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Discriminative Stimulus Effects of the PCP/σ-Ligand (+)-*N*-Allylnormetazocine in Monkeys

STEPHEN G. HOLTZMAN

Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322

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HOLTZMAN, S. G. *Discriminative stimulus effects of the PCP/σ-ligand (+)-N-allylnormetazocine in monkeys.* PHARMACOL BIOCHEM BEHAV **44**(2) 349-355, 1993. – (+)-*N*-Allylnormetazocine [(+)-NANM] binds to both the phencyclidine (PCP) receptor and the σ-site in brain, with some selectivity for the latter. In rats, the discriminative stimulus effects of (+)-NANM are primarily PCP like. The present study was performed to determine if the discriminative effects of (+)-NANM in a primate species might reflect the actions of this drug at the σ-site. Six squirrel monkeys were trained to discriminate between IM injections of saline and 1.0 mg/kg (+)-NANM in a two-choice discrete-trial avoidance procedure. In tests of stimulus generalization, dose-dependent increases in trials completed on the (+)-NANM choice lever were produced by (+)- and (−)-NANM, by PCP and the PCP-like drugs MK-801 and thienylcyclohexyl-piperidine, and by the opioids (+)- and (−)-cyclazocine and dextrorphan; order of potency correlated with reported affinities for the PCP receptor. High-affinity σ-ligands, (+)-pentazocine, 1,3-di-*ortho*-tolylguanidine (DTG), haloperidol, and BMY 14802, as well as agonists at μ- and κ-opioid receptors, occasioned selection of the saline-appropriate choice lever. Selection of the (+)-NANM choice lever was reduced by up to 35–50% when 1.0 mg/kg (+)-NANM was given concurrently with haloperidol or BMY 14802, but was not affected substantially by (−)-butaclamol, another σ-ligand, or by naltrexone, an opioid antagonist. The discriminative effects of (+)-NANM in squirrel monkeys appear to be mediated largely by the PCP receptor and not by the σ-site or opioid receptors.

N-Allylnormetazocine Haloperidol-sensitive σ-site Phencyclidine Drug discrimination
Squirrel monkeys Opioid drugs BMY 14802 MK-801

PHENCYCLIDINE (PCP) and its analogs and some opioid drugs, in particular benzomorphan derivatives, have in common at least two binding sites in brain tissue. One site is the PCP receptor, located in the cation channel of the NMDA-receptor complex (14,17). Drugs bind to the PCP receptor with the relative affinity of MK-801 > PCP > *N*-allylnormetazocine (NANM) >> pentazocine ≥ 1,3-di-*ortho*-tolylguanidine (DTG) (22). The other site (or sites) is not part of the NMDA-receptor complex and, because it can bind some drugs that have antipsychotic activity, has been referred to as the "high-affinity haloperidol-sensitive" σ-site (38–40). Relative affinity for the σ-site is DTG ≥ pentazocine > NANM > PCP >> MK-801 (22). Occupation of the PCP receptor blocks the cation conductance induced by activation of the NMDA receptor (14,18). Biologic correlates of binding to the σ-site have been less convincingly documented. Numbered among the high-affinity σ-ligands are drugs that are either psychotomimetic or clinically effective in treating psychoses and affective disorders and drugs that can affect motor function. The activities of these drugs suggest a potential role for the σ-site in the pathogenesis of mental illness and motor dysfunction (5,11,34,49).

Drug-discrimination has proven a valuable method of studying behavioral correlates of the interaction of drugs with their neuronal substrates (10). Rats, monkeys, and pigeons trained to discriminate PCP generalize to other ligands of the PCP receptor (20,28,33,50). The order of potency of these drugs as PCP-like discriminative stimuli correlates well with relative affinity for the PCP receptor (2,51). The discriminative effects of σ-site ligands, like their effects in other bioassays, have tended to be less consistent than are the discriminative effects of PCP-like drugs. In rats, the discriminative effects of 3.0 mg/kg racemic NANM are largely PCP like (30). So are the discriminative effects of 5.0 mg/kg (+)-NANM, the isomer with higher affinity for the σ-site than for the PCP receptor (1). PCP receptor ligands also produce (+)-NANM-like discriminative effects in rats trained with 3.0 mg/kg (+)-NANM, but order of potency does not correlate significantly with affinity at either the PCP receptor or σ-site (36). Rats trained to discriminate 2.0 mg/kg (+)-pentazocine, a drug with high affinity and selectivity for the σ-site relative to the PCP receptor, generalized completely to (+)-NANM at 1.0 mg/kg and partially to PCP at 2.0 mg/kg (35). DTG is another compound that has a high affinity and selectivity for

the σ-site relative to the PCP receptor (47). A variety of opioids and PCP-like drugs engender DTG-like discriminative effects in rats trained with 3.0 mg/kg DTG; here, too, order of potency does not correlate with affinity for either the σ-site or the PCP receptor (9).

The drug discrimination studies that have used selective σ-ligands as the training drug have been performed on rats. There are species differences in the absolute affinity of ligands for the σ-site in the CNS, the neuroanatomic distribution of σ-binding sites, and the density of σ-sites relative to PCP receptors (12,32,45,46). It is possible, therefore, that a species other than the rat would afford a better separation of the σ-site-mediated activity of a drug from its PCP-receptor-mediated activity. In the present study, squirrel monkeys were trained to discriminate a relatively low dose of (+)-NANM, 1.0 mg/kg, from saline. (+)-NANM has at least a moderate selectivity for the σ-site vs. the PCP receptor, approximately an order of magnitude, and has a particularly high affinity for the σ_1-binding site (25,46). Moreover, because it is the original prototypic σ-ligand (19) there exists a large database on the binding properties and behavioral effects of NANM to facilitate the interpretation of experimental outcomes. Once the discrimination was trained, monkeys were tested for stimulus generalization to PCP-like drugs, opioid and nonopioid σ-ligands, and opioid drugs of other classes. In addition, the opioid antagonist naltrexone and several selective σ-ligands were evaluated for their ability to block the discriminative effects of the (+)-NANM training dose.

METHOD

Subjects

Subjects were six adult, male squirrel monkeys (*Saimiri sciureus*) that were experimentally naive at the beginning of the study. Between experimental sessions, monkeys were housed in individual cages where they had continuous access to food and water. The room containing the cages was maintained on a 12 L : 12 D cycle (light on at 0700 h).

Discrimination Training

Monkeys were trained in a discrete-trial avoidance/escape procedure (26,42) to discriminate between IM injections of 1.0 mg/kg (+)-NANM and 0.9% saline solution given 10 min before a session. During experimental sessions, monkeys were seated in a small primate testing chamber and held in place by a Plexiglas waist plate. The chamber was placed inside a ventilated sound-attenuating enclosure. The testing chamber had two levers mounted 10 cm apart on the front panel facing monkeys. A Plexiglas barrier with 2.5 × 4.0-cm openings on each side was between the animal and the levers. To press a lever, the monkey had to extend an arm through the opening on the same side as the lever. This arrangement prevented the monkey from pressing both levers simultaneously. The start of the trial was signaled by illuminating the house light in the test chamber. Beginning 5.0 s later, an electric current (3.0 mA) was passed through two brass electrodes that rested lightly on a shaved portion of the monkey's tail. This stimulus lasted 1.0 s and was repeated at intervals of 2.0 s. A response on the correct lever at any time during a trial ended the trial immediately and initiated a 50-s intertrial interval (ITI); the houselight was off during the ITI and the testing chamber was illuminated by a dim yellow stimulus lamp located at eye level between the two levers. Each response during the ITI resulted in the delivery of a 30-ms electrical pulse to the electrodes on the tail, a contingency that helped to restrict responding to the period when a trial was in progress. A response on the incorrect lever during a trial had no programmed consequences but resulted in the trial being recorded as incorrect. The right lever was the correct lever for three monkeys on days when they had been injected with (+)-NANM and the left lever was correct on days when they had been injected with saline. The other three monkeys had the opposite lever assignments. A session ended after either 25 trials had been completed or 40 min had elapsed.

Discrimination training sessions were conducted 5 days per week; (+)-NANM and saline were administered on alternate days. The behavior of a monkey was considered under the stimulus control of (+)-NANM and saline when the monkey finished 6 consecutive sessions in which all 25 trials had been completed and at least 22 of the trials (88%) had been correct. The first four of those sessions were conducted as training sessions, two with (+)-NANM and two with saline. The last two sessions were conducted as test sessions, with (+)-NANM administered before one and saline administered before the other. Test sessions were similar to training sessions except a response on either lever ended a trial regardless of what the monkey had been injected with before the session.

Stimulus Generalization Tests

After the criterion for stimulus control of behavior had been met, test sessions to assess stimulus generalization usually were conducted twice weekly, 3-4 days apart. Training sessions in which 1.0 mg/kg (+)-NANM or saline were administered on an alternating basis were conducted 3 days of the week to maintain stable discrimination performance. If an animal failed to maintain a performance level of at least 22 correct trials of 25 during training sessions, test sessions were postponed and additional training sessions were held instead.

A stimulus-generalization (i.e., dose-response) curve for (+)-NANM was determined first in each monkey and again at the end of the study in five of the same monkeys. One monkey died during the study, apparently of causes unrelated to the drug testing. Between, stimulus-generalization curves for novel drugs were determined in an unsystematic order, usually in three monkeys per drug. Doses of the drug being examined were administered in a random sequence that included the vehicle for the drug and, in the case of antagonism experiments, the training dose of (+)-NANM as well. Drugs tested for stimulus generalization were injected IM 10 min before a session. Drugs tested as antagonists were injected IM 15 min before a session, 5 min before either the 1.0-mg/kg training dose of (+)-NANM or 0.25 mg/kg PCP. For drugs that were not generalized completely from 1.0 mg/kg (+)-NANM, the highest dose tested usually was either a) the lowest dose that impaired performance during an experimental session (i.e., significantly increased response latency and/or resulted in failures to avoid) or b) one dose lower than a dose that produced observable motor deficits or other adverse effects when administered to an untrained monkey not part of the current study.

Drugs

The following drugs used in this study were obtained from the National Institute on Drug Abuse (Rockville, MD): NANM, (+)-and(−)-cyclazocine base, (+)-pentazocine succinate, PCP HCl, thienylcyclohexylpiperidine HCl (TCP), and naltrexone HCl. Other drugs used and their source were: levorphanol tartrate and dextrorphan tartrate (Hoffmann-

LaRoche, Inc., Nutley, NJ), (+)-MK-801 hydrogenmaleate and (−)-butaclamol HCl (Research Biochemicals, Inc., Natick, MA), butorphanol tartrate and BMY-14802 (Bristol-Myers Co., Wallingford, CT), haloperidol (McNeil Pharmaceutical, Springhouse, PA), ethylketocyclazocine base (EKC; Sterling-Winthrop Research Institute, Rensselaer, NY), morphine sulfate (Penick Corp., Newark, NJ), and DTG (Dr. E. Weber, Univ. of California, Irvine, CA). The salts were dissolved in 0.9% saline except for dextrorphan (distilled water), MK-801 (distilled water and a few drops of 1.0 N HCl), and butaclamol (5% absolute ethanol and distilled water). Free bases were dissolved in three parts 8.5% lactic acid and two parts 1.0 N sodium hydroxide. Drugs and vehicles were injected into a thigh muscle in a volume of 0.5 ml/kg body weight. Doses of the drugs are expressed in terms of the free base.

Data Analysis

Discrimination data are presented as the number of trials completed on the (+)-NANM-appropriate lever; the remaining trials of the 25-trial session were completed on the saline-appropriate lever. The ED_{50} was defined as the dose resulting in selection of the (+)-NANM-appropriate lever in 12.5 trials of a test session. ED_{50} values for individual animals were estimated by linear regression of the ascending limb of the stimulus-generalization curve using at least three points or, in the few instances where only two points were available, by simple interpolation. These values were then used to calculate average ED_{50}s and 95% confidence limits for the group. The latencies to respond during a trial were summed over the 25 trials of the test session. Response latency data are presented as means ± SEM. The response latencies for each drug series were subjected to analysis of variance (ANOVA) with repeated measures followed, where appropriate, by the Student-Newman-Keuls test (8).

RESULTS

Stimulus Control of Behavior by (+)-NANM

The six monkeys satisfied the criterion for stimulus control of behavior by saline and 1.0 mg/kg (+)-NANM in an average of 37 sessions (range: 32–46). The stimulus-generalization curve for (+)-NANM (0.25–2.0 mg/kg) was relatively steep, with trials completed almost exclusively on the saline-appropriate lever at 0.25 mg/kg and almost exclusively on the (+)-NANM-appropriate lever at 1.0 and 2.0 mg/kg (Fig. 1), giving an ED_{50} of 0.5 mg/kg (Table 1). The ED_{50} for (+)-NANM was essentially unchanged at the conclusion of the study in the five surviving monkeys: 0.47 (0.43–0.51) mg/kg. Response latencies initially were increased dose dependently by (+)-NANM, $F(4, 20) = 3.02$, $p < 0.05$, with average latencies going from 46 ± 5 s after saline to 43 ± 5, 59 ± 9, 92 ± 25, and 115 ± 31 s after 0.25, 0.5, 1.0, and 2.0 mg/kg, respectively. In contrast, average response latencies were not affected significantly during redetermination of the stimulus-generalization curve for (+)-NANM, $F(4, 16) = 1.29$, $p > 0.1$: 44 ± 9, 42 ± 9, 64 ± 15, and 57 ± 12, respectively, after saline, 0.25, 0.5, 1.0, and 2.0 mg/kg of (+)-NANM.

Stimulus Generalization to Novel Drugs

(−)-NANM, tested over the same range of doses as (+)-NANM, was approximately one third as potent (Table 1) and was generalized only partially at 2.0 mg/kg (Fig. 1). This dose

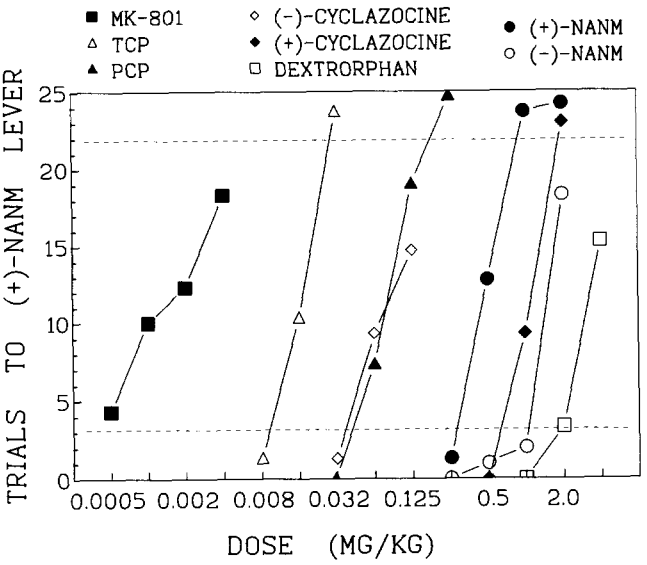

FIG. 1. Stimulus-generalization curves for those drugs that produced dose-dependent increases in the number of trials completed on the (+)-*N*-allylnormetazocine [(+)-NANM]-appropriate choice lever in squirrel monkeys trained to discriminate between IM injections of saline and 1.0 mg/kg (+)-NANM. Each point is the mean number of trials completed on the (+)-NANM-appropriate choice lever in a 25-trial session; the remaining trials of the session were completed on the lever appropriate for saline. Means are based upon one observation in each of three to four or six, [(+)-NANM] monkeys. The upper and lower horizontal broken lines indicate the minimum levels at which the discrimination performance of the monkeys was maintained in training sessions with 1.0 mg/kg (+)-NANM and saline, respectively.

increased the average response latency to 130 ± 40 s from 49 ± 11 s after saline, and higher doses were not tested. Two other pairs of opioid enantiomers were tested for stimulus generalization: (+)-cyclazocine and (−)-cyclazocine and levorphanol and dextrorphan. Of these, only (+)-cyclazocine (0.5–2.0 mg/kg) was generalized completely (Fig. 1), being half as potent as (+)-NANM (Table 1). (−)-Cyclazocine (0.031–0.125 mg/kg) was an order of magnitude more potent than (+)-cyclazocine (Table 1) but produced a dose-dependent increase in response latencies, $F(3, 6) = 7.28$, $p < 0.05$; at the highest dose tested, 0.125 mg/kg, response latencies averaged 89 ± 11 s as compared to 36 ± 6 s after vehicle, and an average of 14.7 trials were completed on the (+)-NANM-appropriate lever (Fig. 1). Dextrorphan (1.0–4.0 mg/kg) also was generalized partially (Fig. 1) and also increased response latencies over the range of doses examined, $F(3, 6) = 5.94$, $p < 0.05$; for example, response latencies averaged 34 ± 4 s after saline and 73 ± 12 s after 4.0 mg/kg dextrorphan. Levorphanol occasioned only saline-appropriate lever selection, while increasing average response latencies from 30 ± 2 s after saline to 32 ± 3, 53 ± 10, and 123 ± 35 s, respectively, after 0.125, 0.25, and 0.5 mg/kg, $F(3, 6) = 6.54$, $p < 0.05$.

Three drugs that bind to PCP receptors—PCP (0.032–0.25 mg/kg), TCP (0.008–0.032 mg/kg), and MK-801 (0.0005–0.004 mg/kg)—produced dose-dependent increases in (+)-NANM-appropriate lever selection; PCP and TCP were generalized completely and MK-801 was generalized partially at the highest dose that could be tested (Fig. 1). All three drugs

TABLE 1

ED_{50} OF DRUGS FOR (+)-NANM-APPROPRIATE LEVER SELECTION

Drug	ED_{50} (95% Confidence limit, mg/kg)	Potency Relative to (+)-NANM
MK-801*	0.0015 (0.0001–0.0157)	333
TCP	0.016 (0.010 –0.028)	31
PCP	0.089 (0.072 –0.110)	5.6
(–)-Cyclazocine*	0.093 (0.018 –0.479)	5.4
(+)-NANM	0.50 (0.40 –0.62)	1.0
(+)-Cyclazocine	1.12 (0.75 –1.66)	0.45
(–)-NANM*	1.58 (1.29 –1.95)	0.32
Dextrorphan*	3.98 (1.86 –8.51)	0.13

*Partial generalization: Maximum average number of trials completed on the (+)-NANM-appropriate choice lever was more than 12.5 but less than 22 trials.

were significantly more potent than (+)-NANM, MK-801 being two orders of magnitude more potent (Table 1). All three drugs more than doubled average response latencies over the dose range tested: PCP, $F(3, 6) = 3.78, p = 0.05$; TCP, $F(3, 6) = 13.81, p < 0.01$; MK-801, $F(4, 8) = 8.94, p < 0.01$.

In addition to the μ-opioid agonist levorphanol, other drugs that occasioned selection of the choice lever appropriate for saline were the μ-opioid agonist morphine, the κ- or mixed μ- and κ-opioid agonists EKC and butorphanol, and the σ-site ligands haloperidol, BMY 14802, (+)-pentazocine, and DTG (Table 2). One of the three monkeys tested with 8.0 mg/kg DTG had a brief tonic-clonic convulsion following removal from the testing chamber and was treated with 2.5 mg/kg diazepam.

Antagonism of (+)-NANM-Like Discriminative Effects

Four drugs were tested over a broad range of doses in combination with 1.0 mg/kg (+)-NANM to determine if they could block the discriminative effects of the training dose. The results are illustrated in the top panel of Fig. 2. Naltrexone and (–)-butaclamol, 0.0625–4.0 mg/kg, had little consistent effect on the selection of the drug-appropriate choice lever occasioned by the training dose of (+)-NANM. However, haloperidol (0.0081–0.0625 mg/kg) and BMY 14802 (0.0625–4.0 mg/kg) both decreased the number of trials completed on the (+)-NANM-appropriate lever, haloperidol to

TABLE 2

DRUGS THAT OCCASIONED SALINE-APPROPRIATE LEVER SELECTION IN SQUIRREL MONKEYS TRAINED TO DISCRIMINATE 1.0 MG/KG (+)-NANM FROM SALINE

Drug	Dose Range Tested (mg/kg)
Haloperidol	0.008–0.064
EKC	0.016–0.064
Levorphanol	0.125–0.50
Butorphanol	0.125–1.0
BMY 14802	0.25 –4.0
Morphine	0.25 –4.0
(+)-Pentazocine	1.0 –4.0
DTG	1.0 –8.0

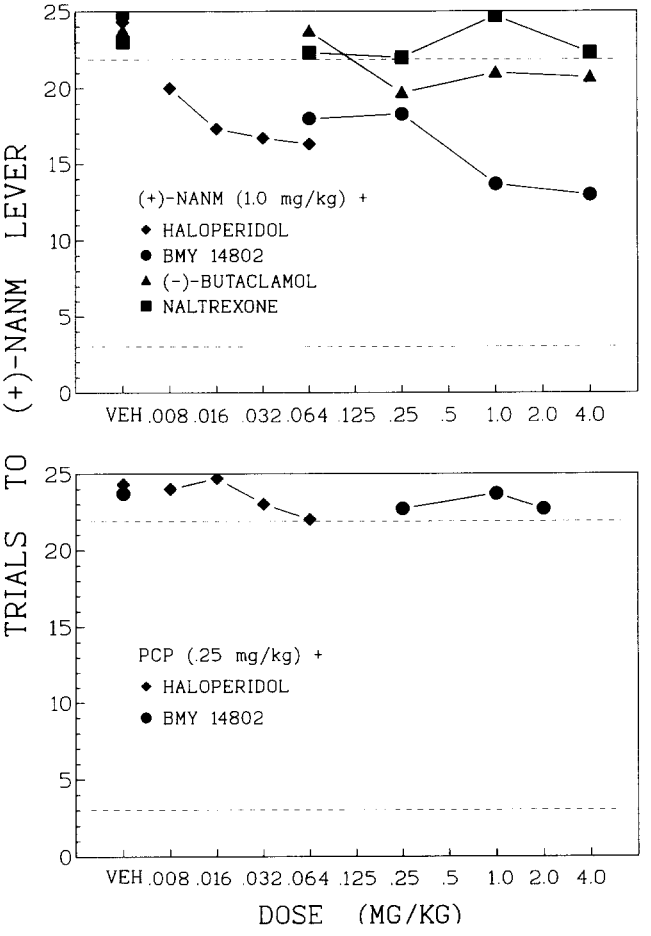

FIG. 2. Effects of graded doses of haloperidol, BMY 14802, (–)-butaclamol, and naltrexone on the discriminative effects of the training dose of (+)-*N*-allylnormetazocine [(+)-NANM] (top) and of haloperidol and BMY 14802 on the (+)-NANM-like discriminative effects of 0.25 mg/kg phencylidine (PCP) (lower panel); $n = 3$. The mean number of trials completed on the (+)-NANM-appropriate lever in sessions that followed administration of drug vehicle plus either 1.0 mg/kg (+)-NANM or 0.25 mg/kg PCP are indicated by the points above VEH. Other details as in Fig. 1.

TABLE 3

ORDER OF POTENCY OF DRUGS AS (+)-NANM-LIKE DISCRIMINATIVE STIMULI IN SQUIRREL MONKEYS COMPARED TO AFFINITY FOR THE PCP RECEPTOR AND SIGMA-BINDING SITE

Tritiated Ligand (ref.)	Correlation Coefficient* (n)†
[^{3}H]MK-801 (21)	$r_s = 0.964, p = 0.002$ (7)
[^{3}H]PCP (23)	$r_s = 0.905, p = 0.004$ (8)
[^{3}H]Dextrorphan (7)	$r_s = 0.810, p = 0.019$ (8)
[^{3}H]TCP (24)	$r_s = 0.750, p = 0.053$ (7)
[^{3}H]DTG (13)	$r_s = 0.029, p < 0.1$ (6)
[^{3}H]NANM (40)	$r_s = -0.143, p > 0.01$ (6)
[^{3}H]Dextromethorphan (15)	$r_s = 0.262, p > 0.1$ (8)

*Spearman rank-order correlation (8) based upon ED_{50}s in Table 1.
†Number of drugs in common between studies.

an average of 16.3 trials at 0.0625 mg/kg and BMY 14802 to an average of 13.0 trials at 4.0 mg/kg. Haloperidol increased average response latencies markedly over its range of doses in combination with (+)-NANM, $F(5, 10) = 7.32$, $p < 0.005$, from 44 ± 7 and 51 ± 6 s after vehicle + vehicle and vehicle + (+)-NANM (1.0 mg/kg), respectively, to 52 ± 4, 67 ± 19, 145 ± 57, and 210 ± 32 s, respectively, for 0.008, 0.016, 0.031, and 0.0625 mg/kg. Average response latencies were also increased significantly by the combination of BMY 14802 and (+)-NANM, $F(5, 10) = 8.15$, $p < 0.005$, but to a lesser extent than they were by haloperidol and (+)-NANM: 47 ± 6 and 38 ± 12 s after vehicle + vehicle and vehicle + (+)-NANM, respectively, and 40 ± 7, 38 ± 4, 44 ± 5, and 95 ± 7 s after 0.0625, 0.25, 1.0, and 4.0 mg/kg BMY 14802 + (+)-NANM.

Haloperidol (0.008–0.0625 mg/kg) and BMY 14802 (0.25–2.0 mg/kg) also were tested in combination with 0.25 mg/kg PCP, a dose that occasioned drug-appropriate lever selection comparable to that occasioned by the training dose of (+)-NANM (Fig. 1). Neither of these drugs reduced the (+)-NANM-appropriate lever selection occasioned by PCP (Fig. 2, bottom). They did, however, increase average response latencies dose dependently: haloperidol, $F(5, 10) = 8.53$, $p < 0.005$; BMY 14802, $F(4, 8) = 5.84$, $p < 0.05$. The magnitude of increases in response latencies for combinations of haloperidol and 0.25 mg/kg PCP was similar to that seen for the combined administration of haloperidol and 1.0 mg/kg (+)-NANM. BMY 14802 when combined with PCP resulted in much greater increases in response latencies than when it was combined with (+)-NANM (e.g., 48 ± 10 s after vehicle + vehicle and 279 ± 74 s after 2.0 mg/kg BMY 14802 + PCP), effectively limiting the highest dose of BMY 14802 that could be tested with PCP.

DISCUSSION

This study showed that it is possible to establish and maintain stimulus control of the behavior of squirrel monkeys with 1.0 mg/kg (+)-NANM. Once established, drug-induced stimulus control of behavior remained stable throughout the study; the ED_{50} of (+)-NANM for drug-appropriate lever selection was virtually the same at the beginning of the study and at the end, 10–12 months later. Early in the study, the training dose of (+)-NANM impaired the performance of monkeys, as reflected by a doubling of response latencies. This effect was not evident when the stimulus-generalization curve for (+)-NANM was redetermined at the conclusion of the study. The differential development of tolerance to effects of (+)-NANM indicates that whatever action of (+)-NANM was responsible for increasing response latencies was not a critical factor in the stimulus control of behavior. This is consistent with the finding that the discriminative and response-rate-decreasing effect of PCP are separable in rats (3). Other characteristics of stimulus control of behavior by (+)-NANM included a modest, threefold stereoselectivity for the dextrorotatory vs. the levorotatory optical isomer and pharmacological selectivity. μ-Opioid and κ-opioid agonists, at doses discriminable in squirrel monkeys trained with either morphine or cyclazocine (26,27,43), occasioned responding only on the choice lever appropriate for saline. Thus, the discriminative stimulus effects of (+)-NANM do not appear to contain an important opioid component, a conclusion also supported by the insensitivity of stimulus control of behavior to antagonism by naltrexone.

A principal objective of this study was to determine if stimulus control of behavior by (+)-NANM in squirrel monkeys could provide a behavioral correlate of binding to the σ-site in the brain, presumably the σ_1-site, for which (+)-NANM has the highest affinity (25,46). The results of tests of stimulus generalization to novel drugs indicate that the answer is no whereas the results of the antagonism experiments are equivocal. Monkeys generalized completely to PCP and TCP and partially to MK-801, drugs with higher affinity for the PCP receptor than for the σ-site. Indeed, MK-801 has a vanishingly low affinity for the σ-site, yet was, by far, the most potent of the drugs tested, two orders of magnitude more potent than (+)-NANM. MK-801 usually has ranged from 4–15 times more potent than PCP in rats and rhesus monkeys trained to discriminate either of these drugs from saline (4,6,16,44,48). Squirrel monkeys seem in particular sensitive to MK-801.

TABLE 4

ORDER OF POTENCY OF DRUGS AS (+)-NANM-LIKE DISCRIMINATIVE STIMULI IN SQUIRREL MONKEYS COMPARED TO RELATIVE POTENCY IN OTHER DRUG DISCRIMINATION STUDIES

Training Drug (mg/kg) (ref.)	Species	Correlation Coefficient (n)
PCP (3.0) (30)	Rat	$r_s = 0.929, p = 0.006$ (7)
(±)-NANM (3.0) (29)	Rat	$r_s = 0.886, p = 0.058$ (6)
PCP (1.5) (20)	Pigeon	$r_s = 0.857, p = 0.019$ (7)
DTG (3.0) (9)	Rat	$r_s = 0.571, p > 0.01$ (7)

Details as in Table 3.

The pattern of stimulus generalization to the other drugs examined also is consistent with discriminative effects mediated by the PCP receptor. For example, (−)-cyclazocine was an order of magnitude more potent than (+)-cyclazocine in producing (+)-NANM-like stimulus control of behavior. Relative to its dextrorotatory counterpart, (−)-cyclazocine has a higher affinity for the PCP receptor (50), is more potent in producing PCP-like discriminative effects (29), but has a lower affinity for the σ-binding site (46). In addition, high-affinity ligands of the σ-site, such as haloperidol, DTG, and (+)-pentazocine, failed to occasion (+)-NANM-appropriate lever selection. Table 3 shows the rank-order correlation between the order of potency of drugs as (+)-NANM-like discriminative stimuli and their affinity for the PCP receptor and σ-site as defined by displacement of the specific binding of various tritiated ligands. Studies that examined at least six of the eight drugs listed in Table 1 are represented. Correlations are significant for ligands of the PCP receptor—MK-801, PCP, TCP, dextrorphan—but not for ligands of the σ-site—NANM, DTG, dextromethorphan. The rank-order of potency of drugs in the present study also correlates significantly with order of potency in animals trained to discriminate PCP or racemic NANM, which is PCP-like in the rat (30), but not with order of potency in rats trained to discriminate DTG (Table 4).

Several high-affinity ligands of the σ-site were examined for their ability to block the discriminative effects of the (+)-NANM training dose. (−)-Butaclamol had a negligible effect on drug-appropriate lever selection, a result similar to that seen in rats trained to discriminate 5.0 mg/kg (+)-NANM (1). However, haloperidol and BMY 14802 (41) produced orderly dose-related decreases in number of trials completed on the (+)-NANM choice lever to a maximum of approximately 65 and 50% of trials, respectively. Haloperidol produced a similarly modest partial antagonism of the discriminative effects of a 10-mg/kg training dose of (+)-NANM in rats (1) and a somewhat greater antagonism of a 3.0-mg/kg training dose (37). It also attenuated, but did not completely prevent, the drug-appropriate lever selection induced by a 3.0-mg/kg training dose of racemic pentazocine in squirrel monkeys (49). There are no reports on the use of BMY 14802 in this particular experimental context. Combinations of the (+)-NANM training dose and the higher doses of haloperidol and BMY 14802 impaired the performance of monkeys, as evidenced by large increases in response latencies. Therefore, it is possible that decreases in selection of the drug-appropriate lever reflect a nonspecific decrease in drug-induced stimulus control as a consequence of a general impairment of behavior. However, responding did not increase during the interval between trials, as might have been expected had stimulus control of behavior been weakened by the combination of drugs. Further, performance was adversely affected just as much, or more, by the combinations of PCP (0.25 mg/kg) and haloperidol or BMY 14802, yet (+)-NANM-appropriate responding was not reduced. The results of these experiments are difficult to interpret, but they do not exclude the possibility that (+)-NANM, haloperidol, and BMY 14802 have in common a site of action that subserves, in part, the discriminative effects of (+)-NANM.

In conclusion, this study provides the first pharmacological characterization of the stimulus control of behavior of a primate species by (+)-NANM. Minor differences notwithstanding, the results are in basic agreement with those of studies performed on rats, which indicate that the discriminative stimulus effects of NANM are largely PCP like in nature.

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