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# Effects of Calcium Channel Blockers on Behaviors Induced by the *N*-Methyl-D-Aspartate Receptor Antagonist, Dizocilpine, in Rats

IRINA A. SUKHOTINA, OLGA A. DRAVOLINA, IVAN O. MEDVEDEV AND ANTON YU. BESPALOV

*Laboratory of Behavioral Pharmacology, Institute of Pharmacology, Pavlov Medical University, Lev Tolstoy str., 6/8, St. Petersburg, 197089, Russia*

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SUKHOTINA, I. A., O. A. DRAVOLINA, I. O. MEDVEDEV AND A. YU. BESPALOV. *Effects of calcium channel blockers on behaviors induced by the* N-*methyl-*D*-aspartate receptor antagonist, dizocilpine, in rats*. PHARMACOL BIOCHEM BEHAV **63**(4) 569–580, 1999.—The present study assessed the ability of voltage-sensitive calcium channel (VSCC) blockers to affect the behavioral effects of the noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, dizocilpine, in male Wistar rats. Dizocilpine produced dose-dependent increases in locomotor activity. Nimodipine, verapamil, and flunarizine suppressed dizocilpine-facilitated vertical activity, while horizontal activity was attenuated by verapamil and nimodipine but not flunarizine. Repeated dizocilpine injections resulted in the development of sensitization to its locomotor stimulating properties. Development of sensitization was not context specific, and was observed following repeated exposures to 0.1 but not 0.056 or 0.3 mg/kg of dizocilpine. Nimodipine retarded the development of sensitization to dizocilpine's stimulating effects on horizontal activity, while verapamil suppressed sensitization to the vertical stimulating effects of dizocilpine. Flunarizine had no significant effects on sensitization to dizocilpine's locomotor stimulating properties. In rats trained to discriminate between injections of 0.056 mg/kg of dizocilpine and vehicle, none of the tested VSCC blockers was able to completely antagonize the discriminative stimulus properties of dizocilpine. Nimodipine, when administered in combination with the training dose of dizocilpine, modestly decreased the dizocilpine-lever selection. Dizocilpine dose dependently decreased the self-determined stimulation threshold implanted in rats with electrodes into the ventral tegmental area. Nimodipine exhibited some tendency to block the facilitating effects of dizocilpine, while verapamil and flunarizine had no effects. In summary, in the present experiments VSCC blockers exerted only modest interactions with the behavioral effects of dizocilpine, and it is unlikely that VSCC blockers have remarkable potential as adjunct treatment aimed at correcting the negative side effects of NMDA receptor antagonists (e.g., dizocilpine). © 1999 Elsevier Science Inc.

Dizocilpine Verapamil Nimodipine Flunarizine Locomotor activity Sensitization Drug discrimination Self-stimulation Rats

DESPITE the remarkable therapeutic potential of NMDA receptor antagonists, only a few are in current clinical use, which is at least in part due to their psychotomimetic properties and addictive potentials (2). Thus, the development of NMDA receptor blockade-based medications continues to be a great clinical interest. There are two developmental strategies that address the problem in the most straightforward manner. First, pharmacologically distinct sites on the NMDA receptor complex may be targeted, and selective drug designs may eventually result in NMDA receptor antagonists with little or no side effects. Second, one may attempt to correct the confounding properties of NMDA receptor antagonists with concurrent administration of another drug. The present study focused on the latter strategy.

Requests for reprints should be addressed to Anton Y. Bespalov, Laboratory of Behavioral Pharmacology, Institute of Pharmacology, Pavlov Medical University, 6/8 Lev Tolstoy St., St. Petersburg 197089 Russia.

In the present experiments, three major criteria were applied in the search for a possible adjunct treatment that may serve to improve the psychopharmacological profile of NMDA receptor antagonists. First, the adjunct medication should represent a well-characterized drug group, so that its clinical use cannot be questioned. Second, these agents have to share or at least not compromise the clinically valuable effects of NMDA receptor antagonists. Finally, experimental evidence is desirable that would suggest that these agents have the ability to counteract the negative behavioral effects of NMDA receptor antagonists.

The voltage-sensitive calcium channel (VSCC) blockers meet the first two criteria. For instance, similar to NMDA receptor antagonists, VSCC blockers have been shown to be effective in improving postischemic brain recovery, they yield positive results when administered to patients with neurodegenerative disorders, and these compounds retard the development of neuroadaptations in the course of chronic antipsychotic, ethanol, psychostimulant, or morphine administration (16,29,33).

As for the third criterion, VSCC blockers were shown to antagonize the addictive potential of various abused drugs in laboratory rodents [(21,24,25); see, however, (37)]. Moreover, because phencyclidine and related NMDA receptor antagonists are characterized by psychotomimetic properties, it is important to note that antipsychotic activity was attributed to certain VSCC blockers (33).

Meanwhile, the experimental data concerning the interaction of NMDA receptor antagonists and VSCC blockers is very diverse. On one hand, dihydropyridines and possibly flunarizine were shown to block phencyclidine (PCP)-induced hyperactivity in mice, whereas verapamil was found to be ineffective (17). PCP-induced increases of dopamine metabolism in prefrontal cortex, nucleus caudatus, putamen, and the amygdala were antagonized by nifedipine, but not by flunarizine (14). On the other hand, verapamil and flunarizine significantly reduced with nimodipine and diltiazem potentiating the behavioral (i.e., ataxia, head weaving) and EEG (increase in the background EEG activity) effects of PCP (31,32). In addition, nifedipine and verapamil were found to potentiate the impairment of rotarod performance produced by PCP (3). Binding studies suggest that verapamil is a potent displacer of PCP binding in rat brain sections (34), and a variety of VSCC blockers displace PCP binding to *Torpedo* electric organ membrane (13) and crayfish muscle membrane (12).

The present study aimed to evaluate the ability of selected VSCC blockers to modify the behavioral effects of dizocilpine relevant to its abuse potential. Dizocilpine was selected as a representative PCP-like noncompetitive NMDA receptor antagonist (39). Verapamil, nimodipine, and flunarizine were chosen as representatives from three major clinically available subclasses of VSCC blockers (i.e., phenylalkylamines, dihydropyridines, and piperazines, respectively). It is important to note that the additional treatment condition is often selected to control for the possible role of cardiovascular effects of VSCC blockers (3). However, we did not follow this strategy in the present study because substantial data suggests that such "control" treatments (e.g., prazosin) may, in their own turn, affect NMDA receptor antagonist-induced behaviors (1).

The locomotor stimulating effects of acute and repeated dizocilpine were measured as a characteristic reflection of psychostimulant drug action. In a second study, the discriminative stimulus control by dizocilpine was established to estimate possible impact of VSCC blockers on subjective effects produced by dizocilpine. There are several earlier reports demonstrating the acquisition of dizocilpine vs. vehicle discrimination in laboratory subjects, including rats (7,8,15).

Finally, electrical brain stimulation reward was selected as a traditional procedure that is often used in studies examining the addictive properties of drugs. Intravenous self-administration and conditioned place preference are two other commonly used experimental approaches for evaluating drug abuse potential. However, we were unable to establish intravenous self-administration of dizocilpine (0.003 or 0.03 mg/kg/infusion; 18 6-h daily sessions) in drug-naive rats with a history of lever pressing for food (Bespalov, unpublished). Effects of dizocilpine in place-conditioning studies are well documented (22,30,38), although certain concerns arise due to the lack of dose dependency (19) and stereoselectivity (10). Moreover, administration of some VSCC blockers (e.g., nimodipine) results in conditioned place aversions, and may significantly confound the results of studies with drug combinations (9,27). Meanwhile, most abused drugs are known to facilitate brain stimulation reward and decrease the stimulation thresholds (36). Dizocilpine is also capable of facilitating self-stimulation behavior (6,18).

## METHOD

### *Subjects*

Adult experimentally naive male Wistar rats (State Breeding Farm "Rappolovo," St. Petersburg, Russia) were used. Animals were kept in groups of five or individually in standard plastic cages with water available ad lib. Food (standard rodent chow from "Volossovo," St. Petersburg, Russia) consumption was unlimited for all subjects except for those involved in the drug discrimination study (see below). All experiments were conducted during the light period of a 12 L:12 D cycle (0800–2000 h). Experiments were approved by the Institutional Ethics Committee of Pavlov Medical University and were performed in accordance with the recommendations and policies of the U.S. National Institutes of Health Guidelines for the Use of Animals.

### *Drugs*

The following drugs were used: dizocilpine maleate {(+)-5-methyl-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene-5,10-imine maleate}, flunarizine dihydrochloride {1-[*bis*(4-fluorophenyl)methyl]-4-(3-phenyl-2-propenyl)-piperazine dihydrochloride}—both from Research Biochemicals Inc., Natick, MA; verapamil hydrochloride (Sigma Chemical Company, St. Louis, MO); nimodipine [1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-nethoxyethyl 1-methylethyl ester]—a gift from Bayer AG, Leverkusen, Germany. Dizocilpine was dissolved in physiological saline. Verapamil, flunarizine, and nimodipine were dissolved in 9% Tween-85 in saline (v/v). All drugs and their vehicles were administered intraperitoneally (IP). All injections delivered a solution in a volume of 1 ml/kg. Doses are based upon the forms of the drugs listed above.

### *Data Analysis*

Data were analyzed using SAS-STAT software (version 6.11, SAS Institute, Cary, NC). Analysis of the descriptive statistics demonstrated that some of the data were not distributed normally (Wilks-Shapiro's test). Wherever appropriate, the distribution-free analysis of variance (ANOVA) was performed. Briefly, data were ranked and the ranks were later

subjected to ANOVA (General Linear Models procedure for unbalanced design with unequal group sizes).

Locomotor activity data (total count of photobeam interrupts per 60-min test) were subjected to multivariate ANOVA (MANOVA) with repeated measures on treatment dosing (horizontal and vertical activity as dependent variables). Sensitization data were analyzed by means of two-way ANOVA with repeated measures on test treatment conditions. Percent of dizocilpine lever responding (after rank transformation) and response rate data were analyzed by means of one- and two-way ANOVA with repeated measures on treatment. Rank transformation was applied to self-stimulation thresholds that were then processed with three-way covariant ANOVA with repeated measures on treatment and test interval. Duncan's multiple-range post hoc test was used wherever between-group pairwise comparisons were permitted by ANOVA results.

### *Locomotor Activity*

*Subjects.* One hundred and nineteen rats (280–330 g) were housed in groups with food and water available ad lib.

*Apparatus.* Locomotor activity was measured in five identical boxes (25 × 35.5 × 34 cm) with transparent Plexiglas walls and a nontransparent plastic floor. General light conditions in the test room were approx. 270 lx. Boxes were equipped with three photocell beams (4 cm off the floor) for measuring horizontal activity, and eight infrared photocell beams (14 cm off the floor) for vertical component of locomotor activity. The total number of photocell interruptions during a 60-min test was used as a measure of locomotor activity. The test procedure was conducted automatically without the presence of the experimenter in the test room. The output from the counters was integrated and analyzed by custom-designed IBM computer software. During each 60-min session, data were collected every 10 min for six intervals by the computer.

*Procedure.* The rats were divided into groups ($n$ = 10 per group), and animals of each group were habituated to handling for 2 days and familiarized with the test environment during three 60-min baseline trials before the start of the experiment. The experiment consisted of three protocols.

*Protocol I. Effects of acute dizocilpine and calcium channel blockers on locomotor activity.* Four groups of rats were injected with dizocilpine (vehicle, 0.03, 0.056, 0.1, and 0.3 mg/kg; 0 min preinjection time), verapamil (vehicle, 0.3, 1, 3, 10, and 20 mg/kg; 15-min preinjection time), flunarizine (vehicle, 0.3, 1, 3, and 10 mg/kg; 15-min preinjection time), and nimodipine (vehicle, 1, 3, 10, and 17.3 mg/kg; 15-min preinjection time) before being placed into the test boxes for 60 min. The order of dose presentations was determined by Latin square design. Drug effects were tested no more than twice a week.

*Protocol II. Effects of calcium channel blockers on acute dizocilpine-induced locomotor stimulation.* Four groups of rats were pretreated with verapamil (10 mg/kg), flunarizine (10 mg/kg), nimodipine (10 mg/kg), or their vehicle, 15 min later injected with dizocilpine (vehicle, 0.03, 0.056, 0.1, and 0.3 mg/kg), and immediately placed into the testing boxes for 60 min. Tests with different doses of dizocilpine were separated by an interval of at least 2 days.

*Protocol III. Effects of calcium channel blockers on sensitization induced by repeated dizocilpine administration.* A preliminary test for baseline activity was conducted immediately after the second of two IP vehicle injections spaced 15 min apart. Treatment groups were formed based upon activity scores from these preliminary tests to exclude any initial differences in spontaneous locomotor activity. Subsequently, during 5 consecutive days, four groups of rats received daily injections of verapamil (10 mg/kg), flunarizine (10 mg/kg), nimodipine (10 mg/kg), or their vehicle followed 15 min later by dizocilpine (0.1 mg/kg). Right after dizocilpine injection animals were placed into the testing apparatuses for 60 min. On days 7 and 8, rats received single injections of either dizocilpine (0.1 mg/kg) or saline prior to placement into the testing boxes for a 60-min observation. An additional three groups of rats received five daily injections of dizocilpine (0.056, 0.1 or 0.3 mg/kg) prior to exposure to the test environment. On days 7 and 8, tests were conducted in the manner described above, except that the test dose of dizocilpine corresponded to the repeated treatment dose.

### *Drug Discrimination*

*Subjects.* Eighteen male Wistar rats were housed individually with water available ad lib. Food consumption was restricted to 10–12 g/day given after behavioral testing to maintain a constant body weight (300–330 g).

*Apparatus.* Four standard two-lever operant conditioning chambers (Coulbourn Instruments, Lehigh Valley, PA) were connected to a microcomputer through an interface and controlled by MED-PC software (MED Associates, Inc., East Fairfield, VT). Each chamber was equipped with a white house light centered above the levers and a food dispenser, which delivered 45-mg food pellets (Noyes Formula A, P. J. Noyes Company, Inc., Lancaster, NH).

*Initial training.* Rats were initially trained to lever press for food pellet delivery according to a fixed-ratio 1 (FR1) schedule of reinforcement using the lever that eventually would become the "saline" lever. All training and subsequent acquisition sessions were conducted once daily (Monday–Sunday). After rats had acquired the lever-press response (1–3 days), the FR value was gradually increased to 10. The active lever was then switched to the opposite side and the FR value was reduced to FR1. As soon as the rats showed evidence of responding on this lever ("dizocilpine" lever), the FR value was rapidly increased to FR10.

*Discrimination training.* At the start of each drug discrimination training session, rats were injected IP with either 0.056 mg/kg of dizocilpine or saline, returned to their home cages, and then 15 min later were placed into the operant chambers for a total of 15 min. The house light was illuminated at the start of each session and extinguished at the end of the session. Animals experienced both saline and dizocilpine training sessions in an alternating sequence predetermined for each 2-month block of training and testing. During the training sessions, both levers were present in the chamber but only correct lever pressing was reinforced under the FR10 schedule of pellet delivery. Half of the rats were trained to press the right lever for food reinforcement after receiving dizocilpine and the left lever following saline injection; the reverse pairing was used with the remaining rats. Incorrect responses reset the FR requirement on the correct lever.

Acquisition training proceeded until the following criteria were met on at least 8 out of 10 consecutive training sessions: 1) the first completed FR (FFR) had to occur on the correct lever; and 2) the percentage of all lever presses emitted on the correct lever was more than 90% during these sessions. After the criteria were met, the rats were given test days. During test sessions, 10 consecutive responses on either lever pro-

duced a pellet delivery. Tests were conducted provided that the following criteria were met: 1) during the most recent training sessions of each type (saline and dizocilpine) the FFR was correct; 2) overall 90% or greater correct-lever responding on each of these sessions; and 3) overall response rate was greater than 0.4 lever presses per second.

Each rat was repeatedly tested with either saline or the training dose of dizocilpine (0.056 mg/kg) until four consecutive test sessions were completed that satisfied criteria 2 and 3 as described above.

*Stimulus generalization testing.* Stimulus generalization tests were conducted with the following drugs: dizocilpine (vehicle, 0.01–0.3 mg/kg; preinjection time 15 min), nimodipine (vehicle, 1–10 mg/kg; preinjection time 40 min), verapamil (vehicle, 1–10 mg/kg; preinjection time 30 min), and flunarizine (vehicle, 1–10 mg/kg; preinjection time 30 min). Each of the VSCC blockers listed above was also tested in combination with the training dose of dizocilpine (0.056 mg/kg).

During each test there were two injections given; one IP with VSCC blocker or its vehicle (preinjection time 30–40 min) and one IP with dizocilpine or saline (preinjection time 15 min). Control tests with the training dose of dizocilpine and with saline were conducted at intervals throughout the study. Each subject was tested with no more than two different VSCC blockers.

The percentage of responses on the dizocilpine-designated lever (DLR) and response rate (responses/s) were calculated for each test session, with means calculated for the group data. Data from rats emitting less than 0.03 responses/s were omitted from calculations of group % DLR but were included in group response rate determinations. The lever on which the first FR was completed was also recorded and used to compare individual subject results.

### *Intracranial Self-Stimulation*

*Subjects.* Twelve male Wistar rats (220–240 g at the time of surgery) were housed individually with food and water available ad lib.

*Apparatus.* Tests were conducted in three standard operant conditioning chambers (Coulbourn Instruments, Lehigh Valley, PA) equipped with two retractable levers. Chambers were connected to an IBM 386/33 MHz microcomputer through a MED interface and controlled by MED-PC software (MED Associates, Inc., East Fairfield, VT). Each chamber was housed within a ventilated, light-proof, and sound-attenuating enclosure. Ventilator fans provided a constant level of white noise masking extraneous noise and sounds. Electrical pulses were produced by a model PHB-150B constant current stimulator (MED Associates, Inc., East Fairfield, VT). The electrical stimuli were delivered to the animal through a custom made one-channel electrical swivel assembly that extended into the test chamber. The electrical stimulus was a 500-ms train of rectangular bipolar wave, with a pulse frequency of 100 Hz and a pulse duration of 0.1 ms. Throughout the experiment the electrical stimuli were displayed on a model C1-55 oscilloscope, which permitted the investigator to determine whether or not the stimulator was functioning properly.

*Surgery.* Each animal was anesthetized with Nembutal (55 mg/kg, IP). Bipolar stainless steel electrodes of 0.2 mm thickness, insulated except at the cross section at the tip, were stereotaxically implanted using a David Kopf Micromanipulator. Electrodes were lowered into the left or right ventral tegmental area (coordinates AP: −4.3 mm from bregma, L: 1.1 mm from the midline, V: 8.1 mm from a flat skull, angle: 0, incisor bar: 0). Four stainless steel jeweler's screws were fastened to the rat's scull forming a perimeter around the electrode. Dental phosphate cement and acrylic plastmass were applied to the skull over and around the jeweler's screws and electrode-forming a pedestal, which firmly anchored the electrode in place.

*Histology.* At the end of the experiment, the rats were euthanised by introducing them into an atmosphere with a high $CO_2$ concentration. Rats were decapitated and their brains were quickly removed and stored in 4% formalin. The stimulation site at the end of the electrode tract was examined under a light microscope in cresyl violet-stained sections of 50 μm thickness. The slices were analyzed by an independent trained observer who was blind to the treatment conditions. Data for four rats with electrode tip placement outside the ventral tegmental area were excluded from the statistical analysis.

*Procedure.* Beginning 1 week after surgery, rats were trained to press one of the levers (stimulation lever) to receive brain

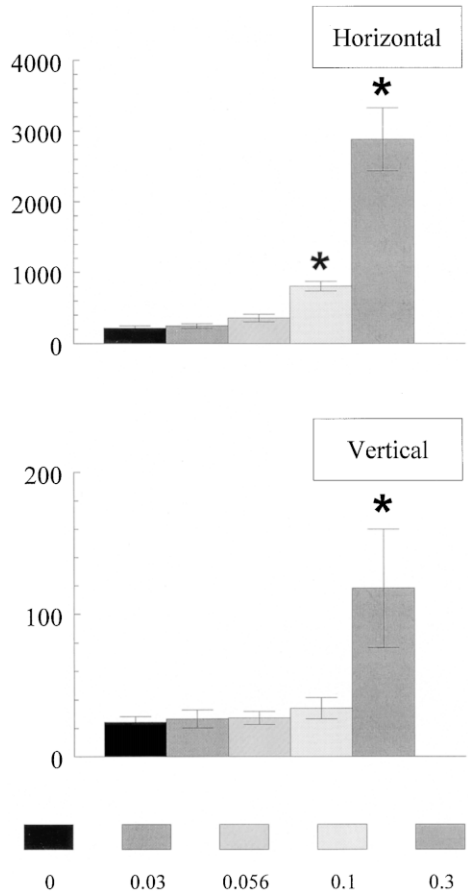


FIG. 1. Effects of VSCC blockers on locomotor activity in rats. Fifteen minutes after IP injections of nimodipine (1, 3, 10, and 17.3 mg/kg), verapamil (0.3, 1, 3, 10, and 20 mg/kg), flunarizine (0.3, 1 , 3, 10, and 17.3 mg/kg), or vehicle (VEH), animals were placed into the automatic activity meters and locomotor activity was measured for 60 min. The values on the vertical axis on the top panels represent counts of photobeam interruptions indicative of horizontal activity, while the values on the vertical axis on the lower panels represent vertical activity. $*p < 0.05$ (Duncan's post hoc test). $n = 10$.

stimulation on a continuous reinforcement (CRF) schedule, while the second lever (reset lever) was retracted into the front wall. The sessions lasted 30 min, and were conducted daily 7 days a week. During the CRF training sessions, the baseline intensity for each animal was obtained by manual titration of stimulation intensity at which the response rate could be stabilized at 50–60 responses per minute. After achieving stable response rate (±10%) during three consecutive sessions, the autotitration schedule training began. The 30-min training sessions began with the stimulation lever being retracted and the reset lever being inserted into the test chamber. Responses on the reset lever, which did not produce stimulation, resulted in insertion of the stimulation lever and the animals continued the session being reinforced on the CRF schedule. After five successive repetitions of these combined sessions, the program controlling the stimulation decrement was activated while both levers had been inserted into the chamber. Every fifth response emitted on the response lever decreased the stimulation current by 2% of baseline intensity. The response on the reset lever returned the stimulation intensity back to baseline levels. The intensity at which the response on the reset lever occurred was considered to be a threshold of stimulation. The individual autotitration thresholds stabilized within 9–14 sessions (less than 4% variation in threshold across 3 consecutive days).

The procedure for drug testing was as follows. Animals were tested 2 days per week. In each session, the animals were given an initial 5-min warmup period, followed by a 10-min baseline period. One hour after the end of the baseline period, the 30-min test session was introduced. Immediately after the end of the baseline period, the animals were injected with either saline or a VSCC blocker. Fifteen minutes after the first injection and 15 min before the beginning of the test the animals were injected with either saline or different doses of dizocilpine. Rats were habituated to the injection procedure during three consecutive test sessions before actual drug testing began. Mean response rate on both levers and mean stimulation threshold were then calculated for three 10-min intervals of the 30-min test. These parameters were also recorded during the last 10 min of the warmup.

## RESULTS

### *Locomotor Activity*

The effects of the calcium channel blockers on spontaneous locomotor activity are shown in Fig. 1. Distribution-free MANOVA with repeated measures found no main effect of either nimodipine [horizontal: $F(4, 49) = 1.7$, $p = 0.17$; vertical: $F(4, 49) = 1.0$, $p = 0.43$] or flunarizine [horizontal: $F(4, 49) = 0.6$, $p = 0.67$; vertical: $F(4, 49) = 0.6$, $p = 0.70$] while verapamil significantly reduced locomotor activity at the highest dose tested [horizontal: $F(5, 59) = 6.1$, $p < 0.01$; vertical: $F(5, 59) = 8.2$, $p < 0.01$].

Dizocilpine produced a dose-dependent increase in both horizontal and vertical locomotor activity (Fig. 2) [horizontal: $F(4, 47) = 31.9$, $p < 0.01$; vertical: $F(4, 47) = 3.3$, $p < 0.05$]. The dizocilpine dose of 0.3 mg/kg increased both horizontal and vertical activity while only horizontal locomotion was affected at the 0.1 mg/kg dose of dizocilpine.

The calcium channel blockers exerted differential effects on dizocilpine-stimulated locomotion (Fig. 3). Statistical analysis revealed that nimodipine, verapamil, and flunarizine exerted an overall suppressive effect upon dizocilpine-facilitated locomotion. These effects reached the level of statistical significance for vertical activity measures [nimodipine: $F(1,$

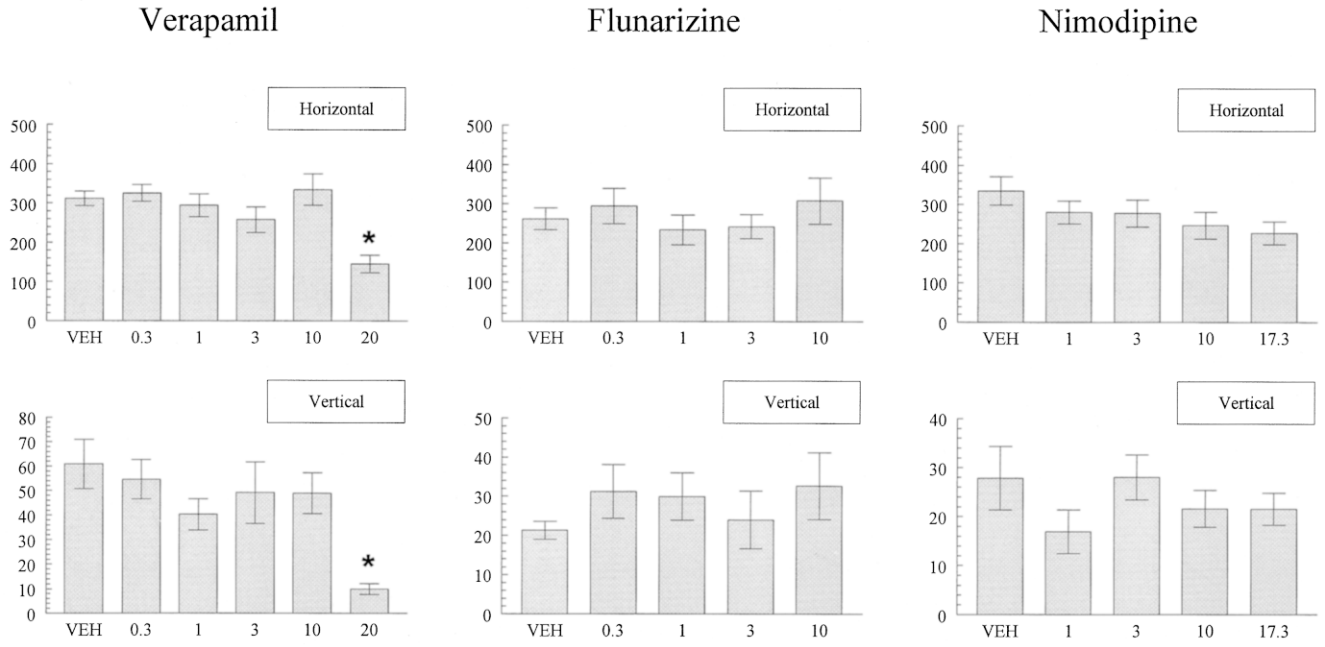


FIG. 2. Effect of dizocilpine on locomotor activity in rats (mean ± SEM). Immediately following injections of dizocilpine (0.03, 0.056, 0.1, and 0.3 mg/kg) or saline ("0"), animals were placed in the activity meters and locomotor activity was measured for 60 min. Data are presented as in Fig. 1. *$p < 0.05$ (Duncan's post hoc test). $n = 10$.

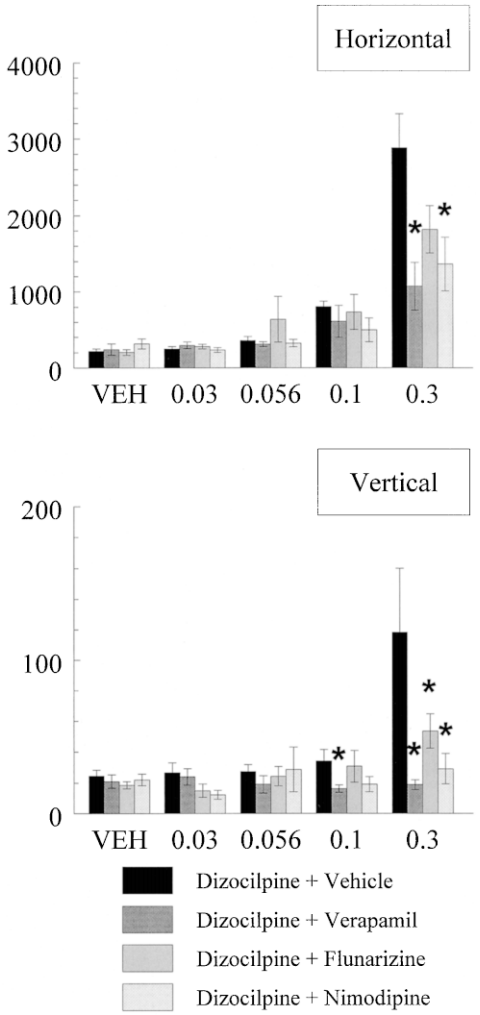


FIG. 3. Effect of VSCC blockers on dizocilpine-induced locomotor hyperactivity in rats. Fifteen minutes after IP injections of verapamil (10 mg/kg), flunarizine (10 mg/kg), nimodipine (10 mg/kg), or vehicle animals were administered various doses of dizocilpine (0.03, 0.056, 0.1, and 0.3 mg/kg) or saline and then placed in the activity meters and locomotor activity was measured during 60 min. Data are presented as in Fig. 1. $n = 10$. *$p < 0.05$ (Duncan's post hoc test).

97) = 11.6, $p < 0.01$; verapamil: $F(1, 96) = 10.2$, $p < 0.01$; flunarizine: $F(1, 95) = 4.7$, $p < 0.05$], but for horizontal activity results were more diverse [nimodipine: $F(1, 97) = 3.4$, $p = 0.07$; verapamil: $F(1, 96) = 12.7$, $p < 0.01$; flunarizine: $F(1, 95) = 1.7$, $p = 0.19$]. In addition, significant interactions between VSCC blocker treatment and the dizocilpine dose were found for horizontal activity in nimodipine, $F(4, 97) = 2.9$, $p < 0.05$, and flunarizine treatment groups, $F(4, 95) = 3.3$, $p < 0.05$.

None of the VSCC blockers significantly attenuated horizontal locomotor stimulation observed in rats treated with 0.1 mg/kg of dizocilpine. However, when combined with the higher dose of dizocilpine (0.3 mg/kg), verapamil (10 mg/kg), and nimodipine (10 mg/kg) but not flunarizine (10 mg/kg) antagonized dizocilpine's stimulating effects on horizontal activity.

The results of experiments with repeated dizocilpine administration are displayed in Fig. 4. Repeated dizocilpine injections led to the gradual increase (sensitization) in locomotor stimulating potency. The development of sensitization was observed following repeated exposures to 0.1 but not 0.3 or 0.056 mg/kg. For horizontal activity, MANOVA found a significant dizocilpine dose by day interaction, $F(10, 233) = 2.5$, $p < 0.01$. For vertical activity, there was a significant main effect of repeated exposures, $F(5, 233) = 2.3$, $p < 0.05$. In addition, there were no differences found after test injection of vehicle when comparisons were made between treatment groups or with regard to the respective pretest activity.

Administration of nimodipine in combination with 0.1 mg/kg of dizocilpine during the repeated-treatment phase (Fig. 5) significantly retarded the development of sensitization to dizocilpine's stimulating effects on horizontal, $F(1, 57) = 13.7$, $p < 0.01$, but not vertical activity, $F(1, 57) = 0.3$, $p = 0.56$. Opposite results were obtained with verapamil (Fig. 5), which suppressed sensitization to the vertical, $F(1, 57) = 3.7$, $p = 0.06$, but not to the horizontal stimulating effects of dizocilpine, $F(1, 57) = 3.1$, $p = 0.15$. Administration of flunarizine in combination with dizocilpine (Fig. 5) produced no significant effects on sensitization to dizocilpine's locomotor stimulating properties [horizontal: $F(1, 57) = 3.5$, $p = 0.07$; vertical: $F(1, 57) = 0.5$, $p = 0.48$].

### *Drug Discrimination*

All 12 rats acquired the dizocilpine–saline discrimination in 31.2 ± 2.7 days (ranging from 22 to 48 days). Control tests with the training dose of dizocilpine and saline produced group averages of more than 95% correct lever responding on every occasion on which the subjects were tested.

Dizocilpine administration resulted in a dose-dependent increase in dizocilpine lever selection (Fig. 6, upper panel), $F(5, 67) = 17.6$, $p < 0.01$, with an $ED_{50}$ of 0.049 mg/kg (CI: 0.031–0.078). Dose-dependent decreases in response rate were obtained at doses above the 0.056 mg/kg training dose (Fig. 6, lower panel), $F(5, 71) = 41.5$, $p < 0.01$.

When dizocilpine was tested in combination with each of the VSCC blockers and their vehicles (Fig. 7), the VSCC blockers produced dose-dependent reductions in response rates [nimodipine: $F(4, 39) = 16.2$, $p < 0.01$; verapamil, $F(5, 47) = 11.6$, $p < 0.01$; flunarizine, $F(4, 34) = 6.2$, $p < 0.01$].

Administration of nimodipine in combination with dizocilpine resulted in a modest but significant reduction of dizocilpine lever selection, $F(4, 37) = 2.8$, $p < 0.05$. Dizocilpine-lever selection was not affected by either verapamil, $F(5, 43) = 0.6$, $p = 0.68$, or flunarizine treatment, $F(4, 34) = 0.4$, $p = 0.78$.

### *Intracranial Self-Stimulation*

Absolute values of autotitration thresholds for intracranial self-stimulation ranged from 8.3 to 15.7 μA (mean ± SEM = 11.4 ± 1.2 μA). Dizocilpine administration dose dependently decreased the self-determined threshold (Fig. 8), $F(4, 144) = 6.4$, $p < 0.01$. This effect of dizocilpine was most pronounced during the third test interval (i.e., 35–45 min after dizocilpine injection). However, ANCOVA failed to find a significant time effect, $F(3, 144) = 2.7$, $p = 0.08$, which may be attributed to the inverse tendency observed at the highest tested dose of 0.3 mg/kg.

Dizocilpine, at the dose of 0.3 mg/kg, markedly disrupted responding with responding on the reset lever, varying dramatically within a single session. On several occasions, stimulation thresholds were not assessed due to the extremely low response rates. This effect was especially evident towards the third (final) test interval. Statistical analysis confirmed the

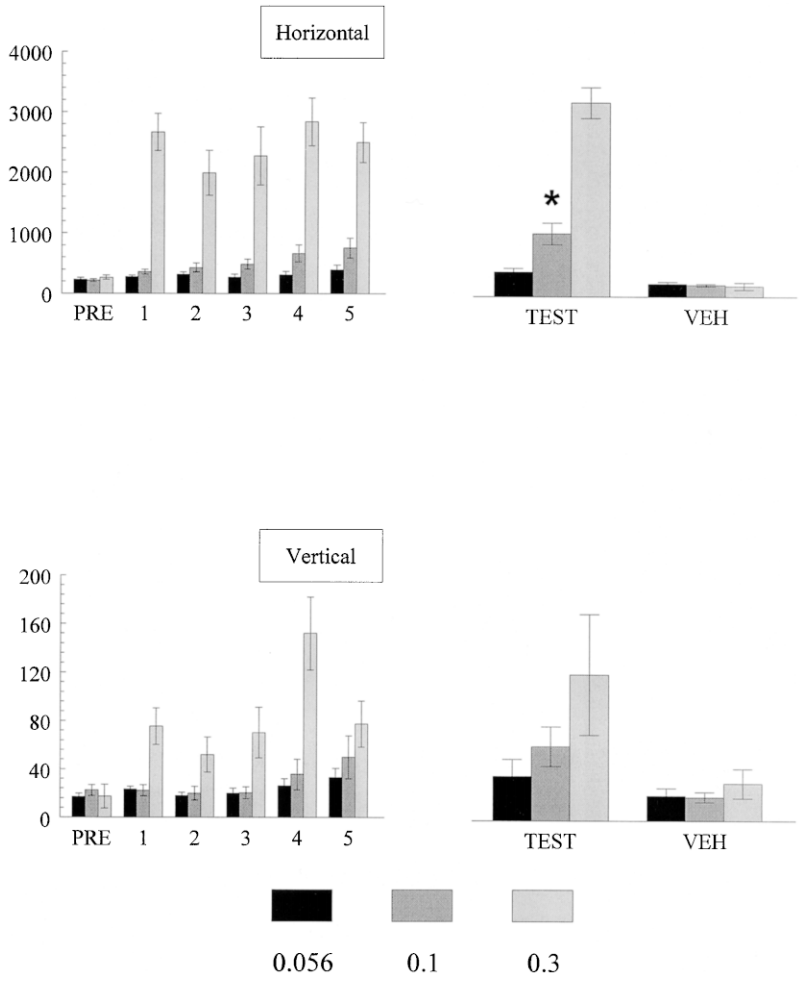


FIG. 4. Sensitization to the dizocilpine-induced locomotor hyperactivity. Left panels show the activity counts recorded during the pretest (PRE) and 5 consecutive days during which rats were administered various doses of dizocilpine (0.056, 0.1, and 0.3 mg/kg) immediately prior to being placed into the activity meters for 60 min. Right panels represent data obtained during a test performed on the sixth and seventh days of experiment when rats received injections of dizocilpine (0.1 mg/kg; TEST) or vehicle (VEH). Data are presented as in Fig. 1. $n = 10$–$19$. $^*p < 0.05$ (Duncan's post hoc test).

main effects of dizocilpine dose, $F(4, 155) = 23.6$, $p < 0.01$, and test interval on operant performance, $F(3, 155) = 55.2$, $p < 0.01$.

Figure 9 illustrates the effects of VSCC blockers on dizocilpine-induced facilitation of electrical brain stimulation reward. Dizocilpine significantly reduced self-stimulation thresholds in rats pretreated with low doses of nimodipine (1 and 3 mg/kg), but not with the high dose of nimodipine (10 mg/kg). However, ANCOVA found neither an overall main effect of nimodipine treatment, $F(3, 94) = 0.8$, $p = 0.52$, nor test interval by dose interaction, $F(9, 94) = 0.7$, $p = 0.72$. Similarly, dizocilpine-induced decreases in self-stimulation thresholds were not affected by verapamil, $F(3, 82) = 0.0$, $p = 0.99$, or flunarizine administration, $F(2, 59) = 0.6$, $p = 0.57$.

Response rates were significantly reduced by nimodipine, $F(3, 95) = 3.9$, $p < 0.05$, verapamil, $F(3, 87) = 15.3$, $p < 0.01$, but not flunarizine, $F(2, 59) = 3.7$, $p = 0.07$. When administered in combination with saline instead of dizocilpine, none of the VSCC blockers had significant effects on stimulation thresholds, while response rates were decreased by all three blockers (Fig. 9).

## DISCUSSION

In agreement with previous studies, dizocilpine produced clear increases in locomotor activity (4,23), and repeated dizocilpine administration resulted in the development of sensitization to its locomotor stimulating properties (5). Dizocilpine-facilitated vertical locomotion was suppressed by nimodipine, verapamil, and flunarizine. General depressant and muscle-relaxant properties of VSCC blockers are likely to contribute to this effect. For instance, nifedipine and verapamil have been shown to potentiate PCP-induced impairment of rotarod performance (3). In addition, VSCC blockers in the present study produced dose-dependent decreases in

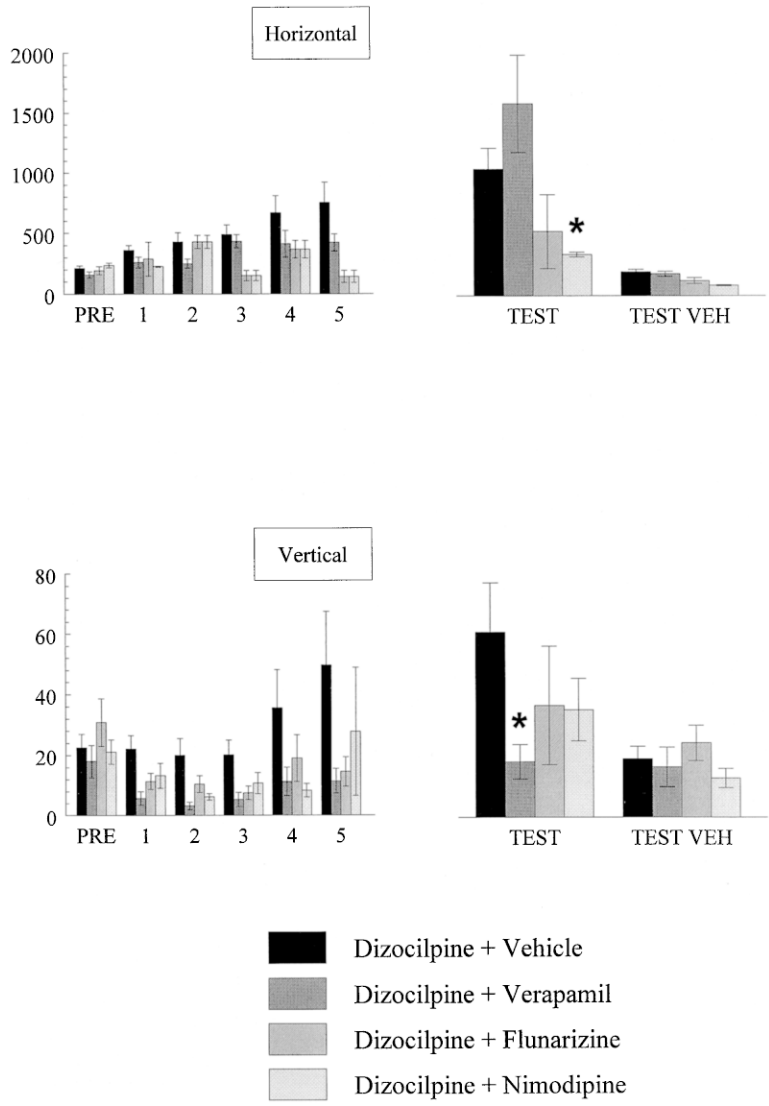


FIG. 5. The effects of VSCC blockers on sensitization to the dizocilpine-induced locomotor hyperactivity. Left panels show the activity counts recorded during the pretest (PRE) and 5 consecutive days during which rats were administered verapamil (10 mg/kg), flunarizine (10 mg/kg), nimodipine (10 mg/kg), or vehicle 15 min prior to injection of dizocilpine (0.1 mg/kg) and then were placed into the activity meters for 60 min. Right panels represent data obtained during a test performed on the sixth and seventh days of experiment when rats received injections of dizocilpine (0.1 mg/kg; TEST) or vehicle (TEST VEH). Data are presented as in Fig. 1. $n = 10$. *$p < 0.05$ (Duncan's post hoc test).

operant performance maintained by food or electrical stimulation of the ventral tegmental area.

Meanwhile, dizocilpine-stimulated horizontal activity was attenuated by verapamil and nimodipine, but not by flunarizine. These findings are consistent with the demonstrations that dihydropyridine VSCC blockers antagonize PCP-induced increases in locomotor activity (3,17). For flunarizine, a nonsignificant tendency to block PCP-induced behavioral stimulation was also reported (17,32). Contrary to our results, there are data (17) showing that verapamil failed to block PCP-stimulated locomotion. However, the direct comparison of the results is not possible, because the experiments were conducted in different animal species and locomotor activity was stimulated by different drugs—dizocilpine and PCP. Interestingly, intracerebroventricular administration of verapamil significantly reduced both behavioral (ataxia, head weaving) and electroencephalographic effects of PCP in a series of experiments that also revealed potentiation of these effects by nimodipine (31,32).

It is important to note that none of the VSCC blockers significantly attenuated horizontal locomotor stimulation observed in rats treated with 0.1 mg/kg of dizocilpine. However, when combined with the higher dose of dizocilpine, dizocilpine's stimulating effects on horizontal activity were antag-

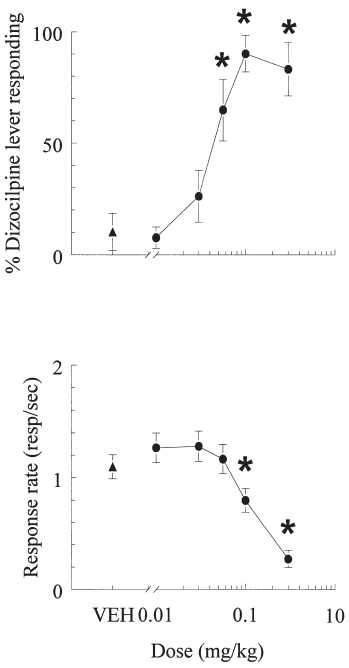


FIG. 6. Mean percentage (±SEM) of dizocilpine-lever responding (DLR; upper panel) and mean response rates (lower panel) following dizocilpine (0.01–0.3 mg/kg; circles) administration in rats trained to discriminate 0.056 mg/kg of dizocilpine from saline ("VEH"; triangles). Each point is based on observations made in 12 rats (DLR data: $n = 8$ for 0.3 mg/kg). *$p < 0.05$ (Duncan's test), compared to saline-treated controls.

onized by verapamil and nimodipine. One may regard these data as evidence for nonspecific interactions between VSCC blockers and dizocilpine-induced behavioral stimulation. The phenomenon of rate dependency (11) may be proposed as a possible nonspecific mechanism.

Repeated dizocilpine injections resulted in the development of sensitization that showed no clear dependence on dizocilpine dose, and was observed only in rats repeatedly exposed to 0.1 but not 0.056 or 0.3 mg/kg of dizocilpine. Results of this study suggest that sensitization to dizocilpine's locomotor stimulation is not context specific. Despite the experimental design that allowed for explicit pairing between drug injections and test environment, administration of saline during the test did not result in increased motor activity.

Somewhat confusing results were obtained when each of the repeated dizocilpine injections was preceded by administration of a VSCC blocker. Nimodipine retarded the development of sensitization to dizocilpine's stimulating effects on horizontal activity, while verapamil suppressed sensitization to the vertical stimulating effects of dizocilpine. Flunarizine had no significant effects on the sensitization to dizocilpine's locomotor stimulating properties.

It is known that VSCC blockers are capable of interfering with sensitization to psychostimulant drug-induced locomotion. Such evidence can be found for nimodipine, verapamil, etc. (20,35). Thus, once again, our data indicate that essential distinction should be made between psychomotor stimulation induced by dizocilpine and classical psychostimulants. Further evidence comes from the experiments with electrical brain stimulation and drug discrimination.

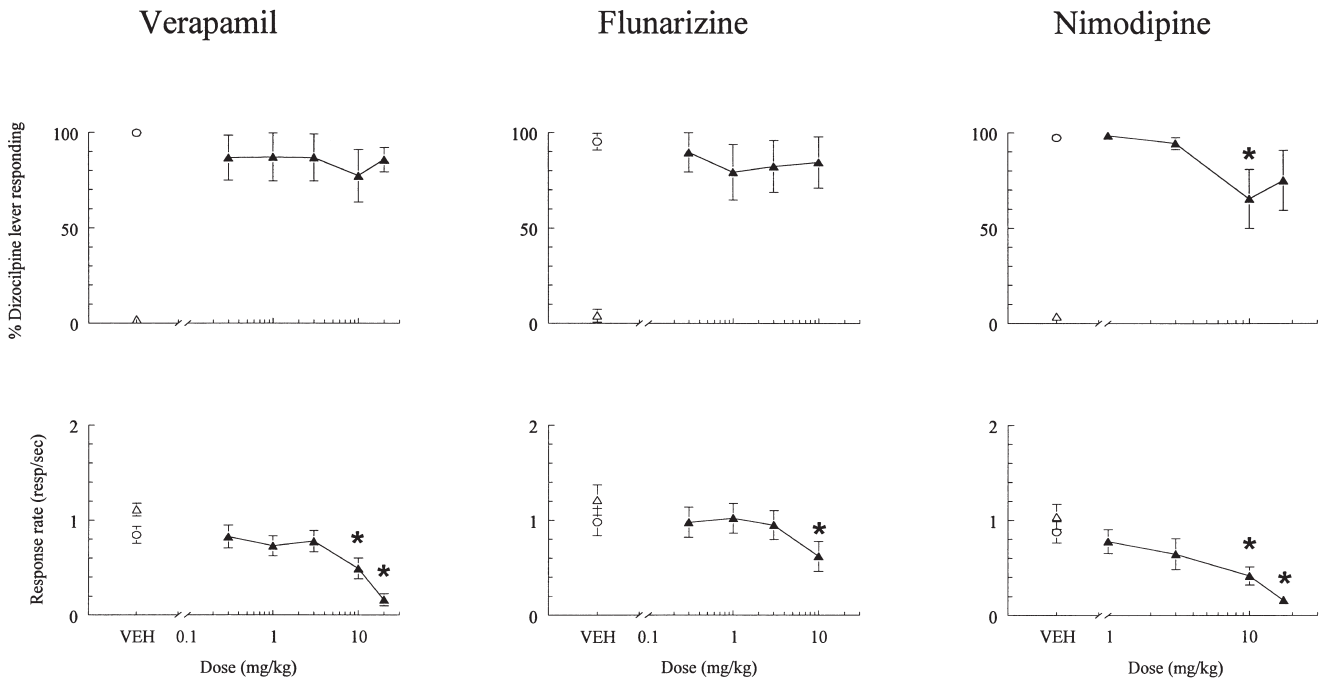


FIG. 7. Mean percentage of dizocilpine-lever responding (DLR; upper panels) and response rates (lower panels) following the administration of different doses of verapamil, flunarizine, and nimodipine in combination with the training dose of dizocilpine in rats trained to discriminate 0.056 mg/kg of dizocilpine from saline. Points above VEH represent tests performed after administration of the training dose of dizocilpine (open circles) and saline (open triangles). Each point is based on observations made in seven (flunarizine) or eight rats (verapamil, nimodipine). Due to low response rates, group size for DLR data analysis was corrected: $n = 6$ for 17.3 mg/kg of nimodipine; $n = 7$ for 10 mg/kg of verapamil; $n = 5$ for 20 mg/kg of verapamil. *$p < 0.05$ (Duncan's test), compared to vehicle-treated controls.

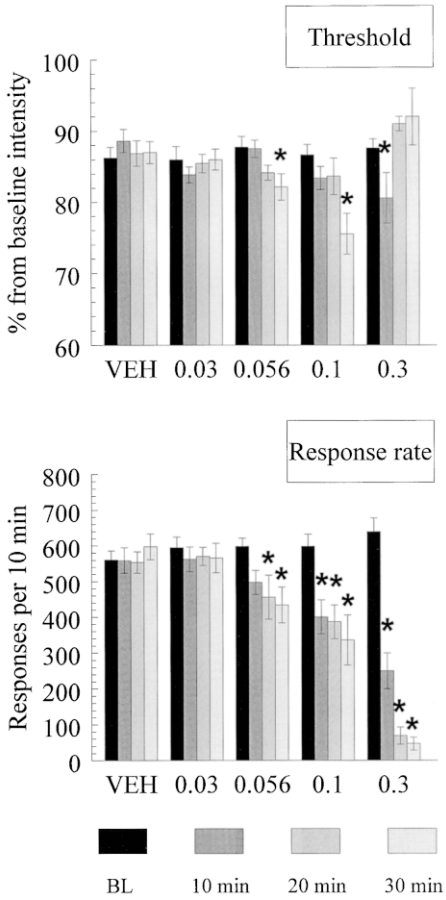


FIG. 8. Effects of dizocilpine on electrical brain stimulation thresholds (percentage from baseline intensity ± SEM; upper panel) and mean response rates (lower panel) in rats trained to lever press in threshold autotitration procedure. Each session comprised one 10-min baseline interval (BL) and three 10-min test sessions. Rats were administered dizocilpine (0.03–0.3 mg/kg) 15 min prior to the first test interval. Each point is based on observations made in seven to eight rats. *$p < 0.05$ (Duncan's test), compared to saline-treated controls.

None of the tested VSCC blockers were able to completely antagonize the discriminative stimulus properties of dizocilpine. Nimodipine, when administered in combination with the training dose of dizocilpine, modestly decreased the dizocilpine lever selection. An earlier study (28) found that nimodipine attenuated the discriminative stimulus properties of *d*-amphetamine. These effects of nimodipine were suggested to be nonspecific, due to the ability of nimodipine itself to induce a discriminable internal state. A similar explanation would be acceptable for the present results provided that out of the three tested VSCC channel blockers, nimodipine produced the most salient interoceptive stimulation. We found no experimental evidence for such speculations, leaving us with the conclusion that nimodipine must partially antagonize the discriminative stimulus produced by dizocilpine.

Among the effects that dizocilpine shares with abused drugs is the ability to facilitate intracranial self-stimulation behavior (6,18). However, certain peculiarities are seen in the actions of dizocilpine. First, facilitating effects on self-stimulation become evident with some delay after drug injection, albeit locomotor stimulation is observed 10–15 min postinjection. Moreover, a 15-min preinjection time was employed in our drug discrimination experiments, and successful acquisition of the dizocilpine-saline discrimination is the best demonstration of salience of dizocilpine-produced internal cue 15-min postinjection. Second, dose–effect characteristics for dizocilpine were far from being perfect. Although one may attempt to attribute this lack of dose dependency to deteriorating effects on operant performance that were observed at the higher doses of dizocilpine (see the Results section), other studies point at poor correlation between dizocilpine dose and behavioral effects (6,19).

Dizocilpine dose dependently decreased the self-determined stimulation threshold, and this effect of dizocilpine was most pronounced during the third test interval. Statistical analyses did not reveal significant effects of any VSCC blockers on dizocilpine-induced decrement in self-determined stimulation thresholds. However, dizocilpine significantly reduced self-stimulation thresholds in rats pretreated with low doses but not the high dose of nimodipine. Thus, nimodipine did exhibit some tendency to block the facilitating effects of dizocilpine.

Overall, nimodipine, verapamil, and flunarizine, which presumably all act to block voltage-operated calcium channels, exerted different effects on dizocilpine-induced behaviors. Marked differences in the behavioral effects between VSCC blockers are paralleled by distinct neurochemical profiles. For example, flunarizine enhanced the increase in regional dopamine metabolism induced by PCP, while dihydropyridine VSCC blockers attenuated the PCP-induced hyperactivity of the dopaminergic neurons (14). Flunarizine and verapamil bind at the site adjacent to the dihydropyridine site on the L-type channel complex. In addition, flunarizine acts at N- and T-type channels. These differences apparently result in differential influences on dopamine and 5-HT neurotransmission: nimodipine decreases dopamine synthesis and release, flunarizine blocks dopamine receptors and uptake, and verapamil acts at 5-HT transmission and sodium channels (24). It is noteworthy that dizocilpine's actions also involve several neurotransmitter systems (26,40).

Although some of the VSCC blockers altered the effects of dizocilpine, the more general conclusion is that these interactive effects were modest, and differed in magnitude among the individual test drugs. Locomotor effects of dizocilpine seemed to be more affected by the VSCC blockers than self-stimulation thresholds or discriminative stimulus effects. However, at present it is not possible to assess the relationship of each of these individual animal behaviors to the negative side-effect profile of dizocilpine and other NMDA receptor antagonists. Thus, based on the reported data it is unlikely that VSCC blockers have any remarkable potential as adjunct treatment aimed at correcting negative side effects of NMDA receptor antagonists, dizocilpine in particular.

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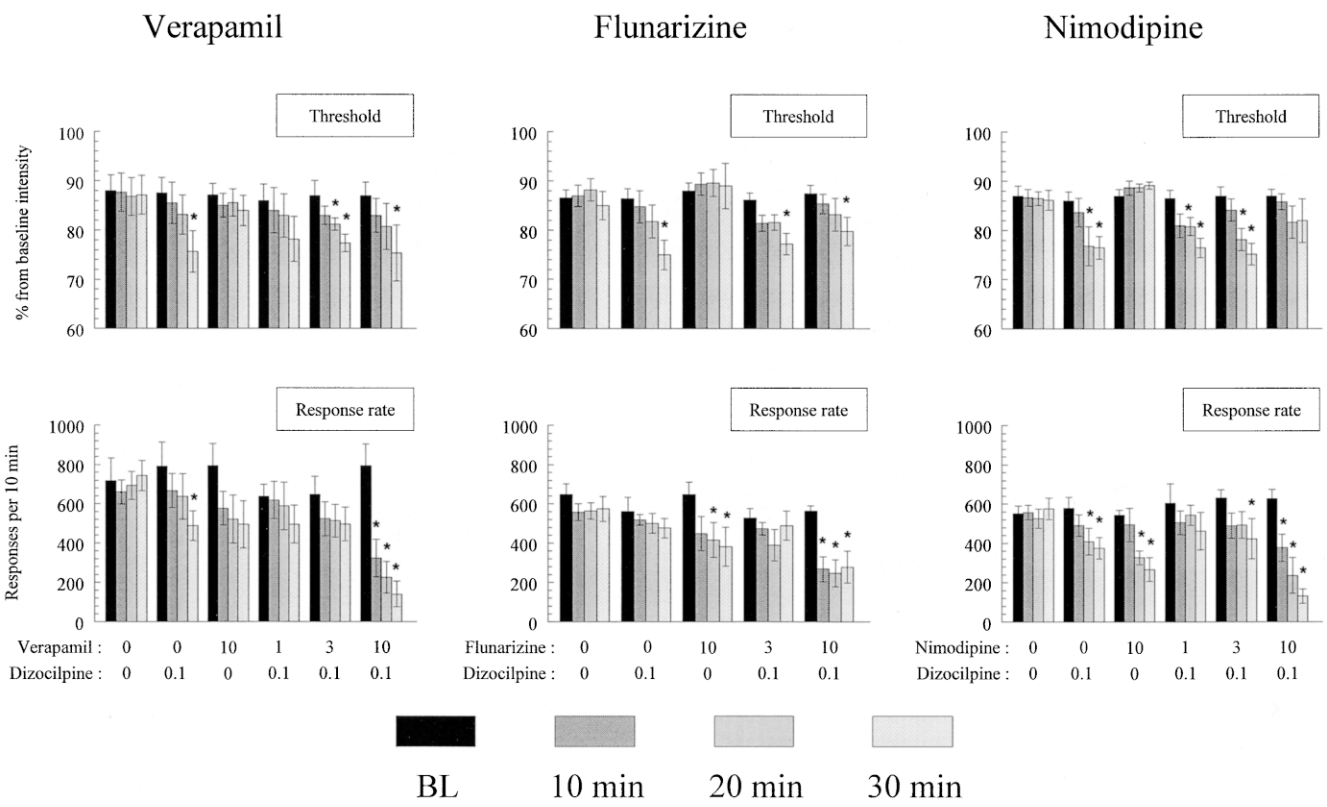


FIG. 9. Effects of VSCC blockers on electrical brain stimulation thresholds (percentage from baseline intensity ± SEM; upper panel) and mean response rates (lower panel). Rats were administered combinations of VSCC blockers and dizocilpine prior to the first test interval. See text for details. Each point is based on observations made in six rats ($n = 5$ for 10 mg/kg of nimodipine, 1 and 3 mg/kg of verapamil).*$p < 0.05$ (Duncan's test), compared to vehicle-treated controls.

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