeit at a dose that by itself depresses locomotor activity, suggests a possible dopamine stimulant component (3). Because of confounding behavioral effects of NMDA, however, the measurement of locomotor activity following NMDA microinjections into nucleus accumbens is not an appropriate method for assessing this interaction. In contrast, the locomotor stimulatory effects of intra-frontal cortex injections of CPP are potently reversed by low doses of haloperidol that by themselves have little or no effect on spontaneous locomotor activity (in preparation). The locomotor stimulant effects of intra-accumbens NMDA receptor antagonists may, therefore, be mediated by indirect stimulation of brain dopamine mechanisms, and this hypothesis warrants further study.

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