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Short communication

Effects of nimodipine, felodipine and amlodipine on electroconvulsive shock-induced amnesia in the rat

Gordana Župan *, Dinko Vitezić, Jasenka Mršić, Damir Matešić, Ante Simonić

Department of Pharmacology, School of Medicine, University of Rijeka, Braće Branchetta 20 / I, 51000 Rijeka, Croatia

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Abstract

The effects of various doses (0.03, 0.1, 0.3 or 1.0 mg/kg) of the Ca^{2+} channel blockers nimodipine, felodipine and amlodipine on the learning ability of rats exposed to electroconvulsive shock were examined. The animals were trained in a passive avoidance procedure. The drugs tested were injected 30 min before the learning trial started. The electroconvulsive shock was given immediately after the learning trial response had been acquired. A passive avoidance retention test was performed 24 h later. It was found that electroconvulsive shock strongly impaired the retention of the passive avoidance response. Nimodipine, felodipine and amlodipine did not influence the passive avoidance behavior in the sham electroconvulsive shock group, but significantly improved the retention deficits in the animals exposed to electroconvulsive shock. These findings support the hypothesis that perturbations in Ca^{2+} homeostasis can contribute to the memory deficits associated with electroconvulsive shock. The antiamnestic effects of the substances tested make them interesting candidates for clinical trials in patients with cognitive impairment caused by electroconvulsive shock therapy.

Keywords: Electroconvulsive shock; Amnesia; Nimodipine; Felodipine; Amlodipine; (Rat)

1. Introduction

Electroconvulsive therapy is widely used in the treatment of certain psychiatric disorders such as endogenous depression with psychotic features, depression with psychomotor retardation, mania, catatonia etc. Besides the beneficial therapeutic effects the electroconvulsive therapy can also cause memory impairment characterized by both anterograde and retrograde amnesia (Itoh et al., 1990). The etiology of the memory dysfunction associated with the electroconvulsive therapy is still not clear.

Following various harmful situations like cerebral hypoxia, ischemia, trauma or electroconvulsive shock administration, a massive influx of extracellular Ca^{2+} occurs, mostly through the L-type of voltage-dependent Ca^{2+} channels (Antkiewicz-Michaluk et al., 1994). Excessive Ca^{2+} entry initiates a cascade of various intracellular processes which provoke the destruction of the cell (Young, 1992).

We hypothesized that a disturbance in Ca^{2+} homeostasis might also contribute to the memory deficits associated with electroconvulsive shock therapy. Therefore, this study was designed to investigate the influence of some Ca^{2+} channel blockers of the dihydropyridine group (nimodipine, felodipine and amlodipine) on memory impairments caused by electroconvulsive shock application in rats.

2. Materials and methods

2.1. Animals

Experiments were carried out on Hannover-Wistar rats weighing 150–200 g. They were kept under standard laboratory conditions, five per cage, with free access to standard laboratory food and tap water, at room temperature (approximately 22°C) with a natural day-night cycle. The experiments were performed between 9.00 a.m. and 6.00 p.m.

2.2. Apparatus

The step-through apparatus for the passive avoidance task (Ugo Basile, Italy) consisted of two compartments (210 × 240 × 210 mm each) with grid floors which could

* Corresponding author. Tel./Fax: (385)-51-514-391.

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be electrified separately. The first compartment was illuminated and was connected by a guillotine door with the dark compartment.

2.3. Experimental plan and procedure

An assessment of electroconvulsive shock-induced convulsions was done. The time of convulsions was measured from the shock to the last convulsive movements.

All animals were trained in a passive avoidance task. During the learning trial each animal was placed in the illuminated compartment, and after the adaptation period of 30 s the guillotine door was raised. The rat spontaneously walked into the dark chamber. The time between opening the door and the rat entering the dark compartment was measured. As soon as the animal placed its four paws in the dark compartment, the guillotine door was lowered and the rat was punished with a brief foot-shock (0.6 mA, 50 Hz, 1 s).

The animals of control group 1 were intact and had no past drug or experimental history. They were only subjected to the passive avoidance task. The animals of control group 2 received an electroconvulsive shock (50 mA, 50 Hz, 400 ms) via earclip electrodes using an electroconvulsive shock apparatus (Electroconvulsive Shock Unit, Ugo Basile, Italy), immediately after the learning trial had been performed. The animals of control group 3 received a sham electroconvulsive shock treatment consisting of handling and application of earclips, but without the shock.

The animals of control group 4 and control group 5 received a vehicle solution containing ethanol and propylene glycol 400 (50:50). The rats of control group 4 were given a sham electroconvulsive shock while the animals of control group 5 received electroconvulsive shock treatment. The other sham or electroconvulsive shock-treated animals received various doses (0.03, 0.1, 0.3 or 1.0 mg/kg) of felodipine, nimodipine or amlodipine. All drugs tested were dissolved in the vehicle solution and given intraperitoneally, in a total volume of 1 ml/kg, 30 min before the learning trial started.

After experimental procedures the rats of all experimental groups were returned to their home cages and were retested 24 h later.

During the retention trial the rat was placed in the illuminated compartment, and the latency to enter the dark compartment was recorded up to the maximum time of 180 s.

2.4. Statistical analysis

The results are presented as the step-through latencies of the learning and retention trials expressed in seconds. Better performance was indicated by longer latencies. Statistical evaluation of the results was done by using a two-way analysis of variance (ANOVA), followed by Duncan's multiple range test at a significance level of $P \leq 0.05$.

3. Results

No statistically significant differences in the strength of convulsions between rats treated with the Ca^{2+} channel blockers and vehicle were noted. The overall mean time of convulsions in all examined groups was 35 ± 5 s.

The step-through latencies during the learning and retention trials of the animals of the control groups are shown in Table 1. An overall of ANOVA on the step-through latencies indicated the main effects of the trials ($F(1,75) = 147.4$; $P < 0.001$) and treatments ($F(4,75) = 25.2$; $P < 0.001$). Subsequent analysis showed that electroconvulsive shock administration caused a statistically significant impairment of the passive avoidance behavior, as demonstrated by the shortening of the step-through latencies in the retention trials ($F(1,75) = 41.9$; $P < 0.001$). The administration of vehicle did not influence significantly the passive avoidance behavior neither in the sham electroconvulsive shock rats ($F(1,33) = 0.66$; $P = 0.42$) nor in electroconvulsive shock-treated rats ($F(1,28) = 0.70$; $P = 0.41$).

The passive avoidance behavior in the sham electroconvulsive shock group was not altered by the doses tested of nimodipine ($F(4,95) = 0.63$; $P = 0.64$), felodipine ($F(4,95) = 0.55$; $P = 0.70$) or amlodipine ($F(4,95) = 0.67$; $P = 0.62$) (Fig. 1A). Thus the step-through latencies of the learning and retention trials did not differ significantly in the animals of control group 4 and in the sham electroconvulsive shock rats receiving the Ca^{2+} channel blockers.

An overall ANOVA on the step-through latencies of the learning and retention trials in electroconvulsive shock-treated rats, injected with various doses of the Ca^{2+} channel blockers tested, showed the main effects of trials ($F(1,168) = 135.7$; $P < 0.001$) and substances ($F(11,168) = 5.7$; $P < 0.001$). It is evident that the step-through

Table 1
Passive avoidance behavior of the control groups

Groups	Treatment	Step-through latency (s)	
		Learning trial	Retention trial
Control 1 [15]	Drug naive Intact	34.14 ± 9.77	151.85 ± 15.13
Control 2 [15]	Drug naive ECS	23.15 ± 3.50	22.09 ± 3.63 [a]
Control 3 [15]	Drug naive Sham ECS	33.65 ± 9.32	153.43 ± 14.20
Control 4 [20]	Vehicle solution Sham ECS	24.70 ± 6.39	136.73 ± 14.25
Control 5 [15]	Vehicle solution ECS	27.80 ± 3.80	26.62 ± 3.98 [a]

The values are means ± S.E.M.; [n] = number of rats; ECS = electroconvulsive shock; [a] $P \leq 0.05$; significantly different from control group 1.

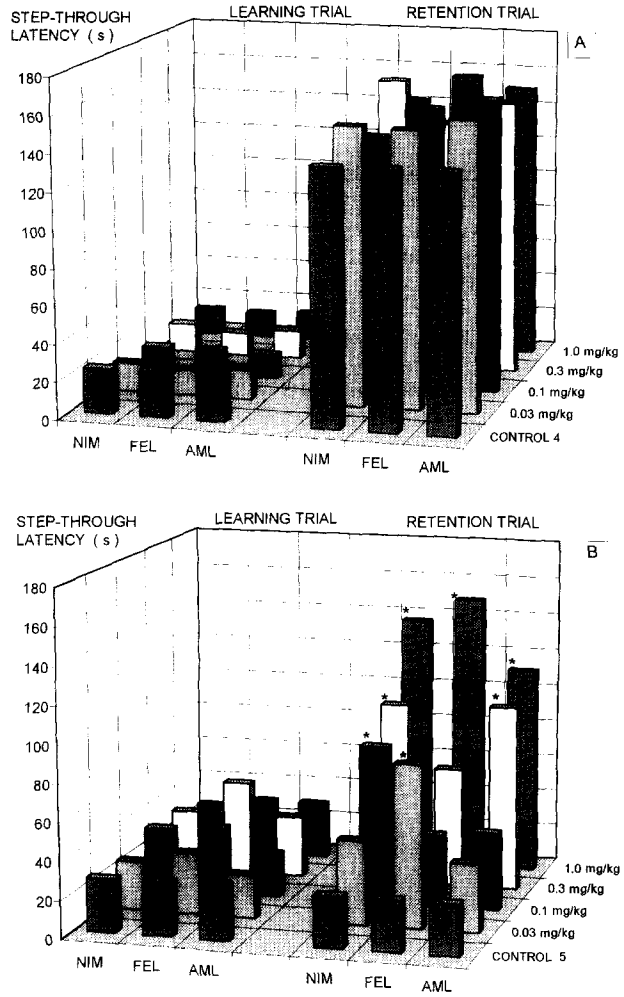

Fig. 1. Step-through latency (s) during the learning and retention trials of the sham- (A) and electroconvulsive shock-treated (B) animals that received various doses of the Ca^{2+} channel blockers. NIM = nimodipine; FEL = felodipine; AML = amlodipine. Columns represent means of 20 (A) or 15 (B) experiments. Asterisks denote statistically significant differences from controls ($P \leq 0.05$).

latencies of the learning trials were not significantly changed by any of tested Ca^{2+} channel blockers. Subsequent analysis of the step-through latencies of the retention trials demonstrated the main effect of the doses, in relation to the animals of control group 5, for nimodipine ($F(4,70) = 10.5$; $P < 0.001$), felodipine ($F(4,70) = 13,7$; $P < 0.001$), and amlodipine ($F(4,70) = 8.05$; $P < 0.001$). An ANOVA followed by Duncan's multiple range test revealed that 0.1, 0.3 and 1.0 mg/kg of nimodipine, 0.03 and 1.0 mg/kg of felodipine, and 0.3 and 1.0 mg/kg of amlodipine produced a statistically significant increase in step-through latencies in electroconvulsive shock-treated rats, in relation to the animals of control group 5 (Fig. 1B).

4. Discussion

The results of the present experiments demonstrate that exposure to electroconvulsive shock, immediately after the learning trial, impairs passive avoidance retention in rats. Our finding is comparable to that of Itoh et al. (1990), who found that electroconvulsive shock induces retrograde amnesia.

Nimodipine, felodipine and amlodipine are potent regulators of the L-type of voltage-sensitive Ca^{2+} channels. Their importance in cardiovascular therapy has been known for quite a long time. There is also considerable evidence for the central effects of nimodipine. The dihydropyridine derivative nimodipine has a beneficial effect in diminishing vasospasm in both experimental (Cohen and Allen, 1980) and clinical (Findlay et al., 1991) subarachnoid hemorrhage. Its protective effects against ischemic brain injury are also documented (Kakarieka et al., 1994). Nimodipine may be used in the treatment of acute mania (Brunet et al., 1990) and hypomanic states (Auby et al., 1992) and may improve learning and memory in aged, cognitively impaired rats, rabbits, monkeys (Deyo et al., 1989; Sandin et al., 1990; Levere and Walker, 1991) and in rats with lesions in certain brain areas, mostly hippocampus or cortex (Andersen et al., 1990; Finger et al., 1990). Felodipine and amlodipine are the Ca^{2+} channel blockers used in cardiovascular therapy. They are also effective in improving the passive avoidance retention deficit caused by hypoxia in rats (Župan et al., 1993a,b).

In our experiments the Ca^{2+} blockers tested did not influence the passive avoidance behavior of sham electroconvulsive shock-treated rats. They also did not change step-through latency in the learning trial, but they prolonged significantly the shortened step-through latency in the retention trial of electroconvulsive shock-treated rats. These results cannot confirm whether the activity of the Ca^{2+} channel blockers was due to vascular and/or neuronal mechanisms, but do confirm our previous hypothesis that memory deficits caused by electroconvulsive shock may be associated with disturbances in Ca^{2+} homeostasis.

In conclusion, we suggest that the antiamnestic effects of nimodipine, felodipine and amlodipine seen in our experiments make them interesting candidates for clinical trials in patients with memory disturbances caused by electroconvulsive shock therapy.

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