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Linopirdine (DUP 996; AVIVA): Its Effects in the Morris Water Escape Task and on Retention of an Incompletely Acquired Bar-Press Response in Rodents

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FLAGMEYER, I. AND F. J. VAN DER STAAY. *Linopirdine (DUP 996; AVIVA): Its effects in the Morris water escape task and on retention of an incompletely acquired bar-press response in rodents.* PHARMACOL BIOCHEM BEHAV **51**(1) 111-117, 1995. -- The present study assessed the effects of linopirdine, a putative cognition-enhancing drug, on the acquisition and retention of a bar-press response [continous reinforcement schedule (CRF)] in young Wistar rats. It was also investigated whether this substance influenced the acquisition and retention of a standard Morris water escape task by young NMRI mice and by young and old Wistar rats. Linopirdine was given subcutaneously (0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg body wt.), 30 min before the first trial of a session and in one experiment immediately after the last trial of each session. A probe trial was given after the last acquisition session. In the CRF task, linopirdine did not affect the response latency and the 24-h retention of young rats. None of the parameters investigated in the Morris maze, including the escape latency (the time the animals need to find the platform), was affected by linopirdine in the rat and mouse experiments. This was also true for performance in the probe trial: linopirdine treatment did not affect the bias of the animals for the quadrant in which the platform had been positioned during acquisition. Thus, we found no experimental evidence for the hypothesized action of linopirdine as a cognition enhancer.

Linopirdine Morris water escape task Operant conditioning Rat Mouse

THE PUTATIVE cognition enhancer linopirdine (DuP 996, AVIVA) has been claimed to be useful for the therapy of Alzheimer's disease. The hypothesis of a central action of this substance is supported by in vitro labeling of binding sites in the rat brain, where tritiated linopirdine shows highest binding densities in the hippocampus and the cerebral cortex (7). In Alzheimer patients, these are the main regions showing neurodegeneration and the highest densities of plaques and tangles. Linopirdine also bound to the dorsal raphe nucleus and the interpeduncular nucleus (7).

Because standard ligands such as noradrenaline, strychnine, and atropine, and neuropeptides cannot displace the specific binding of linopirdine (16), it has been suggested that linopirdine acts at a novel binding site that might mediate its pharmacologic effects. It has been postulated that the mode of action of linopirdine is to enhance potassium-evoked transmitter release (acetylcholine, dopamine, and serotonin) in brain tissues without affecting the basal release (13). Linopirdine increases the release of norepinephrine in the hypothalamus but not in the cerebral cortex and hippocampus of rats (24), and increases acetylcholine (ACh) synthesis (21) but has no influence on ACh-esterase activity (13).

It is not possible to evoke linopirdine-stimulated transmitter release by electrical stimulation (15). Therefore, the action of linopirdine in combination with high extracellular potassium concentrations cannot be explained by potassium-evoked membrane depolarization. Frey et al. (11) suggested that the increased stimulated transmitter release might be related to blockade of voltage-activated Ca^{2+}-dependent potassium channels, which results in membrane depolarization and thereby increased transmitter release.

Tsai et al. (18) investigated the action of linopirdine on

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electrophysiologic parameters in the skeletal muscle of rodents. They found no effects on compound- and single-action potentials, whereas the amplitude and frequency of the endplate potential were increased. This leads to the hypothesis that synaptic processes mainly mediate the action of linopirdine.

Evidence for the cognition-enhancing effects of linopirdine has been found with different animal models. Brioni et al. (3) found that linopirdine facilitates retention and improves performance in the two-platform water maze task in septal-lesioned rats. DeNoble et al. (5) reported that the compound protects against hypoxia-induced passive avoidance deficits. Other substances such as physostigmine and tetrahydroaminoacridine, which influence ACh transmitter metabolism, were found to be active in the same passive-avoidance test, but did not show as good a safety ratio as linopirdine (6). Baxter et al. (2) investigated the cognition-enhancing properties of linopirdine by measuring its effects on discrimination learning in a water maze in old rats. Whereas all previously described effects were found in defect models (i.e., lesions, hypoxia, aging), Cook et al. (4) reported that linopirdine enhanced acquisition of active avoidance tasks and lever pressing for food in normal adult rats, and that performance was enhanced after both pre- and posttraining administration of the compound.

In the present study, we examined the effects of linopirdine treatment using several different tests with mice and rats. The first experimental paradigm was acquisition and retention of lever pressing on a continuous reinforcement schedule (CRF) in the Skinner box. In this experiment, food-deprived rats learn to press a lever to get a food reward. The response schedule of this task consists of a very restricted acquisition period followed by a retention test 24 h later. Retention is measured by comparing the performance at the end of the acquisition phase and at the beginning of the retention phase. In this setting, incomplete learning is achieved by interrupting a session after the predetermined number of 10 lever presses.

Previous experiments have shown that the CRF is sensitive to the cognition-enhancing effects of Nimodipine (9,17). We used young male Wistar rats and tested linopirdine at different dosages, including those that had been effective in the study of Cook et al. (4).

In a series of four experiments we investigated whether presession administration of linopirdine improves the acquisition of the standard Morris water escape task in Wistar rats and in NMRI mice. In a fifth Morris maze experiment the effect of postsession administration of the compound on the performance of aged rats was assessed. The Morris water escape task, in which a rat or mouse is required to localize a submerged platform, measures predominantly spatial reference memory (12). The reference memory (RM) holds trial-independent information (1) about, for example, the position of the escape platform in the water tank. Cognition enhancers such as AF102B (22) are effective in this task.

Given the effects of linopirdine in learning and memory tasks reported by others, we expected that the substance would improve acquisition and retention.

MATERIALS AND METHODS

Animals

We used 3-, 19-, and 25-mo-old male Wistar (WISW : Bor) rats and 7-week-old male NMRI mice. The body weights of the young rats ranged from 264–334 g and those of the old rats from 399–543 g. The body weights of the young mice ranged from 28–39 g. The animals appeared to be healthy and showed no signs of abnormalities or physical impairments. The rats and mice used in the Morris maze were group-housed (four animals per cage). The rats used in the CRF were housed individually in standard Makrolon cages because of food deprivation. Temperature (ca. 21.5°C) and humidity (50%) in the vivarium were controlled. Food and water were available ad lib. Lights were on from 0700–1900 h. Before testing started, all animals were transferred to the experimental room, where they were housed during the entire testing period. The light–dark regimen was the same as in the vivarium. Before testing, the weights of the rats used in the CRF were gradually reduced over 5 days to 85% of their free-feeding values.

Apparatus

For the CRF task, 10 identical Skinner boxes (Electronic and Computer Engineering, and Mechanical Engineering Departments, Psychology Laboratory, University of Nijmegen, Nijmegen, The Netherlands) were used. The left-side wall served as a control panel and included manipulanda (response levers) and discriminanda (LED displays and speakers). A recess was built into this panel above the floor and contained a food tray, into which a pellet dispenser delivered 45-mg food pellets (Bio-Serve). Retractable stainless-steel levers projected through the panel 2 cm into the Skinner box. The levers were located equidistant to the recess on both sides.

The conditioning chamber was enclosed in a sound-attenuating housing. Its inner surface was entirely covered with acoustic plastic foam. The front wall consisted of a horizontally opening "double-glazed" swing door made of two layers of transparent Plexiglas. An Apple Macintosh IIsi computer controlled the experimental equipment and collected the data.

A rat was placed in a transparent PVC holding cage at the beginning of a session. This cage was inserted into the conditioning chamber. The left- and right-side walls of the holding cage were sliding doors. After removal of the left sliding door, the rat had free access to the panel. At the end of a session the sliding door was put back and closed, and the rat was withdrawn from the apparatus while remaining in the holding cage.

The apparatus used for the Morris maze task with mice has been described in detail by van der Staay et al. (19), and the apparatus used for the experiments with rats has been described by van der Staay and de Jonge (20). However, the water tanks had different diameters from those used in these studies. The tank for the Morris maze with rats had a diameter at the top of 153 cm and a diameter at the bottom of 143 cm; the depth was 63 cm. The tank for the Morris maze with mice had a diameter at the top of 73 cm and a diameter at the bottom of 66 cm; the depth was 54 cm. Both tanks and the escape platforms were black. The water was not made opaque to prevent the platform from being visible to the rats and mice, as even the human observers had difficulty locating it.

Test Substance

Linopirdine was synthesized and supplied by Bayer AG (Wuppertal-Elberfeld) as a free amine. The compound was freshly dissolved in 1 M HCl in 0.9% NaCl solution (saline) shortly before each experiment and neutralized with 1 M NaOH (pH 7–7.4).

Experimental Procedure

General methods. One Skinner box experiment and five Morris maze experiments were performed (Table 1).

TABLE 1
ANIMALS AND DOSES OF LINOPIRDINE USED

No.	Species	Age	Groups	*n* per Group	Dose of Linopirdine
CRF					
	Wistar rats	3 mo	4	10	0.03, 0.1, 0.3 mg/kg
Morris maze					
1	Wistar rats	3 mo	4	8	0.3, 1.0, 3.0 mg/kg
2	NMRI mice	7 weeks	4	8	Ultracain; 1.0, 3.0 mg/kg
3	NMRI mice	7 weeks	4 (matched)	8	Ultracain; 1.0, 3.0 mg/kg
4	Wistar rats	24 mo	3	8	Ultracain and 0.1 mg/kg
5	Wistar rats	19 mo	3	8	0.1, 0.25 mg/kg

Linopirdine was administered before the acquisition session(s), except in the fifth Morris maze experiment, where posttraining administration of Linopirdine was investigated.

The maximal dose of linopirdine that can be administered without disturbing the normal behavior of rats and mice (3 mg/kg) was determined previously. We also used doses that had been effective in other experiments [e.g., (4)]. Linopirdine was administered subcutanously at concentrations of 0.03, 0.1, 0.25, 0.3, 1.0, and 3.0 mg/kg body wt. The injection volume was 1 ml/kg in rats and 10 ml/kg in mice. In the CRF task, the test substance was injected 30 min before the acquisition session.

Because the animals showed a strong aversion to the subcutaneous (SC) administration of linopirdine, local anesthetic (Ultracain) was applied 15 min before injection of the test substance in the Morris maze Experiments 2, 3, and 4. The rats were injected SC into the neck with 0.1 ml Ultracain in saline (application vol. 0.5 ml); mice received 0.05 ml Ultracain SC in a total injection volume of 0.25 ml saline. The administered dose was the same in the two species (independent of body weight).

In the Morris maze, in three of five experiments vehicle or linopirdine was applied SC 30 min before each first daily acquisition trial (and 15 min after administration of Ultracain).

In the third experiment, linopirdine was only administered once, 30 min before the last testing session started. All mice were treated with saline during the first 4 days. The animals were matched for performance during the first four acquisition sessions and four similar groups were formed.

In the fifth experiment, linopirdine was administered on days 1–4 immediately after the last trial to investigate the posttraining effects of the compound.

CRF. On the first 2 days, the food-deprived rats were trained in the Skinner boxes in daily 30-min sessions until they had consumed at least 20 food pellets in the second of two successive sessions. The pellets were randomly supplied at intervals ranging from 20–100 s; levers were retracted from the operant conditioning chamber during this phase. On the 3rd day, formal training in the CRF task was given. Two levers were presented alternately. As soon as the rat pressed a lever, it was retracted and a food pellet was delivered. An intertrial interval of 10 s was allowed between a rat's visit to the food tray after having pressed the lever and the presentation of the other lever. The dependent variable was the latency (in seconds) to press the lever. The session was terminated when the rat had performed 10 lever presses. Retention was tested 24 h later. The retention session was terminated after 10 lever presses. Retention was measured by comparing the performance at the end of the acquisition session and at the beginning of the retention session.

Morris Maze.

Acquisition. The animals received four massed trials during each of five daily sessions. Details of the procedure have been described by van der Staay and de Jonge (20).

Probe trial. After the fourth trial of the fifth session, an additional trial was given as a probe trial. The platform was removed, and the time an animal spent in the four quadrants was measured for 30 s in the young animals and for 60 s in the old rats. In the probe trial, all rats started from the same start position, opposite the quadrant where the escape platform had been positioned during acquisition.

Statistical Analysis

CRF. To analyze the data of the incompletely acquired operant conditioning task, five block means of two response latencies each were calculated for the acquisition session and the retention session, respectively. Treatment effects on acquisition and reacquisition of the lever-pressing task in the retention session were assessed with a two-way analysis of variance (ANOVA) with repeated measures over blocks [SAS GLM procedure (10)]. When appropriate, the results of ANOVAs on treatment effects within particular sessions are included. Treatment effects of the 24-h retention interval were evaluated by a two-way ANOVA in which the last block mean of the acquisition session and the first block mean of the retention session were considered to be levels of a repeated-measures factor.

Morris Maze.

Acquisition. The following parameters were analyzed: a) escape latency, or the time taken to find and escape onto the submerged platform; b) the total number of line crossings; and c) swimming speed. The total number of line crossings can be taken as index of the distance swum to reach the platform. The scores within each session were averaged over trials per rat. Treatment effects on the acquisition of the water escape task were assessed with an analysis of variance (ANOVA) with repeated measures over sessions [SAS GLM procedure (10)]. When appropriate, the ANOVAs for particular sessions are included.

Probe trial. Treatment effects on the swimming time during the probe trial were assessed with a repeated-measures

ANOVA over quadrants (time spent in the northern, eastern, southern, and western quadrants is considered to be a level of the repeated measures factor), complemented by ANOVAs on the swimming times per quadrant.

RESULTS

CRF

One rat of the control group, three of the 0.03-mg/kg linopirdine group, three of the 0.1-mg/kg group, and four of the 0.3-mg/kg group did not press the lever 10 times during the acquisition session; therefore, the retention performance of these animals was not assessed 24 h later. The remaining rats learned to press the lever faster as the acquisition session progressed [blocks: $F(4, 100) = 27.50$, $p < 0.01$]; the speed of acquisition (Fig. 1), however, was similar for the four groups [blocks × treatment interaction: $F(12, 100) = 1.67$, NS]. During the retention session, the latency to press the lever decreased further [blocks: $F(4, 100) = 16.88$, $p < 0.01$]. Again, linopirdine (0.03, 0.1, and 0.3 mg/kg) had no differential effect on the decrease in lever-press latencies. Retention was also not affected by the treatment [latency during the last block of acqusition session vs. latency during first block of retention session: $F(3, 25) < 1.0$, NS). Note that linopirdine was administered once only before the acquisition session.

Morris Maze

Experiment 1. All young rats showed a reduction in the escape latency [sessions: $F(4, 112) = 37.77$, $p < 0.01$] and a decrease in line crossings over the five testing sessions [$F(4, 112) = 41.58$, $p < 0.01$]. Linopirdine administered every day 30 min before the first trial did not affect any of the parameters investigated (all Fs for treatment effects and treatment by sessions interactions had associated probabilities > 0.05). Linopirdine at doses of 0.3, 1.0, and 3.0 mg/kg did not influence the escape latency, line crossings, or swimming speed (Fig. 2). The parameters measured during the probe trial (time in quadrant, line crossings in quadrant, time in annulus, annulus crossings, and quadrant entries) were also unaffected by linopirdine (Fig. 2). All groups showed a clear bias for the training quadrant [quadrants: $F(3, 84) = 59.59$, $p < 0.01$].

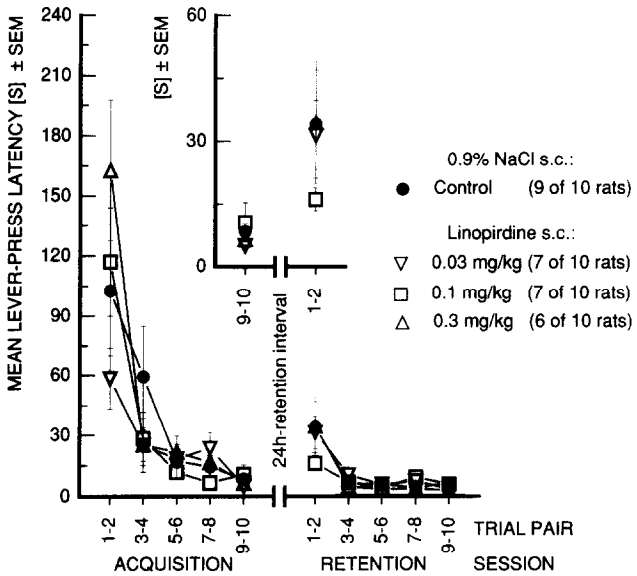

FIG. 1. Effects of linopirdine on the acquisition and retention of responding on a continous reinforcement schedule in the Skinner box. The mean response latencies (in seconds ± SEM) of five trial pairs of the acquisition session and of five trial pairs of the retention session, performed after a 24-h retention interval, are depicted. Linopirdine was administered once, 30 min before the start of the acquisition session. Insert: Comparison of the means of the last trial pairs of the acquisition session with the means of the first trials of the retention session. Note that for clarity the Y-axis has been enlarged.

Experiments 2 and 3 (young mice). Because of hardware problems in the second experiment two animals could not be tested 30 min after linopirdine administration. Their data were omitted from the analysis. In Experiment 3, one animal of the group treated with 3.0 mg/kg linopirdine was accidentally tested twice during the fourth acquisition session. The results of this mouse were therefore also omitted from the statistical evaluation.

The mice acquired the task in both experiments when escape latency [sessions: Experiment 2, $F(4, 108) = 14.69$, $p < 0.01$; Experiment 3, $F(4, 104) = 10.86$ $p < 0.01$] and line crossings [sessions: Experiment 2, $F(4, 108) = 17.17$, $p < 0.01$; Experiment 3, $F(4, 104) = 15.15$ $p < 0.01$] are considered (results not shown). The daily administration of linopirdine (1 and 3 mg/kg) in the second experiment did not affect acquisition (all Fs for treatment effects and for treatment by sessions interactions had associated probabilities > 0.05).

A single dose of linopirdine (1 or 3 mg/kg) in the matched groups of Experiment 3 neither influenced the performance on the 5th day of testing [all $F(3, 26) < 1.0$, NS] nor affected the performance in the probe trial [all $F(3, 26) < 1.0$, NS].

Experiment 4. The old rats acquired the Morris water escape task [sessions: escape latency, $F(4, 84) = 6.08$, $p < 0.05$; line crossings, $F(4, 84) = 5.97$, $p < 0.01$]. During the probe trial, the old rats showed no bias for the training quadrant [$F(3, 63) < 1.0$, NS). Linopirdine (0.1 mg/kg SC) administered 15 min after Ultracain injection had no effect on acquisition or performance in the probe trial (Fig. 3).

Experiment 5. The aged rats acquired the Moris water escape task [sessions, escape latency $F(4, 104) = 20.96$, $p < 0.01$; line crossings, $F(4, 104) = 6.69$, $p < 0.01$]. The acquisition curves, however, were not differentially affected by the posttraining administration of linopirdine. Linopirdine also did not affect the bias for the training quadrant in the probe trial (results not shown).

DISCUSSION

Linopirdine did not affect any of the behavioral parameters investigated in either the CRF or Morris water escape tasks. At the concentrations used, linopirdine did not influence learning and memory performance in young mice or in young and old rats.

In the CRF task, the latency to press the lever decreased further during the retention session. This indicates that the bar-press response was acquired incompletely during the acquisition session. Previously, we had found that nimodipine improves the performance of an incompletely acquired bar-press response in the retention session of the CRF schedule we used (9,17). We expected linopirdine to improve retention in this task, but we were not able to find effects on this paradigm. Cook et al. (4) reported an improvement of acquisition in a CRF-autoshaping schedule with delayed reinforcement (8-s delay) after linopirdine treatment. Their experimental setup, however, differed from ours. They tested the animals

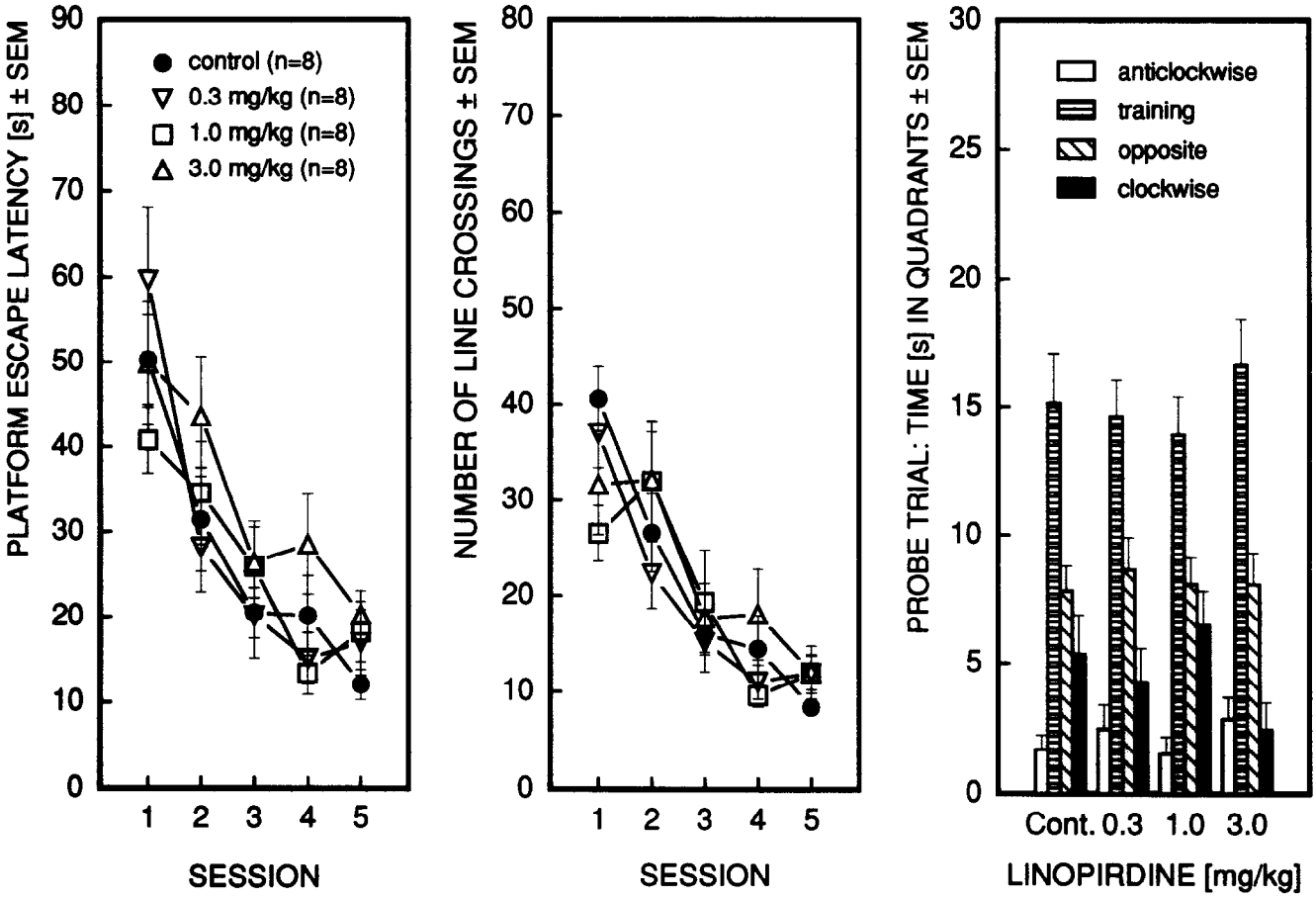

FIG. 2. Session means (in seconds ± SEM) for platform escape latencies (left panel) and number of quadrant entries (central panel) of naive young Wistar rats trained to find a submerged platform after SC administration of linopirdine or vehicle. In the linopirdine-treated groups, the compound was administered every day 30 min before the first trial. The means and SEMs of the linopirdine- and vehicle-treated groups per acquisition session are depicted. The right panel shows the mean time (in seconds ± SEM) spent by the animals in each quadrant of the circular pool during a 1-min probe trial.

over a period of about 8 h after administration of linopirdine. Because of the short half-life of the substance [0.4–3.2 h in humans (14)], we tested the animals within 1 h of its administration.

We chose the Morris maze task to investigate the learning and memory effects of linopirdine because cognition enhancers, such as AF102B, and peptides, such as α-melanocyte-stimulating hormone, are effective in this task (22,23). In the Morris maze task, all animals showed a clear improvement over sessions. The learning curves of the mice were not as steep as those of the young rats. In the mice, even on the 5th day of testing, it was still possible to improve acquisition, as the learning curves did not show asymptotic values. Therefore, in the third experiment we matched the animals for their performance after the 4th day and adminstered linopirdine only before the fifth testing session. Linopirdine was still ineffective.

When Figs. 2 and 3 are compared, it becomes clear that the old rats showed a poorer learning performance than did the young animals. In the probe trial the young animals showed a clear bias for the training quadrant, whereas the old rats did not. On the basis of the results of van der Staay and de Jonge (20), who described an impairment of old rats in the Morris maze task, we expected linopirdine to improve the acquisition and retention of the rats. However, we found no effect of linopirdine on the parameters investigated in the Morris maze, in either old nor young animals. An additional experiment in which we tested the posttraining effects of linoirdine in the Morris maze also showed no effects of this compound.

The animals showed a strong aversion to repeated linopirdine administration not only in this study but also in our general pharmacology experiments (8). Therefore, we injected a local anesthetic SC 15 min before linopirdine was administered in Experiments 2, 3, and 4. One group of animals received Ultracain only and no linopirdine to exclude an influence of anesthetic on the behavioral parameters. Neither saline nor Ultracain had a detectable effect on the behavior of the animals. Therefore, it is unlikely that the local anesthetic had a negative influence on the performance of the animals.

Brioni et al. (3) described an effect of linopirdine in septal-lesioned rats in the Morris maze. The animals were tested 15 min after administration of the substance. During this period (10–20 min after administration), we found linopirdine to have a sedative effect in naive animals in the modified Irwin test (8). Referring to his open-field and plus-maze data, Brioni concluded that linopirdine did not modify the hyperactivity of

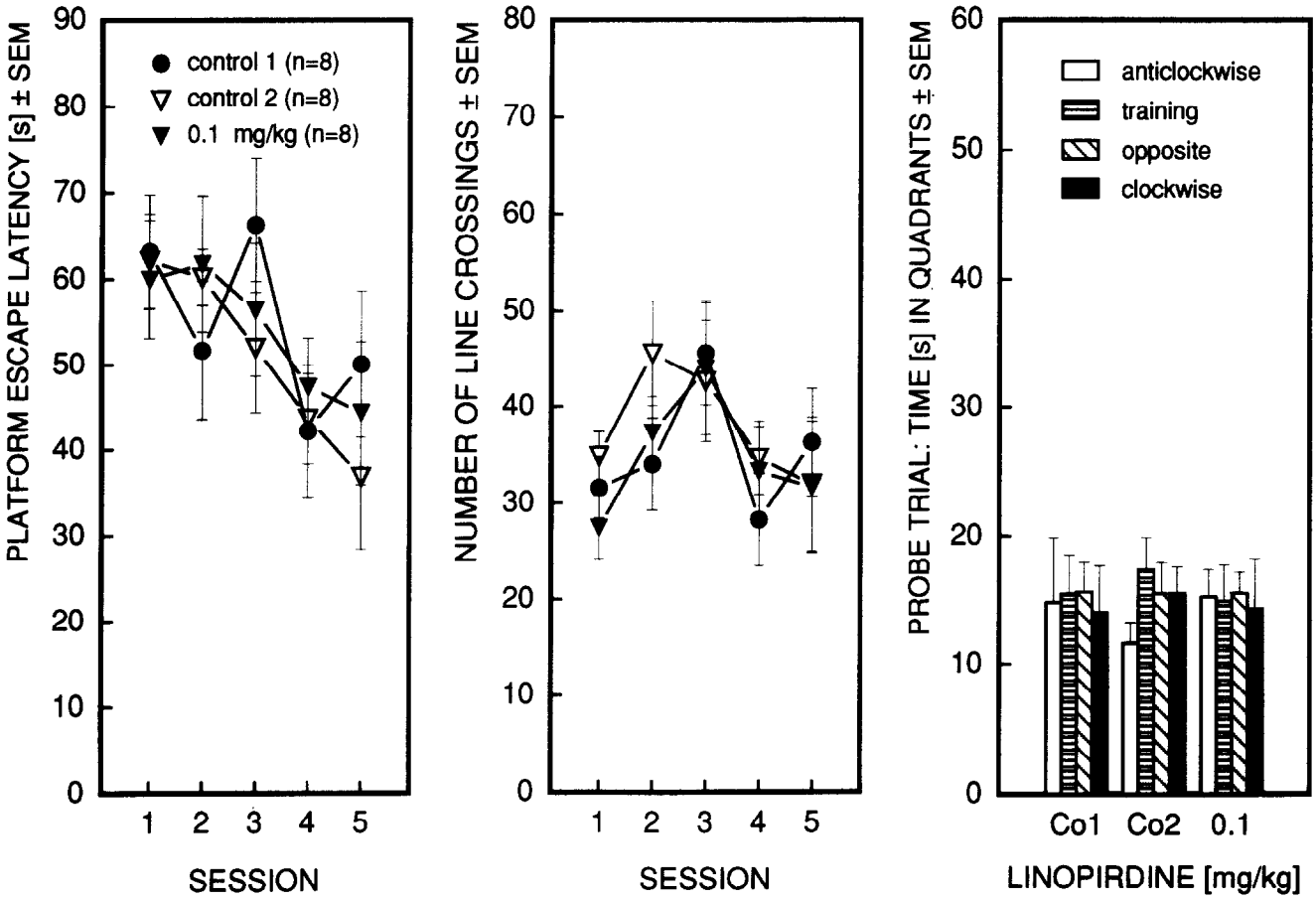

FIG. 3. Session means (in seconds ± SEM) for platform escape latencies (left panel) and number of quadrant entries (central panel) of naive 24-mo-old Wistar rats trained to find a submerged platform after SC administration of linopirdine or vehicle. For further information, see Fig. 2.

septal-lesioned rats. However, on the basis of our investigations, we suggest that a linopirdine-induced sedation might have influenced the learning behavior of the animals.

In conclusion, the present study evaluated the effects of linopirdine in two different learning tasks with rats and mice. We found no indications that the compound has cognition-enhancing effects. Our experiments assessed the putative cognition-enhancing properties of linopirdine in two different species in normal and deficient animals (i.e., aged animals) and after pre- and postsession application. Dependent on the kinetic properties of the substance, presession administration might influence acquisition and/or memory consolidation. Postsession administration of linopirdine might modulate processes underlying memory consolidation. The data are inconclusive because the lack of effects might be due to either the weak efficacy of the compound or the low sensitivity of our animal models to detect beneficial effects of this class of compounds. However, to extend our knowledge about putative cognition-enhancing compounds, these substances should be asssessed in a broad spectrum of tests and animal models.

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