Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 3, pp. 757–759, 1994

0091-3057/94 $6.00 + .00

BRIEF COMMUNICATION

# Disruption of Two-Way Active Avoidance Behavior Produced by Nimodipine

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Received 4 June 1993

NIKOLAEV, E. AND L. KACZMAREK. *Disruption of two-way active avoidance behavior produced by nimodipine.* PHARMACOL BIOCHEM BEHAV 47(3) 757–759, 1994.—Nimodipine, a voltage-sensitive calcium channel blocker, has been suggested to be a procognitive drug. In the studies reported herein, we found that low doses of IP-injected nimodipine (0.5 and 0.05 mg/kg) impaired two-way active avoidance behavior. The acquisition phase of the training was the same for drug-treated and control animals. However, the nimodipine-injected rats achieved a significantly lower level of performance. The no-shock tests revealed much faster extinction of the learned behavior in drug-treated vs. control animals. These results could be interpreted as indicating learning-disruptive effects of nimodipine.

Shuttle box  Procognitive drugs  Rat  Calcium channels

NIMODIPINE has been described as a specific blocker of voltage-dependent calcium channels (L-type channels), with a reasonably good ability to penetrate the blood–brain barrier (4). Several reports documented procognitive properties of this drug, in particular in the aged and damaged brain (1,3,5,6). For instance, Deyo et al. (3) reported that nimodipine facilitated associative learning in aging rabbits, and Nyakas et al. (6) documented the protective effect of nimodipine on discrimination learning deficits caused by prenatal nitrite exposure in rats. Additionally, Levy et al. (5) showed that this drug improves spatial working memory in young rats.

To extend these data further, we decided to carry out studies on the effects of nimodipine on learning of two-way active avoidance behavior in normal, young adult rats.

## METHOD

### *Animals*

Thirty young adult Wistar rats weighing 180–240 g, obtained from the Nencki Institute Animal House, were used in this study. The animals were divided into three groups of 10 animals each, and were kept in a single home cage (43 cm long, 25 cm wide, 18.5 cm high) containing food and water available ad lib. A normal 12 L : 12 D cycle from natural external lighting was maintained.

### *Apparatus*

A shuttle-box apparatus consisted of two identical opaque dark compartments (31 cm long, 18 cm wide, 29 cm high) separated by a wall with a rectangular (7 cm wide, 10 cm high) opening with a sill situated on the grid floor level. Each compartment was illuminated by a 5-W lamp mounted centrally on the top of the apparatus. The floor in each compartment was constructed from 16 stainless steel bars, 0.4 cm in diameter and located parallel to the central partition 1.5 cm apart from each other. The shuttle box apparatus was placed in a dark soundproof room. Subjects' behavior was watched on a TV monitor in an adjoining room in which equipment for automatic programming of the experiment and recording of data was located.

### *Behavioral Procedures*

The behavioral procedure consisted of a 10-min habituation session (no shock provided), then 12 training sessions, one session a day. Each session consisted of 20 trials separated

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by 30-s intertrial interval on average (randomly distributed intertrial intervals of: 15, 30, and 45 s). During each trial the subject was exposed to a conditioned stimulus (darkness). Then the animal had 3 s to avoid the unconditioned stimulus (2.0 mA scrambled foot shock). The CS lasted up to 5 s or until the conditioned reaction was emitted, whichever came first. After the training sessions, three test sessions (I, II, and III) were performed 5, 10, and 20 days, respectively, after the termination of the training. The test sessions differed from the training ones by the lack of the US.

For each animal, the number of avoidance responses (Av), defined as moving of the subject to the opposite compartment of the apparatus within 3 s and, therefore, not receiving the US, was recorded.

*Drug Delivery*

Nimodipine was dissolved in 100 $\mu$l of ethanol and then diluted with 50 ml of water at the final concentration of 4 mg/ml. One hour before each of the training and test sessions each subject received a single IP injection of nimodipine at two doses of 0.05 and 0.5 mg/kg. Control animals were injected with vehicle without the drugs.

*Statistics*

The results were analyzed with repeated measures analysis of variance (ANOVA) and Duncan tests.

## RESULTS AND DISCUSSION

The summary of the main training results are presented in Fig. 1, where the mean number of avoidances for each of the groups are presented for of all the training sessions. There was a similar rate of acquisition of the two-way active avoidance behavior for both of the drug-injected groups as well as for the control group during the first three training sessions. Then, starting from day 4, the control animals achieved significantly higher performance levels than subjects from the drug-treated groups. Statistical analysis revealed that performance reached a plateau level starting from the fourth session, when

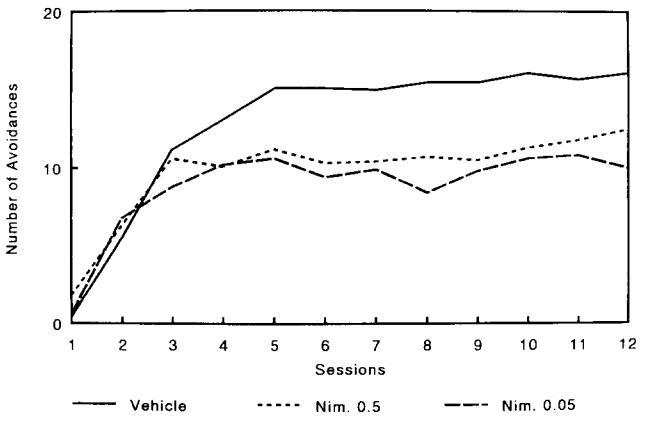


FIG. 1. The performance of the nimodipine-treated rats during acquisition of the two-way active avoidance reaction. The mean number of avoidances during each 20-trial training session is shown for each group (vehicle control, 0.5 mg/kg of nimodipine, and 0.05 mg/kg of nimodipine).

TABLE 1

THE PERFORMANCE OF THE NIMODIPINE-TREATED RATS DURING THE TEST (NO SHOCK) SESSIONS

| Training Session | Group of Animals | | |
|---|---|---|---|
| | Control | Nimodipine (0.5 mg/kg) | Nimodipine (0.05 mg/kg) |
| I | 6.5 (3.0–9.0) | 1.5 (0.0–10.0) | 0 (0–0) |
| II | 5.5 (4.0–9.0) | 0.5 (0.0–15.0) | 0 (0–0) |
| III | 3.0 (0.0–9.0) | 0.0 (0.0– 4.0) | 0 (0–0) |

Presented are median values for each group with 25–75 percentiles in parentheses.

significant differences could also be observed between the control and drug-treated subjects, $F(11, 27) = 59.7, p < 0.001$.

The extinction tests again clearly distinguished between drug-treated and control subjects (Table 1). The no-shock driven extinction of the avoidance reaction was much more rapid in the nimodipine-treated animals than in the controls. Interestingly, the extinction was the fastest in the rats receiving the low dose of the drug. This result could be interpreted either as poorer memory of the trained reaction in the drug-treated animals, or as their ability for quick learning of the new situation. We would favor the first explanation as it should be noted that usually a single trial not reinforced by the US leads to giving up of the avoidance behavior. Not performing the avoidance reaction offered, therefore, is a clear advantage to the subjects during this stage of the experiment. Moreover, the drug treatment during test sessions should also be impairing extinction, which is a learning phenomenon.

Alternatively, one might view poor performance in the two-way active avoidance task as indication of faster classical conditioning, or rather extinction of classically conditioned fear. Once the rat avoids the shock on 50% of the trials, many CS-alone trials are presented. This might lead to rapid extinction of the fear of the CS, and therefore lack of performance of the avoidance response. The extinction test data demonstrate that the drug-treated rats extinguish quickly.

The results reported suggest that nimodipine may display learning/memory disruptive activity. Although repeatedly shown to be a memory-enhancing agent, this drug proved to have opposite effects, which was aslo shown by Deyo (2) in a study on visual discrimination task in 5-day-old chicks. Interestingly, the doses used for amnesic effects of nimodipine in that study were significantly higher (5 mg/kg) then those used in our experiments. At 1.0 mg/kg, the drug was improving the acquisition of the visual discrimination task and 0.5 mg/kg was without any significant effect. In our hands, both doses (0.5 and 0.05 mg/kg) clearly impaired performance of two-way active avoidance in adult rats.

This is, to our knowledge, the first demonstration that quite low doses of nimodipine could disrupt learning. However, other interpretations are also to be considered. In particular, it is of note that practically the same acquisition phase of the training was observed in both nimodipine-treated and control animals, implying that the drug does not interfere with learning processes but it has effects on performance only. This last suggestion could be explained by peripheral effects of the drug influencing the behavior. However, the short latencies

of the escape responses (not shown) do not support any simple explanation (like modification of motor activity or the pain threshold) of this phenomenon. Another simple explanation, that the drugs influenced the ability to perceive the CS, cannot be excluded.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Dr. J. Lazarewicz for providing the nimodipine and critical reading of the manuscript, and to Drs. J. Vetulani, J. Wilson, and K. Zielinski for helpful comments. This work was supported in part by KBN grant 2228/4/91.

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