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Evaluation of ADCI Against Convulsant and Locomotor Stimulant Effects of Cocaine: Comparison With the Structural Analogs Dizocilpine and Carbamazepine

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SEIDLECK, B. K., A. THURKAUF AND J. M. WITKIN. *Evaluation of ADCI against convulsant and locomotor stimulant effects of cocaine: Comparison with the structural analogs dizocilpine and carbamazepine.* PHARMACOL BIOCHEM BEHAV 47(4) 839–844, 1994. – Both the antiepileptic, carbamazepine, and the *N*-methyl-D-aspartate receptor antagonist, dizocilpine, have shown preclinical efficacy against behavioral and toxic effects of cocaine. Nonetheless, side effects or toxicity of these compounds either alone or in conjunction with cocaine are problematic. 5-Aminocarbonyl-10,11-dihydro-5h-dibenzo[a,d]cyclohepten-5,10-imine (ADCI), a molecular hybrid of these compounds, has been shown to have a broad anticonvulsant profile with a good protective index (behavioral TD_{50}/anticonvulsant ED_{50}). In male Swiss Webster mice, ADCI and dizocilpine produced dose-dependent protection against the convulsant effects of cocaine that were insensitive to carbamazepine. However, in contrast to dizocilpine, ADCI did not produce behavioral impairment on the inverted screen test demonstrating a protective index of greater than 15; the protective index for dizocilpine was 1.2. All three compounds attenuated the locomotor stimulant effects of cocaine without significantly decreasing locomotor activity on their own, although the cocaine antagonism was not always dose dependent. Only dizocilpine increased spontaneous locomotor activity when given alone and augmented the locomotor stimulant effects of cocaine. The results confirm the novel anticonvulsant activity of ADCI and its lack of phencyclidine-like behavioral side effects. The data also suggest a modest blocking action of these compounds against the locomotor stimulatory effects of cocaine.

Cocaine Anticonvulsants Dizocilpine Carbamazepine Locomotor activity Mice

SEIZURES are a prominent feature of cocaine toxicity [cf. (24)]. Although typically responsive to standard emergency treatment, such seizures are sometimes resistant to standard anticonvulsants like diazepam (2,17). In a mouse model of anticonvulsant-resistant cocaine convulsions, antagonists of *N*-methyl-D-aspartate (NMDA) receptors, like dizocilpine [(+)-MK-801], have demonstrated anticonvulsant effects when given prophylactically (34). Dizocilpine has also been shown to prevent cocaine-induced seizure kindling or sensitization to the locomotor stimulatory effects and stereotypies induced by repeated administration of cocaine or amphetamine (13–15,35). Ujike et al. (28) reported that dizocilpine prevented the expression but not the development of methamphetamine-induced sensitization. Although dizocilpine has demonstrated efficacy against these behavioral and toxic effects of cocaine, dizocilpine, like other noncompetitive NMDA antagonists, produces phencyclidine-like behavioral side effects in preclinical tests of motor and subjective effects of drugs [cf. (32)].

Carbamazepine, a drug used in the control of generalized tonic–clonic and partial seizures, and in the treatment of trigeminal and glossopharyngeal neuralgias and bipolar mood disorders (22), has received attention as a potential cocaine treatment agent based on preclinical efficacy against cocaine-kindled seizures (21,30) and initial suggestions of clinical efficacy (10,11). Post and Weiss (21) have drawn a parallel be-

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tween the sensitization that develops to the stimulatory, seizurogenic effects, and mania induced by cocaine with repeated administration and the use of carbamazepine in the treatment of manic-depressive psychosis. Carbamazepine can attenuate the development of cocaine-kindled seizures but not sensitization to the locomotor stimulatory effects of cocaine in rats; however, carbamazepine does not alter the convulsions induced by high doses of cocaine once kindling has progressed [cf. (21,30,31)]. Rats self-administering cocaine at high rates showed decreases in cocaine intake when high doses of carbamazepine were mixed in their diet; however, other behaviors were also suppressed, and convulsions and death occurred in some rats (1). Sharpe et al. (25) did not find any consistent effect of carbamazepine on cocaine self-administration by rats, and higher doses suppressed food-maintained responding as well. Enhanced cardiovascular responses and the lack of effect of carbamazepine on the subjective responses to smoked cocaine base in humans has been reported in a double-blind, placebo-controlled crossover study (12). Moreover, controlled clinical investigations have failed to substantiate the initial suggestions of efficacy against cocaine craving and intake (9).

Thus, although carbamazepine and NMDA antagonists like dizocilpine may be effective in blocking some behavioral and/or toxic effects of psychomotor stimulants, side effects of these compounds alone or in conjunction with cocaine would appear to limit their utility as cocaine treatment agents [cf. (33)]. A low affinity noncompetitive NMDA antagonist, 5-aminocarbonyl-10,11-dihydro-5h-dibenzo[a,d] cycloheptene-5,10-imine (ADCI), is a hybrid molecule of dizocilpine and the anticonvulsant carbamazepine (20) which has efficacy in a variety of seizure models (23). ADCI was shown to have a protective index (separation between doses producing anticonvulsant and behavior impairing effects) comparable to that of carbamazepine, both of which were better than dizocilpine (23). The favorable protective index of ADCI, along with its structural relationship to dizocilpine and carbamazepine, suggest that ADCI may effectively alter behavioral and toxic effects of cocaine; at the same time, ADCI may be without the side-effect profile of its congeners. The present study, therefore, compared ADCI, carbamazepine, and dizocilpine for the ability to block anticonvulsant-resistant cocaine convulsions, to block or augment the locomotor stimulant effects of cocaine, and to produce sedative or motor impairing effects and phencyclidine-like behavioral effects. Locomotor activity was studied because dizocilpine has been shown to alter the sensitization that develops to the stimulatory and stereotypic effects of cocaine or amphetamine (14,35). Because dizocilpine increases locomotor activity when given alone [cf. (8)], this compound may also enhance the locomotor stimulant effects of cocaine; comparison with carbamazepine and ADCI will provide additional information on the comparative pharmacology of these compounds.

METHOD

Subjects

Experimentally naive, male Swiss Webster mice (Taconic Farms, Germantown, NY) between 10 and 12 weeks old were housed five per cage in a temperature-controlled vivarium. All animals were acclimated to their home cages and the light: dark cycle for at least 5 days prior to testing. Water was continuously available for all animals in their living cages. Experiments were conducted during the light phase of a 12 L : 12 D cycle.

Anticonvulsant Effects

The mice were food deprived for about 18 h prior to testing between 0900 and 1400. Mice (at least eight per group) were pretreated with either vehicle or test compound and returned to their home cage for the appropriate pretreatment interval. A convulsant dose of cocaine (75 mg/kg) was then administered and the mice were placed in individual Plexiglas containers (14 × 25 × 36 cm high) for observation. The presence or absence of convulsions was recorded for 15 min following injection. The dose of cocaine was chosen on the basis of previous observations that convulsions are produced in nearly 100% of the mice tested; such convulsions appear resistant to diazepam or phenobarbital pretreatment, but show a dose-dependent protection by dizocilpine (34). Convulsions were defined as loss of the righting response for at least 5 s and the occurrence of clonic limb movements; tonus was rarely if ever observed. Mice in this experiment were used only once.

Inverted Screen Test

The inverted screen test was used to assess one form of behavioral disruption induced by the test compounds. This test was an adaptation (8) of that initially described by Coughenor et al. (4). In this test, compounds with sedative and ataxic properties produce dose-dependent increases in screen failures, whereas other classes of drugs (e.g., psychomotor stimulants) do not (8). Mice (six per group) were placed individually on a 14 × 14 cm wire mesh screen (0.8 cm screen mesh) elevated 38 cm above the ground. After slowly inverting the screen, the mice were tested during a 2 min trial for their ability to climb to the top. Mice not climbing to the top (all four paws on upper surface) were counted as a failure. After the inverted screen test, mice were evaluated for locomotor activity as described below; after the locomotor activity experiements, these mice were not used again.

Locomotor Activity

Locomotor activity was used to assess the abilities of the test compounds to block or augment the locomotor stimulant

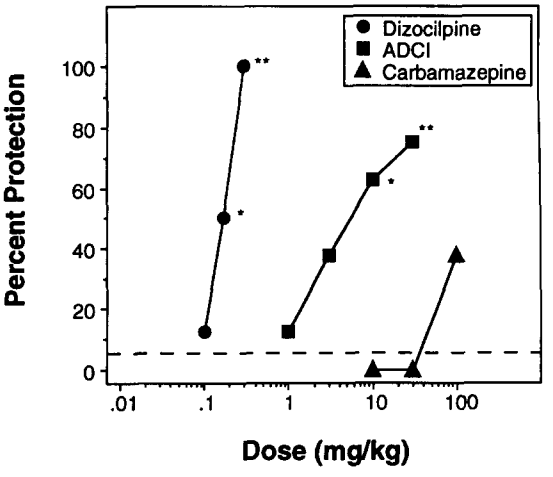

FIG. 1. Effects of dizocilpine, ADCI, and carbamazepine on convulsions induced by 75 mg/kg cocaine in male, Swiss-Webster mice (n = 8). The dashed line represents the percentage of mice not convulsing after 75 mg/kg cocaine alone (with vehicle pretreatment; n = 24). *$p < 0.05$; **$p < 0.01$ compared to cocaine alone (Fisher's exact probability test).

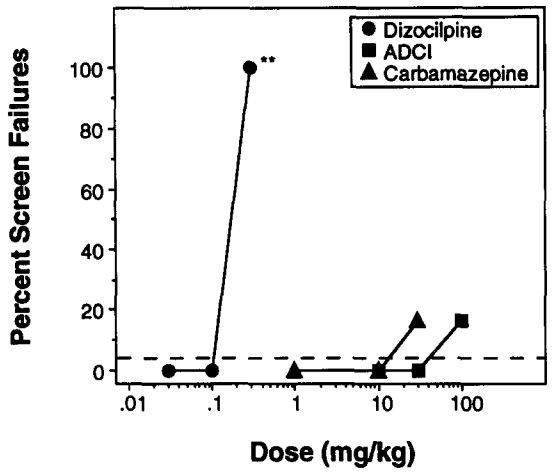

FIG. 2. Effects of dizocilpine, ADCI, and carbamazepine on the inverted screen test in male Swiss-Webster mice (n = 6). **$p < 0.01$ compared to vehicle control (n = 18)(Fisher's exact probability test).

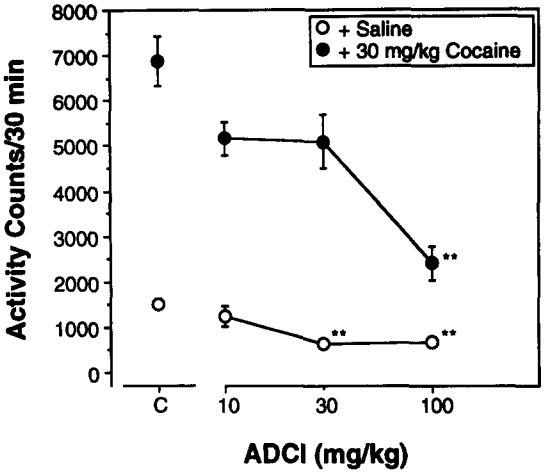

FIG. 4. Effects of ADCI alone (○) or in conjuntion with 30 mg/kg cocaine (●) in male, Swiss-Webster mice (n = 6). Control values (unconnected points above C) represent effects of saline + saline (○) or saline + 30 mg/kg cocaine (●). **$p < 0.01$ compared to respective control value (Dunnett's test).

effects of cocaine relative to their effects on spontaneous locomotor activity. Doses of 10 and 30 mg/kg cocaine were used to investigate augmentation and blockade of behavioral effects of cocaine, respectively, based on the shape of the cocaine dose-effect function (pilot experiments). In addition, locomotor activity was used in concert with the inverted screen test as a method of predicting phencyclidine-like behavioral side effects; drugs with phencyclidine-like actions produce increases in screen failures and increases in locomotor activity at comparable doses (8). Mice (six per group) were tested individually in 40 cm^3 Digiscan activity monitors equipped with photoelectric detectors placed 2.6 cm apart along the perimeter capable of sensing movement at a height of up to 20 mm off the floor (Omnitech Electronics, Columbus, OH). Drugs were injected prior to either saline or cocaine. Activity levels were then recorded for 30 min. Experiments with a drug dose alone or with cocaine were conducted simultaneously with the same drug solutions and during the same day. These mice were not used again in this or other tests.

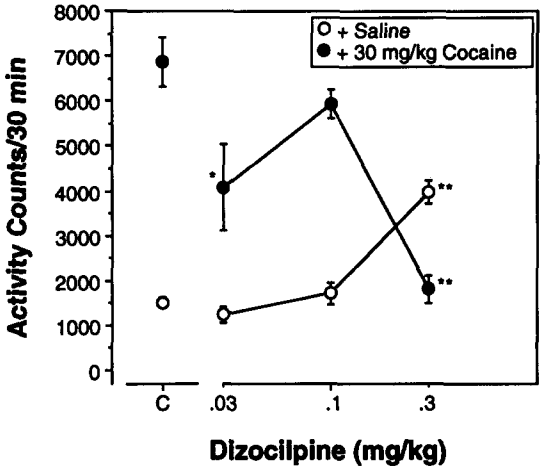

FIG. 3. Effects of dizocilpine alone (○) or in conjuntion with 30 mg/kg cocaine (●) in male, Swiss-Webster mice (n = 6). Control values (n = 18) (unconnected points above C) represent effects of saline + saline (○) or saline + 30 mg/kg cocaine (●). **$p < 0.01$ compared to respective control value (Dunnett's test).

Drugs

(−)-Cocaine HCl (Mallinckrodt) was dissolved in 0.9% NaCl. ADCI (Neurogen Corp.) and dizocilpine hydrogen maleate (Research Biochemicals, Inc.) were dissolved in distilled water. Carbamazepine (Sigma Chemical Co.) was dissolved in propylene glycol with mild heat and sonification. While heating, the final drug concentration was achieved by slow addition of distilled water to a final concentration of 20% (v/v) propylene glycol. This concentration of propylene glycol does not alter the convulsive effects of cocaine (Witkin, unpublished observations). Drugs were injected in a volume of 0.01 ml/g except at 100 mg/kg carbamazepine where twice the drug volume was given. Carbamazepine and dizocilpine were given by SC injection 30 min prior to testing, whereas ADCI was given IP, 15 min prior based on anticonvulsant efficacy data with these parameters (23,34). Cocaine was also given by the IP route. Drug doses are expressed in terms of the drug forms listed above. Test compounds were studied across a range of doses from inactive doses to those producing effects alone or in conjunction with cocaine.

Data Analysis

Dose-effect functions for the locomotor activity experiments were analyzed using data from the linear portion of the curves using standard bioassay analysis of variance (ANOVA) techniques (7,26). Individual contrasts were evaluated with Dunnett's test (27). Quantal data (screen test, convulsions) were evaluated according to the methods described by Litchfield and Wilcoxon (16), with specific comparisons between treatments with Fisher's exact probability test. Group size was based upon minimum number of animals predicted to reveal significant effects [cf. (8,34)]. Although separate control groups were run for each dose-effect function, these data were pooled into a common control group for statistical analysis be-

cause there were no significant differences across the individual control groups. Effects with statistical probabilities of error of greater than 0.05 were considered to be nonsignificant.

RESULTS

Anticonvulsant Activity

Cocaine when injected at 75 mg/kg, produced convulsions in most mice; only 1 of 16 mice tested did not convulse. Dizocilpine produced dose-dependent protection against these convulsions. Mice were completely protected at 0.3 mg/kg (Fig. 1). The ED_{50} for dizocilpine was 0.16 (95% confidence limits: 0.11-0.23). ADCI also produced dose-dependent protection against cocaine-induced convulsions, with significant blockade occurring at doses of 10 and 30 mg/kg (ED_{50} = 6.84, 95% CI: 2.39-19.55). Carbamazepine did not significantly attenuate the convulsant effects of cocaine when given up to doses of 100 mg/kg. At 100 mg/kg, one mouse died prior to cocaine administration.

When given alone, 75 mg/kg cocaine was lethal in 6 of the 16 mice tested (37.5%), with death occurring within 15 min of injection; no further deaths were observed at 24 h post injection. Death was preceeded by convulsions, piloerection, and exopthalmy. None of the drugs significantly affected lethality rates.

Inverted Screen Test

Testing for behavioral disruption on the inverted screen test revealed that only dizocilpine produced disruption; drug vehicles produced screen failures in less than 5% of the mice tested (Fig. 2). Dizocipline, when administered at 0.3 mg/kg, produced failure on this test in 100% of the mice tested, but lower doses (0.03 and 0.1 mg/kg) were completely ineffective. The ED_{50} for dizocilpine-induced screen failures was 0.19 (95% conf. limits: 0.15-0.25). In contrast, neither ADCI nor carbamazepine significantly altered behavior in this test.

The protective indices for these compounds (TD_{50}—screen/ED_{50}—anticonvulsant) was >14.6 for ADCI and 1.2 for dizocilpine. No protective index could be computed for carbamazepine because it was essentially inactive in both tests.

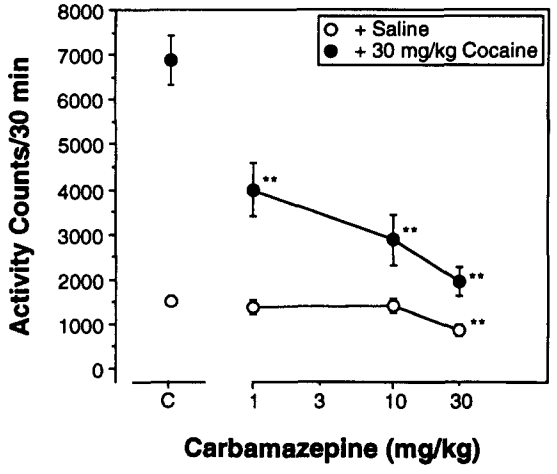

FIG. 5. Effects of carbamazepine alone (○) or in conjuntion with 30 mg/kg cocaine (●) in male, Swiss-Webster mice (n = 6). Control values (n = 18) (unconnected points above C) represent effects of vehicle + saline (○) or vehicle + 30 mg/kg cocaine (●). **p < 0.01 compared to respective control value (Dunnett's test).

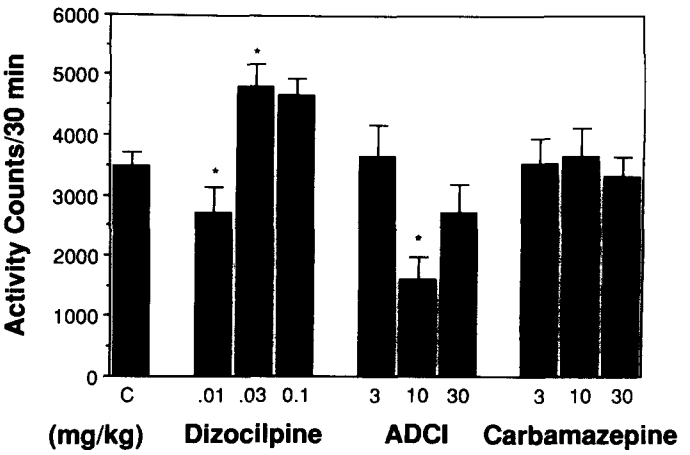

FIG. 6. Effects of dizocilpine, ADCI, and carbamazepine in combination with locomotor stimulatory effects of 10 mg/kg cocaine in male, Swiss-Webster mice (n = 6). Bar above C represents effects of 10 mg/kg cocaine alone (with saline or vehicle pretreatment) (n = 18). *p < 0.05 compared to cocaine alone control (Dunnett's test).

Locomotor Activity

The ability of ADCI and its structural analogs to block the locomotor stimulant effects of cocaine were compared to the effects of these compounds on spontaneous locomotor activity. Dizocilpine increased locomotor activity when given alone (+ saline) at 0.3 mg/kg (Fig. 3, unfilled circles). This dose of dizocilpine also attenuated the stimulation in activity produced by 30 mg/kg cocaine (Fig. 3, filled circles). At a lower dose (0.03 mg/kg), dizocilpine significantly attenuated the cocaine-induced enhancements in locomotion.

In contrast to dizocilpine, ADCI only decreased spontaneous locomotor activity (Fig. 4, unfilled circles) with doses of 30 and 100 mg/kg producing significant effects. ADCI decreased the stimulatory effects of cocaine, but only when given at 100 mg/kg. Carbamazepine displayed a dose-dependent blockade of the locomotor stimulant effects of cocaine (Fig. 5, filled circles) but only produced small decreases in spontaneous locomotor activity when tested at the highest dose of 30 mg/kg (Fig. 5, unfilled circles).

Interactions of ADCI and its structural analogs with a lower dose of cocaine were also evaluated to assess potential augmentation of the locomotor stimulant effects of cocaine. When given alone, 10 mg/kg cocaine produced a significant increase in locomotor activity compared to control (saline + saline) (p < 0.05) but the increases were about half of those achieved with 30 mg/kg in the aforementioned experiments. A low dose of dizocilpine slightly attenuated this stimulant effect of cocaine, whereas a somewhat higher dose significantly enhanced the locomotor stimulant effects of cocaine (Fig. 6). ADCI (10 mg/kg) attenuated the locomotor stimulant effects of 10 mg/kg cocaine but did not augment the stimulatory effects of cocaine at any doses tested. Carbamazepine was without effect in this experiment.

DISCUSSION

Convulsions induced by high doses of cocaine can be unresponsive to standard anticonvulsants such as diazepam or phe-

nobarbital (34). Carbamazepine, a widely used anticonvulsant in the treatment of both generalized tonic-clonic and partial seizures, was completely devoid of efficacy against cocaine-induced convulsions in the present study. Nonetheless, carbamazepine is an effective anticonvulsant against a host of other convulsants (23) and also blocks the kindling of cocaine-induced seizures in rats (21,30). In addition, the doses of carbamazepine studied were sufficient to block the locomotor stimulant effects of cocaine, and higher doses of carbamazepine suppressed spontaneous locomotor activity. As reported earlier (34), these anticonvulsant-resistant convulsions were blocked in a dose-dependent manner by dizocilpine. The dose-dependent protection against the convulsant effects of cocaine by ADCI is consistent with the NMDA- antagonist actions reported for this compound (23).

ADCI demonstrated significant separation in doses that protect against cocaine-induced convulsions (ED_{50} = 6.8 mg/kg) and doses producing behavioral or toxic side effects. Doses of 30 mg/kg were required to decrease spontaneous locomotor activity, and a dose of 100 mg/kg did not produce any deleterious effects in the inverted screen test. Thus, ADCI had protective indices for these reference behavioral side effects ranging from 4.4 to over 14.6. Moreover, ADCI did not produce any notable overt toxicity over the dose range investigated. This contrasts with a protective index of only 1.2 for dizocilpine in this study.

The antagonist effects of ADCI at NMDA receptors suggests the possibility that, like dizocilpine, ADCI could produce phencyclidine-like behavioral side effects. However, ADCI did not increase locomotor activity or increase the probability of failures on the inverted screen test, a combination of behavioral effects validated for prediction of phencyclidine-like behavioral effects (8). Carbamazepine was also devoid of these behavioral effects across the dose range studied. In contrast, dizocilpine increased locomotor activity and screen failures, with both effects occurring at comparable doses as with other drugs with phencyclidine-like pharmacological actions.

Another potential side effect of compounds for use in the treatment of cocaine dependence is an enhancement of the behavioral effects of cocaine. In the present study, the locomotor stimulant effects of a submaximally effective dose of cocaine were augmented by dizocilpine. This drug interaction occurred at doses of dizocilpine that were one-log unit lower than those that significantly stimulated locomotor activity when given alone. In contrast, ADCI did not affect performance on the inverted screen test, increase locomotor activity, or enhance the locomotor stimulant effects of cocaine. The pharmacology of ADCI could, thus, be differentiated from that of dizocilpine in being devoid of phencyclidine-like side effects and cocaine-enhancing effects, which by inference may be due to the low affinity binding of ADCI to NMDA receptors (23).

All of the compounds studied also blocked, at least to some degree, the locomotor stimulant effects of cocaine. The reduction in cocaine-stimulated activity depended upon cocaine dose. When maximal stimulation of activity was produced by cocaine (30 mg/kg), decreases in cocaine-stimulated activity were produced only by a dose of dizocilpine that also increased activity alone, questioning the selectivity of this interaction. When given in conjunction with a lower dose of cocaine, however, a behaviorally inactive dose of dizocilpine slightly attenuated the stimulatory effects of cocaine. Similarly, ADCI attenuated the locomotor stimulant effects of 30 mg/kg cocaine only at a dose that had significant effects on locomotor activity when given alone. Nonetheless, a behaviorally inactive dose of ADCI blocked the locomotor stimulation produced by 10 mg/kg cocaine. The ability of NMDA antagonists to block behavioral effects of cocaine is consistent with the other cocaine-blocking effects of these compounds (see the introductory paragraphs) and may be related to glutamatergic input to dopamine neurons. NMDA receptors have been autoradiographically localized in a number of forebrain structures, including the striatum and nucleus accumbens (18,19), two areas that have been linked to the behavioral stimulant, subjective, and reinforcing effects of cocaine [cf. (3,5,6)].

Carbamazepine also blocked the locomotor stimulant effects of cocaine, and against 30 mg/kg cocaine, carbamazepine produced significant blockade at doses that did not alter spontaneous activity levels. Surprisingly, carbamazepine did not block the stimulatory effects of 10 mg/kg cocaine. Although the mechanisms underlying these interactions are unknown, the influence of carbamazepine on dopamine turnover [cf. (28)] is a potential candidate. The general inactivity of carbamazepine against the convulsant effects of cocaine combined with the toxicity reported in long-term interaction studies (1) would not recommend carbamazepine for further clinical evaluation for cocaine-related indications. Recent negative reports from controlled clinical trials with cocaine abusers (9) are in congruence with this recommendation.

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REFERENCES

1. Carroll, M. E.; Lac, S. T.; Asencio, M.; Halikas, J. A.; Kragh, R. Effects of carbamazepine on self-administration of intravenously delivered cocaine in rats. Pharmacol. Biochem. Behav. 37: 551-556; 1990.
2. Choy-Kwong, M.; Lipton, R. B. Seizures in hospitalized cocaine users. Neurology 39:425-427; 1989.
3. Cools, A. R. Basic considerations on the role of concertedly working dopaminergic, GABA-ergic, cholinergic and serotonergic mechanisms within the neostriatum and nucleus accumbens in locomotor activity, stereotyped gnawing, turning and dyskinetic activities. In: Ellinwood, E. H., Jr.; Kilbey, M. M., eds. Cocaine and other stimulants. New York: Plenum Press; 1977:97-141.
4. Coughenor, L. L.; McLean, J. R.; Parker, R. B. A new device for the rapid measurement of impaired motor function in mice. Pharmacol. Biochem. Behav. 6:351-353; 1977.
5. Cunningham, K. A.; Dworkin, S. I.; Smith, J. E. Neurobiology of cocaine: Reinforcing and stimulus effects. In: Lakoski, J. M.; Galloway, M. P.; White, F. J., eds. Cocaine: Pharmacology, physiology, and clinical strategies. Boca Raton, FL: CRC Press; 1991:91-113.
6. Di Chiari, G.; Imperato, A. Drugs abused by humans preferen-

tially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 85: 5274–5278; 1988.
7. Finney, D. J. Statistical methods in biological assay, 2nd ed. New York: Hafner; 1964.
8. Ginski, M.; Witkin, J. M. Sensitive and rapid behavioral differentiation of *N*-methyl-D-aspartate receptor antagonists. Psychopharmacology; in press.
9. Gorelick, D. A.; Weinhold, L. L.; Henningfield, J. E. Carbamazepine (CBZ) does not alter cocaine self-administration in human cocaine addicts. College of Problems of Drug Dependence, abstracts; 1993.
10. Halikas, J. A.; Crosby, R. D.; Carlson, G. A.; Crea, F.; Graves, N. M.; Bowers, L. D. Cocaine reduction in unmotivated crack users using carbamazepine versus placebo in a short-term, double-blind crossover design. Clin. Pharmacol. Ther. 50:81–95; 1991.
11. Halikas, J. A.; Kemp, K. D.; Kuhn, K. L.; Carlson, G.; Crea, F. Carbamazepine for cocaine addiction. Lancet March 18:623–624; 1989.
12. Hatsukami, D.; Keenan, R.; Halikas, J.; Pentel, P. R.; Brauer, L. H. Effects of carbamazepine on acute responses to smoked cocaine-base in human cocaine users. Psychopharmacology (Berlin) 104:120–124; 1991.
13. Itzhak, Y.; Stein, I. Sensitization to the toxic effects of cocaine in mice is associated with the regulation of *N*-methyl-D-aspartate receptors in the cortex. J. Pharmacol. Exp. Ther. 262:464–470; 1992.
14. Karler, R.; Calder, L. D.; Chaudhry, I. A.; Turkanis, S. A. Blockade of "reverse tolerance" to cocaine and amphetamine by MK-801. Life Sci. 45:599–606; 1989.
15. Karler, R.; Chaudhry, I. A.; Calder, L. D.; Turkanis, S. A. Amphetamine behavioral sensitization and the excitatory amino acids. Brain Res. 537:76–82; 1990.
16. Litchfield, J. T.; Wilcoxon, F. A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 95:99–113; 1949.
17. Lowenstein, D. H.; Massa, S. M.; Rowbotham, M. C.; Collins, S. D.; McKinney, H. E.; Simon, R. P. Acute neurologic and psychiatric complications associated with cocaine abuse. Am. J. Med. 83:841–846; 1987.
18. Maragos, W. F.; Penney, J. B.; Young, A. B. Anatomic correlation of NMDA and ^{3}H-TCP-labelled receptors in rat brain. J. Neurosci. 8:493–501; 1988.
19. Monaghan, D. T.; Cotman, C. W. Distribution of *N*-methyl-D-aspartate-sensitive L-[^{3}H]glutamate binding sites in rat brain. J. Neurosci. 5:2909–2919; 1985.
20. Monn, J. A.; Thurkauf, A.; Mattson, M. V.; Jacobson, A. E.; Rice, K. C. Synthesis and structure-activity relationship of C5-substituted analogues of (±)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine [(±)-desmethyl-MK801]: Ligands for the NMDA receptor-coupled phencyclidine binding site. J. Med. Chem. 33:1069–1076; 1990.
21. Post, R. M.; Weiss, S. R. B. Sensitization, kindling, and anticonvulsants in mania. J. Clin. Psychiatry 50:23–30; 1989.
22. Rall, T. W.; Schleifer, L. S. Drugs effective in the therapy of the epilepsies. In: Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P., eds. Goodman and Gilman's the pharmacological basis of therpeutics. New York: Pergamon Press; 1990:436–462.
23. Rogawski, M. J.; Yamaguichi, S-I.; Jones, S. M.; Rice, K. C.; Thurkauf, A.; Monn, J. A. Anticonvulsant activity of the low-affinity uncompetetitive *N*-methyl-D-aspartate antagonist (±)-5-aminocarbonly 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (ADCI): Comparison with the structural analogs dizocilpine (MK-801) and carbamazepine. J. Pharmacol. Exp. Ther. 259:30–37; 1991.
24. Schrank, K. S. Cocaine-related emergency department presentations. Acute cocaine intoxication: Current methods of treatment. NIDA Res. Monogr. 123:110–128; 1992.
25. Sharpe, L. G.; Jaffe, J. H.; Katz, J. L. Carbamazepine produces nonspecific effects on cocaine self-administration in rats. Life Sci. Pharmacol. Lett. 51:PL13–18; 1992.
26. Snedecor, G. W.; Cochran, W. G. Statistical methods, 6th ed. Ames, IA: Iowa State University Press; 1967:135–171.
27. Tallarida, R. J.; Murray, R. B. Manual of pharmacological calculations, 2nd ed. New York: Springer Verlag; 1987.
28. Ujike, H.; Tsuchida, H.; Kanzaki, A.; Akiyama, K.; Otsuki, S. Competitive and noncompetitive *N*-methyl-D-aspartate antagonists fail to prevent the induction of methamphetamine-induced sensitization. Life Sci. 50:1673–1681; 1992.
29. Waldmeier, P. C.; Baumann, P. A.; Feur, B. D.; Herdt, P.; Maitre, L. Carbamazepine decreases catecholamine turnover in the rat brain. J. Pharmacol. Exp. Ther. 231:166–172; 1984.
30. Weiss, S. R. B.; Post, R. M.; Costello, M.; Nutt, D. J.; Tandeciarz, S. Carbamazepine prevents the development of cocaine-kindled seizures but not sensitization to cocaine's effects on hyperactivity. Neuropsychopharmacology 3:273–281; 1990.
31. Weiss, S. R. B.; Post, R. M.; Szele, F.; Woodward, R.; Nierenberg, J. Chronic carbamazepine inhibits the development of local anesthetic seizures kindled by cocaine and lidocaine. Brain Res. 497:72–79; 1989.
32. Willetts, J.; Balster, R. L.; Leander, J. D. The behavioral pharmacology of NMDA receptor antagonists. Trends Pharmacol. Sci. 11:423–4428; 1990.
33. Witkin, J. M. Pharmacotherapy of cocaine abuse: Preclinical development. Neurosci. Biobehav. Rev.; in press.
34. Witkin, J. M.; Tortella, F. C. Modulators of *N*-methyl-D-aspartate protect against diazepam- or phenobarbital-resistant cocaine convulsions. Life Sci. Pharmacol. Lett. 48:PL51–PL56; 1991.
35. Wolf, M. E.; Khansa, M. R. Repeated administration of MK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine. Brain Res. 22:164–168; 1991.