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NMDA Antagonists: Lack of Antipunishment Effect in Squirrel Monkeys[1]

ROBERT S. MANSBACH,[2] JOYCE WILLETTS,[3] SAEED A. JORTANI AND ROBERT L. BALSTER

Department of Pharmacology and Toxicology, Medical College of Virginia
Virginia Commonwealth University, Richmond, VA 23298

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MANSBACH, R. S., J. WILLETTS, S. A. JORTANI AND R. L. BALSTER. *NMDA antagonists: Lack of antipunishment effect in squirrel monkeys*. PHARMACOL BIOCHEM BEHAV **39**(4) 977–981, 1991.—Effects of the noncompetitive N-methyl-D-aspartate (NMDA) antagonist phencyclidine (PCP) and competitive antagonists 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) and 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid (NPC 12626) were studied in 6 squirrel monkeys trained under a multiple schedule of unpunished and punished lever pressing. PCP (0.03–0.3 mg/kg, IM) failed to produce increases in punished responding, even at doses that produced extreme response-rate decreases in nonpunishment components. Similarly, CPP (1–17 mg/kg) and NPC 12626 (3–30 mg/kg) did not produce increases in punished responding at any dose tested. Repeated administration of NPC 12626 (17 mg/kg) for 4 consecutive days did not result in increased rates of punished responding. The benzodiazepine anxiolytic midazolam (0.3 mg/kg) and, to a lesser extent, the barbiturate pentobarbital (5.6 mg/kg), produced increases in punished responding in the same subjects at doses that did not markedly affect unpunished responding. Coadministration of PCP (0.03 mg/kg) with doses of midazolam ranging from 0.03–3 mg/kg did not produce changes in the midazolam dose-response curve for either unpunished or punished responding. These results fail to support findings in rats that NMDA antagonists produce antipunishment effects similar to those of benzodiazepine anxiolytics.

N-Methyl-D-aspartate Phencyclidine CPP NPC 12626 Midazolam Pentobarbital Squirrel monkey Punishment Anxiolytics

N-METHYL-D-ASPARTATE (NMDA) antagonists have been of considerable recent interest because of their documented anticonvulsive, neuroprotective, and unique discriminative stimulus effects (1,12). Several studies have also reported that competitive and noncompetitive NMDA antagonists produce antipunishment ("anticonflict") effects similar to those of classical anxiolytics in rats [e.g., (7, 19, 22, 26, 27)] and pigeons (9,28).

Because a number of common CNS depressant actions are shared by NMDA antagonists and known clinical anxiolytics (2, 5, 14, 30), it has been proposed (27) that inhibition of excitatory amino acid neurotransmission might have physiological consequences similar to the enhancement of benzodiazepine-induced facilitation of gamma-amino butyric acid (GABA)-induced inhibitory function, and thereby produce anxiolytic-like behavioral effects. Positive effects of NMDA antagonists in punishment models, however, have not been consistently observed, and the magnitude of their effects frequently falls short of those produced by benzodiazepines. For example, a recent study Sanger and Jackson (24) reported no significant antipunishment activity by any NMDA antagonist tested except for the specific PCP-receptor ligand, dizolcilpine.

The present study investigated the effects of noncompetitive and competitive NMDA antagonists on punished and unpunished responding in squirrel monkeys. Increases in punished responding suppressed by punishment are considered to reflect potential anxiolytic activity in humans and are typically observed following administration of benzodiazepines and barbiturates to squirrel monkeys (3,25). Phencyclidine (PCP), which is thought to bind to a site located within the NMDA-associated Ca^{++} ionophore (16), was selected as a prototypical NMDA antagonist with little activity at the NMDA-preferring site itself. In addition, two recently developed competitive NMDA antagonists, 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) (18) and 2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid (NPC 12626) (13), were also tested in order to assess the possible role of this site in the production of antipunishment effects. Both of these compounds competitively antagonize NMDA-induced responses and both can produce discriminative stimulus effects which are qualitatively separable from those of PCP and PCP-like drugs (13, 31, 32). Midazolam and pentobarbital were selected as positive controls for the effects of benzodiazepines and barbiturates on punished behavior (3,33).

Because PCP has been reported to augment the CNS depressant effects of barbiturates (2), it is possible that antipunishment or rate-disruptive effects of a benzodiazepine might be potentiated as well. Therefore, various doses of midazolam were tested

[1]Supported by National Institute on Drug Abuse Grant DA-01442.
[2]Requests for reprints should be addressed to Robert S. Mansbach, Ph.D., Department of Pharmacology and Toxicology, Medical College of Virginia, Box 613 MCV Station, Richmond, VA 23298.
[3]Present address: Nova Pharmaceutical Corp., 6200 Freeport Centre, Baltimore, MD 21224-2788.

in the presence of a dose of PCP which, when given alone, had little effect on food-maintained behavior.

If antagonism of NMDA function through either the competitive or noncompetitive site were to produce reliable antipunishment effects in primates, then further investigation of the NMDA complex as a novel target site for antianxiety medications would be warranted. Demonstration of anxiolytic-like effects by NMDA antagonists whose discriminative stimulus effects are different from those of PCP and also do not support response-contingent self-administration would be especially useful because of the known abuse liability of PCP-like drugs.

METHOD

Subjects and Apparatus

The subjects were 6 experimentally naive adult male squirrel monkeys (*Saimiri sciureus*) weighing between 600–800 g. Monkeys were housed in a temperature- and humidity-controlled animal facility. The subjects were maintained at 85% of their free-feeding body weights with postsession supplemental feedings of Purina New World Monkey Chow and fresh fruit. Tap water was always available in the home cage.

Prior to experimental sessions monkeys were seated in Plexiglas chairs which loosely restrained them about the waist, yet allowed complete upper-body mobility. Several devices were mounted on the chair's clear Plexiglas front wall: a stainless steel response lever on the right side, pairs of white and red 28-V stimulus lights mounted above eye level, and a brass food receptacle mounted on the lower central region of the wall. The shaved distal portion of each monkey's tail was placed into a small Plexiglas stock located below the waist plate. Electrode paste was applied to the tail in order to improve electrical conductivity with two brass electrodes mounted to the stock. During sessions, chairs were placed in ventilated sound-attenuating enclosures (BRS/LVE, Beltsville, MD). A Gerbrands (Arlington, MA) food dispenser delivered 95-mg banana-flavored pellets. Sessions were controlled by a PDP 11/83 minicomputer (Digital Equipment Corp., Nashua, NH) running SKED11 software (State Systems, Kalamazoo, MI).

Procedure

Subjects responded under a multiple schedule of reinforcement with two components. When the white lights were illuminated, every 30th response (fixed-ratio or FR 30) produced a food pellet (nonpunishment component); when the red lights were illuminated, responding under the FR 30 schedule produced both food and a simultaneous 250 ms, 0.2 mA DC electric tail shock (punishment component). Punishment and nonpunishment response components, which were presented 5 times each in alternation, were 3 min in duration and separated by 30-s timeout periods during which all lights were extinguished and responses had no programmed consequences. The total session length was approximately 35 min.

NMDA Antagonist Dose Curves

Drug studies were begun when responding stabilized under the multiple schedule. Drugs were typically administered on Tuesdays and Fridays, and the results were compared with data collected on those Thursdays when saline injections were administered before the session.

Data are expressed as mean response rates (±S.E.), in responses/s, presented separately for nonpunishment and punishment components and averaged across subjects. Maximally effective doses of midazolam and pentobarbital were first determined; these doses (0.3 mg/kg midazolam and 5.6 mg/kg pentobarbital) were administered as a comparison treatment to subjects after completion of each NMDA antagonist dose curve. PCP was studied first, followed by CPP and then NPC 12626. NMDA antagonist doses were administered once to each subject. Drug effects were considered significant if mean response rates fell more that 2 S.E. outside of corresponding saline control values.

Repeated Dosing of NPC 12626

Four subjects were selected for repeated dosing of NPC 12626. The drug was given before the session (17 mg/kg) on each of 4 consecutive days. Resulting data were compared to the Thursday saline control days falling immediately before and after the dosing series.

PCP-Midazolam Interaction

One dose of PCP (0.03 mg/kg) was selected for coadministration with various doses of midazolam in 4 monkeys, in an attempt to assess possible synergistic effects on punished and unpunished responding. This dose was chosen as the highest dose that would not produce changes in response rate when given alone (Fig. 1). In this phase of the experiment, two injections (1 ml/kg) were administered 10 min prior to the session. When only one drug was being tested, the other syringe contained saline. On Thursdays, 2 saline injections were administered before the session. The effects of PCP were determined first, then of 0.01, 0.03, 0.1, 0.3, 1.0 and 3.0 mg/kg of midazolam. Next, each of the midazolam doses was tested in the presence of PCP. Finally, the effects of PCP alone were redetermined. The highest dose combination of midazolam (3 mg/kg) and PCP was tested in only 3 of the 4 monkeys. A significant PCP-midazolam interaction was considered to have occurred if the mean response rate fell more than 2 S.E. outside of the rate for tests of midazolam given alone.

Drugs

Phencyclidine HCl (supplied by the National Institute on Drug Abuse) was dissolved into sterile 0.9% saline. Midazolam maleate (Roche, Nutley, NJ) was supplied in a 5 mg/ml solution of 0.8% saline which was further diluted with 0.9% saline. Pentobarbital sodium (Harvey Labs, Philadelphia, PA) was diluted from a 65 mg/ml stock solution with sterile water. (±)CPP (Research Biochemicals Inc., Wayland, MA) and NPC 12626 (gift from NOVA Pharmaceuticals, Baltimore, MD) were dissolved into an equimolar solution of NaOH and diluted with saline. The pH of the resulting solution was approximately 7.0. Injections were administered intramuscularly in a volume of 1 ml/kg. Presession injection times were: PCP and midazolam, 10 min before the session; pentobarbital, 15 min; CPP, 60 min; NPC 12626, 30 min.

RESULTS

Control Performances and Effects of Midazolam and Pentobarbital

On control days, high stable rates of responding were maintained in all subjects during nonpunishment components; in contrast, very low rates were maintained during punishment components, with food and shock presentations occurring only infrequently. The mean nonpunishment rate during Thursday saline control sessions was 1.89 responses/s (range 1.21–3.60); the mean punishment rate was 0.02 responses/s (range 0–0.05).

Administration of midazolam produced large increases in

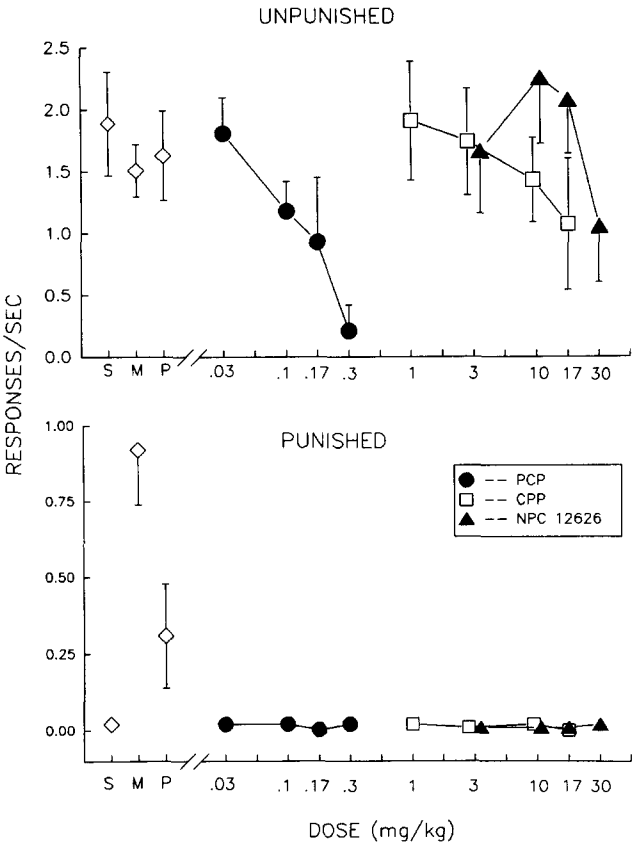

FIG. 1. Drug effects on unpunished and punished behavior of squirrel monkeys (n = 6). Represented in top (unpunished) and bottom (punished) panels are mean rates of lever pressing (±S.E.) following administration of PCP (filled circles), CPP (open squares) and NPC 12626 (filled triangles). Unconnected open diamonds on the left side of each panel illustrate the effects of saline (S), midazolam 0.3 mg/kg (M) and pentobarbital 5.6 mg/kg (PB). For administration of vehicle, midazolam and pentobarbital, means were taken for all presentations of the substance within and then across all subjects. Points without error bars indicate that the S.E. fell within the area of the symbol.

punished responding in all monkeys (>2500% of control rates). The greatest increases in punished responding were observed at 0.3 mg/kg (Fig. 1), and this dose was therefore selected as a comparison treatment for the NMDA test compounds. Pentobarbital, at a maximally effective dose of 5.6 mg/kg, produced a mean response rate of 0.31 responses/s in the punishment condition, and, although increases were seen in 5 of the 6 subjects studied, only 3 subjects responded at a rate higher than 0.1 responses/s in this schedule component. Unpunished responding was not significantly affected at this dose (Fig. 1). Other doses of pentobarbital, ranging from 1–10 mg/kg, were administered in all subjects (data not shown), but maximal increases in punished responding occurred at 5.6 mg/kg. The highest dose produced sedation and large decreases in unpunished responding.

Effects of NMDA Antagonists

Administration of the noncompetitive NMDA antagonist PCP (0.03–0.3 mg/kg) produced no increases in punished responding even at doses that significantly decreased unpunished responding (Fig. 1). Sedation and hypersalivation were frequently apparent at the highest dose.

The competitive NMDA antagonist CPP did not increase punished responding up to a dose of 17 mg/kg, which produced a mean nonpunishment response rate 43% below that of saline and produced a punishment response rate of zero in all subjects. Administration of NPC 12626 (3–30 mg/kg) also produced no effect on punished responding and resulted in mean nonpunishment response rates 45% below that of saline at the highest dose.

Repeated Presentations of NPC 12626

Because of previous reports that antipunishment effects of drugs are not always fully expressed on the first administration [e.g., (21)], four monkeys were selected for repeated dosing of NPC 12626 at a dose of 17 mg/kg. The response rates in the Thursday saline control session preceding repeated dosing averaged 1.78 responses/s in the nonpunishment component and 0.005 responses/s in the punishment component. Administration of NPC 12626 before the session once per day for 4 consecutive days resulted in punishment response rates of zero in all subjects on all test days, suggesting that the lack of anxiolytic-like effect seen with this compound was not due to insufficient exposure to the drug. Rates of unpunished responding were unaffected (mean of 1.82 responses/s) during repeated dosing of NPC 12626. Rates on the Thursday saline session following the dosing series were 1.83 and 0.003 responses/s respectively in the nonpunishment and punishment components.

PCP-Midazolam Interaction

Figure 2 illustrates the effects of midazolam alone and in combination with 0.03 mg/kg PCP. When given alone, this dose of PCP had no significant effects on either punished or unpunished responding. Midazolam produced significant increases in punished responding at all doses above 0.03 mg/kg. Rates of unpunished responding at doses above 0.3 mg/kg were significantly decreased relative to saline. Response rates following the PCP/midazolam combination in both schedule components closely paralleled those following administration of midazolam alone, with one exception at the 0.3 mg/kg dose, in which there was a nonsignificant increase in punished responding over the effect of midazolam alone.

DISCUSSION

The results of the present experiment fail to confirm reports of anxiolytic-like behavioral effects by NMDA antagonists in laboratory animals. The benzodiazepine midazolam, and to a lesser extent pentobarbital, did nevertheless produce increases in punished responding at doses that did not affect or decreased unpunished responding. Neither the noncompetitive antagonist PCP nor the competitive antagonists CPP and NPC 12626 elevated punished responding to any appreciable degree, even at doses which produced apparent response disruption in nonpunishment components. One other published experiment with squirrel monkeys (10) demonstrated a similar lack of antipunishment action by dizocilpine, a PCP-like noncompetitive NMDA antagonist, while showing positive effects of the drug in a related model using rats.

The present data are in contrast with the majority of studies using rats in various behavioral models for detection of anxiolytic drugs. In several of the rat experiments, however, NMDA antagonists were not as effective as benzodiazepines or barbiturates. For example, Bennett and Amrick (6) reported that CPP and AP7, both competitive NMDA antagonists, increased punished responding in rats, but these effects were considerably smaller than those produced by the most effective dose of diazepam. In the same study, the PCP analog ketamine did not increase punished responding, and dexoxadrol, another PCP-like drug, did so only poorly. However, in a subsequent study, Ben-

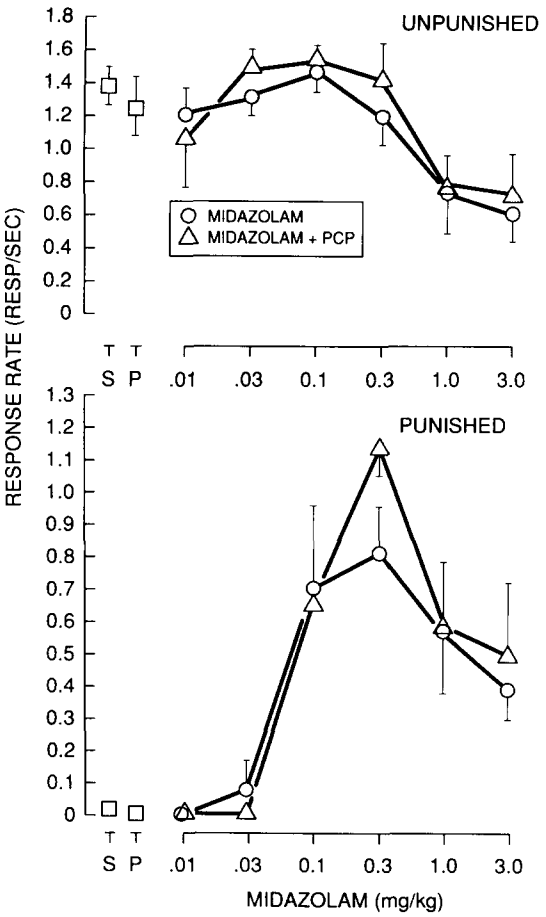

FIG. 2. Effects of midazolam and midazolam-PCP combinations on unpunished and punished behavior (n=4). Open circles illustrate effects (±S.E.) of midazolam alone; open triangles present the effects of midazolam in combination with 0.03 mg/kg PCP. Open squares at the left of each panel present the effects of saline injections (S) and of PCP 0.03 mg/kg given alone (P). The effects of PCP were assessed both before and after the two dose-response curves were determined. The data point for PCP alone represents the mean of these two observations. The highest dose combination was tested in only 3 of the 4 monkeys.

nett et al. (7) reported quantitatively similar antipunishment effects of diazepam and the competitive NMDA antagonist 1-(cis-2-carboxypiperidine-4-yl)methyl-1-phosphonic acid (CGS 19755). Other studies have reported a lesser effectiveness of NMDA antagonists than benzodiazepines under punishment procedures (8, 22, 24, 28), and some of these experiments report no effect at all of one or more NMDA antagonists. The inconsistency of results with this behavioral model makes an evaluation of potential anxiolytic activity difficult.

There is at present no clear basis for ascribing the reported antipunishment effects of NMDA antagonists in rats to a single component of the NMDA receptor complex. Reports that PCP, ketamine, dizocilpine, CPP and CGS 19755 all elevate response rates on punishment baselines suggest that either competitive or noncompetitive antagonism of NMDA receptor function may be sufficient in producing behavioral effects similar to those of anxiolytics. This contrasts with known actions of anxiolytics acting at the GABA-benzodiazepine receptor complex, where only noncompetitive facilitation of GABA function through actions at the benzodiazepine or chloride ionophore recognition site is consistently effective in producing elevations in punished behavior (23). However, as noted earlier, NMDA antagonists and GABAergic anxiolytic drugs do share common anticonvulsive and sedative-hypnotic effects, and competitive NMDA antagonists appear to produce stimulus effects similar to those of pentobarbital under some circumstances (30).

Nevertheless, the present results do not provide supportive evidence for synergistic antipunishment effects of PCP and GABAergic CNS depressants, as has been reported for other behaviors (2). PCP did not produce a leftward shift in the midazolam dose-effect curve, and did not augment low-dose effects of this benzodiazepine on punished responding or alter high-dose rate-disruptive effects (Fig. 2). Noncompetitive NMDA antagonism, therefore, does not appear to be equivalent to enhancement of GABA-ergic function in this behavioral model.

Although the present results do not support suggestions that NMDA antagonists might represent a new class of anxiolytics, a lack of antipunishment effects in primates does not always predict poor anxiolytic efficacy in humans. For example, buspirone, an atypical nonbenzodiazepine anxiolytic, does not elevate punished responding in squirrel monkeys (29) and does so only inconsistently in rats [e.g., (11,20)]. Buspirone and several of its analogs do, however, produce large antipunishment effects in pigeons [e.g., (4)] and some preliminary evidence also indicates that NPC 12626 (J. E. Barrett, unpublished observations), CPP and CGS 19755 (17) also produce sizable increases in punished responding in this species.

A clinically viable anxiolytic medication based on NMDA antagonism would be devoid of reinforcing effects that might lead to its illicit diversion. Because of the known abuse liability and untoward behavioral side-effects of PCP-like drugs (1), noncompetitive NMDA antagonists acting at this site would probably be poor candidates for clinical development. On the other hand, there is a greater likelihood that clinical utility would result from antagonists which produce their effects on NMDA neurotransmission either through direct actions at the NMDA site, on the NMDA-associated strychnine-insensitive glycine binding site (15), or at an as-yet unidentified modulatory site of NMDA function. Antagonistic actions at these sites have not as yet been clearly associated with PCP-like euphoric effects in humans or PCP-like stimulus effects in animals. The present evidence for lack of efficacy in a squirrel monkey punishment model suggests that if anxiolytic activity emerges from these diverse classes of NMDA antagonists, they are likely to differ from those of noncompetitive GABA agonists which traditionally produce positive effects in this procedure. Further study of NMDA antagonists in other animal models, and eventually in human studies, will be necessary to complete an assessment of their possible utility in treating anxiety disorders.

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