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RAPID PRELIMINARY COMMUNICATION

ELECTROCONVULSIVE SHOCK-INDUCED IMPAIRMENT OF SPATIAL LEARNING IS AGGRAVATED BY NIFEDIPINE

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Electroconvulsive shock-induced impairment of spatial learning is aggravated by nifedipine. P. POPIK, J. MAMCZARZ, J. VETULANI. Pol. J. Pharmacol., 1993, 45, 185–190.

Chronic electroconvulsive treatment applied immediately after a training session or with a 15 min delay impairs spatial learning and memory in the Morris water maze paradigm, and this impairment is not counteracted, but rather aggravated by co-administration of a calcium channel blocker, nifedipine.

Key words: Electroconvulsive treatment, memory, Morris water maze, calcium channel blocker, nifedipine

Calcium is intimately involved in memory formation (see [3]) but the effects of pharmacological manipulation of calcium inflow into the neurons are not clear. Thus, inhibition of calcium inflow through NMDA-sensitive calcium channels by antagonists such as MK-801 impairs memory [2] but inhibitors of calcium inflow through voltage-dependent channels, particularly nimodipine, were described as agents improving memory (see [6]).

Electroconvulsive treatment (ECT), a very effective therapeutic means in depression, interferes both with calcium channels and memory: ECT

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augments the density of voltage-dependent calcium channels [1] and results in memory impairment in humans and animals [7]. Although amnesic effect of ECT was evidently demonstrated in many memory paradigms, the amnesic action of ECT in spatial memory remains controversial. In the present study, using the Morris water maze paradigm, we investigated how ECT given immediately or with a 15 min delay after the training session affects learning and memory and whether nifedipine, given before the trial, affects the effect of post-trial ECT.

The experiment was carried out on male Wistar rats (250–300 g) kept in standard animal house conditions (grouped by 6 in large community cages, food and water *ad lib*, natural light-dark conditions for the spring: sunset around 20:00 h). Experiments were done between 9:00 and 17:00 h.

The training was carried out in a gray circular tank (180 cm of diameter, 50 cm of height), filled to a height of 25 cm with tap lukewarm (22°C) water which was changed every day. The room arrangement provided numerous stable extra-maze cues. The gray metal platform (10 × 15 cm) submerged by 1 cm was present inside the tank. The area of the tank was arbitrarily divided into 4 quadrants (N-W, S-W, S-E and N-E) with signs on the TV screen on which the training was observed. The platform was placed 45 cm from the wall. The rats within each group were randomly assigned to one of platform position (S-E, S-N or N-W). For a given rat the position of the platform remained unchanged during the whole experiment.

A trial consisted of placing a rat at one of the four starting positions (N, W, S, E) around the tank perimeter. The rat was put into water by hand, facing the tank wall. Every day, the starting position was changed. If a rat escaped onto the platform, it was permitted to remain there for 30 s before it was picked up and placed into the tank again. If a rat failed to find the platform within 120 s it was placed onto the platform by hand and allowed to remain there for 30 s. For each trial the time a rat needed to escape onto the platform (escape latency) was measured. The behavioral testing was conducted on 13 consecutive days with each rat receiving 12 swimming trials on Days 1–12. On Day 13, a 'transfer test' was performed: the rat was placed into the tank, from which the escape platform was removed, for 60 s. The swimming behavior of the rats was recorded using a video camera recorder (Hitachi Model VM-2380). The sessions were analyzed by the second experimenter, unaware of rats' treatment. During the session, the time spent by a rat in every quadrant, number of correct "hits" (swimming directly above the former platform position, total path swum and the mean distance from the wall were

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Electroconvulsive treatment consisted in daily shocks caused by passing a current (50 Hz, 150 mA, 200 ms) via lightweight alligator clips attached to rat's ears wetted with saline. The shock elicited a full tonic-clonic seizures in all rats.

Two schedules of administration of nifedipine and ECT were employed. In the first rats were injected with nifedipine (Polfa) (5 mg/kg *ip*, suspension in Tween 80) 15 min before the learning trial, and ECT was given immediately after removal of the rat from the platform. In the second schedule, nifedipine was given immediately after training session, and ECT – 15 min later. Tween solution and sham ECT (clips on the ears, no shock) were used for controls.

The control rats learned the task well. Nifedipine given before training sessions slowed down the rate of learning but after 12 days of training the mean escape latencies did not differ significantly from those of control groups. The learning of rats receiving ECT was significantly impaired by the end of training, particularly in the group receiving ECT 15 min after the trial. Even more impaired were the rats receiving nifedipine before trail and ECT just after: the difference between rats receiving ECT alone and with nifedipine reached statistical significance in the group receiving ECT immediately after training (Tab. 1).

Table 1. Escape latencies at the end of training in the Morris water tank test

Group	Escape latency in seconds	
	Injection before, ECT immediate	Injection after, ECT delayed
Saline	9.3 ± 1.4 (10)	16.4 ± 2.8 (9)
Nifedipine	19.4 ± 8.4 (9)	17.4 ± 1.9 (10)
ECT	28.0 ± 5.8 (10)[a]	39.6 ± 10.3 (6)[a]
Nifedipine + ECT	44.0 ± 7.6 (10)[ab]	39.7 ± 6.3 (9)[a]

The data are mean latencies of the last three training trials (days 10–12). The overall three-way analysis of variance demonstrated a significant effect for ECT ($F_{1/64} = 27.4$, $p < 0.001$), with insignificant effects of injection/ECT schedule and nifedipine treatment. [a] significantly different from control ($p < 0.01$), [b] significantly different from the group receiving ECT alone (Fisher's LSD test)

The memory measured in the transfer test was impaired both by nifedipine and ECT. In rats receiving an injection before the training the

time of swimming of the controls in the correct quadrant was 152% of that expected if swimming were random. After nifedipine treatment the time was only 122%, while the rats receiving ECT alone or with nifedipine swam randomly (the time in correct quadrant was 104 and 102% of that expected). Nifedipine given before the trial reduced significantly the number of direct swimming over the platform position by 50% (from 2.2 ± 0.3 to 1.1 ± 0.4); ECT, given with or without nifedipine produced a slightly stronger effect (0.9 hits). The rats receiving ECT swam closer to the wall, and those receiving ECT with placebo swam faster: the total swimming path in this group was approximately 30% longer than that of controls (the rats receiving nifedipine with or without ECT had swimming path very similar to that of controls: 101–105%). Similar results were obtained in experiments in which nifedipine was administered immediately after each training session, and ECT was delivered 15 min later. The representative swimming pattern of a control rat and the rat receiving nifedipine and ECT is presented in Figure 1.

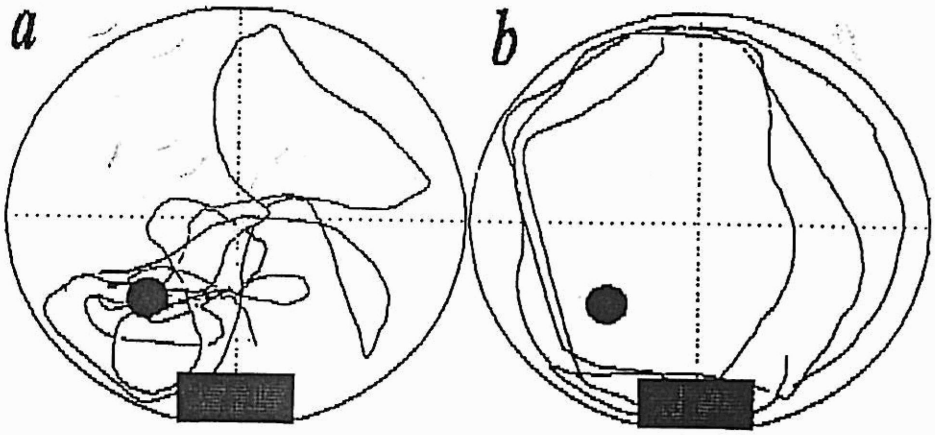

Fig. 1. The path swum in Morris water maze on the transfer test (after 12 days of training) by a representative rat: a. control, b. receiving nifedipine, 5 mg/kg immediately after each trial and ECT 15 min later. The black dot represents the position of the platform during training, the shadowed area: the starting point

The present results confirm that ECT impairs memory and show that this treatment may exert a powerful amnesic effect on long-term, spatial memory in rats in the Morris water maze. In drug-free animals, ECT was effective when given both just after the learning trial and after delayed application. In our hands the amnesic effect of ECT was more pronounced than in the experiments of Holzhauer and Bures [5], who found

that ECT exerted an almost exclusive anterograde amnesic effect on spatial memory.

As clinical results demonstrate the memory-improving effect of calcium channel blockers [6], we expected that nifedipine treatment would counteract the ECT-induced amnesia. In our hands, however, the calcium channel blocker was ineffective, or even aggravated the effect of ECT. It should be noted that calcium channel blockers were also ineffective in alleviating amnesia induced by short term hypoxia [4]. This might suggest that the effectiveness of calcium channel blockers may be limited mainly to memory impairment of vascular origin.

The present results suggest that generalizing the memory-enhancing properties of calcium channel blockers to other clinical situations may be inappropriate. Particularly, they suggest that calcium channel blockers might not be useful in counteracting amnesic effects of ECT encountered in clinical practice. On the other hand, the enhancement of amnesic effect of ECT by nifedipine is in line with the findings that calcium channel blockers enhance the biochemical and behavioral effects of ECT regarded as characteristic for its antidepressant action [8] (see also this symposium).

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