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Attenuation by Nimodipine of Amitriptyline-Induced Avoidance Impairment in Mice

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SANSONE, M., M. BATTAGLIA AND F. PAVONE. *Attenuation by nimodipine of amitriptyline-induced avoidance impairment in mice.* PHAMACOL BIOCHEM BEHAV **62**(4) 613–618, 1999.—The effects of the dihydropyridine calcium channel blocker nimodipine on avoidance impairment induced by the tricyclic antidepressant amitriptyline were assessed during shuttle-box training and in previously trained mice of the DBA/2 strain. Nimodipine (0, 0.5, 1, 2.5, or 5 mg/kg) had no effect alone, but attenuated the avoidance impairment induced by 5 mg/kg amitriptyline on avoidance acquisition, as well as on a previously learned avoidance response. The avoidance improving action of the calcium channel blocker was less evident in mice receiving a larger dose (7.5 mg/kg) of the antidepressant drug. The effect of nimodipine did not appear to be specifically related to the avoidance impairment induced by amitriptyline, because the calcium antagonist also attenuated the avoidance impairing action of the neuroleptic chlorpromazine. The avoidance impairment induced by amitriptyline and chlorpromazine, and the related ameliorating action of nimodipine, seem imputable to drug effects on the performance of the avoidance response, rather than to interferences with learning processes. The results suggest that, in the case of concomitant administration, nimodipine could alleviate adverse side effects of tricyclic antidepressant, i.e., psychomotor disturbances.

Antidepressants Amitriptyline Nimodipine Psychomotor disturbances Avoidance behavior Mice

IN recent studies (21,27) we investigated whether cognition enhancers, drugs able to improve learning and memory and to protect the brain from physical and chemical injuries (16,30, 31), may also prevent the impairment of cognitive and psychomotor functions induced by acute administration of tricyclic antidepressants (1,8). In a first study (27), the nootropic drug oxiracetam was unable to attenuate the impairment of avoidance acquisition induced by the tricyclic antidepressant desipramine in mice, while a preventing action was exerted by minaprine, a psychotropic agent, possessing dopaminergic and related memory-enhancing properties (25). In subsequent research (21), the nootropic agent piracetam had slight or no effect in mice receiving amitriptyline, while shuttle-box avoidance impairment induced by the antidepressant drug was prevented by tacrine, a cognitive enhancer acting mainly through a central cholinergic activation due to acetylcholinesterase inhibition (10).

In the present study, we investigated whether the avoidance impairment induced by amitriptyline may be prevented by a concomitant treatment with nimodipine, a dihydropyridine calcium channel blocker able to improve learning and memory of old or brain-damaged animals (9,13,26) and to exert a protective action on drug-induced behavioral disturbances (24). Nimodipine and amitriptyline were tested, alone or combined, during shuttle-box avoidance training and in previously trained mice. To assess whether the action of nimodipine may be specifically related to the avoidance impairment induced by amitriptyline, an additional experiment was carried out, as previously done with piracetam and tacrine (21), to test the effects of the calcium channel blocker on the

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impairment of avoidance performance induced by chlorpromazine, a neuroleptic agent that selectively inhibits avoidance behavior (6). Spontaneous locomotor activity was also tested to assess whether drug effects on avoidance performance may reflect general behavioral changes.

METHOD

Subjects

The subjects were naive male mice, 9–10 weeks old, belonging to the inbred DBA/2 strain (Charles River, Calco-Como, Italy). Upon their arrival in the laboratory (at least 1 week before the experiment) the mice were housed in standard transparent plastic cages (eight per cage) under standard animal room conditions (free access to food and water, 12 L:12 D cycle, ambient temperature of 23°C). The experiments were carried out between 0900 and 1600 h, by using different animals for different behavioral tests.

Care and handling of the animals were in accordance with NIH ethical regulations. The experimental protocol was approved by the Italian Ministry of Health on 27 November 1995 (Decree no. 285/95-B).

Drugs

Nimodipine (Drug Institute, Warsaw, Poland), dissolved in 50% polyethylene glycol, molecular weight 400 (PEG; Sigma), was injected intraperitoneally (IP) in a volume of 4 ml/kg; control animals received 50% PEG. Amitriptyline hydrochloride, and chlorpromazine hydrochloride (Sigma), dissolved in distilled water, were injected IP in a volume of 10 ml/kg; control injections (dose 0) consisted of the administration of saline solution (0.9% NaCl).

Apparatus

The same apparatus was employed to measure active avoidance and spontaneous locomotor activity, as previously reported (18,21,29). The apparatus was computer controlled and consisted of eight shuttle-boxes, each one divided into two 20 × 10-cm compartments, connected by a 3 × 3-cm opening.

The experimental procedure for avoidance training of mice, utilized in this and several previous researches [see (22,28,29,34,35)], was described many years ago by Bovet et al. (4,5). A light (10 W) was switched on alternately in the two compartments and used as a conditioned stimulus (CS). The CS preceded the onset of the unconditioned stimulus (US) by 5 s, and overlapped it for 25 s. Using this procedure the light was present in the compartment for 30 s (5 s alone and 25 s together with the US). At the end of the 30-s period both CS and US were automatically terminated, and the cycle begun in the other compartment. The US was an electric shock (0.2 mA) continuously applied to the grid floor. An avoidance response was recorded when the animal avoided the US by running into dark compartment within 5 s after the onset of the CS. If animals failed to avoid the shock they could escape it by crossing during the US. Failure of either avoidance or escape response seldom occurred in the present experiments. Thus, as a matter of fact, the sequence of the trials was always respected by the animals, also because intertrial responses (spontaneous crossings from the dark to the lighted, electrified compartment) were punished by electric shock, so that the mice were forced to remain in the dark compartment and wait for the following cycle.

To measure spontaneous locomotor activity, the lamps of the shuttle-boxes were switched off, and no electric shock was applied to the floor. The number of crossings from one compartment to the other was recorded for each mouse.

Avoidance Acquisition

Mice were subjected to three daily 50-trial avoidance sessions. With this schedule, the rate of avoidance acquisition allowed both impairing or improving effects of drugs to be ascertained in well-performing DBA/2 mice (14,21).

Before the first session mice were given an adaptation period of 5 min in the apparatus. The animals received a first injection of nimodipine (0, 0.5, 1, 2.5, or 5 mg/kg), 30 min before each session, and a second injection of amitriptyline hydrochloride (AMT; 0, 5, or 7.5 mg/kg), 15 min before testing. In an additional experiment, mice received a first injection of nimodipine (0, 0.5, or 1 mg/kg) and a second injection of chlorpromazine hydrochloride (0, 0.5, or 1 mg/kg). The doses of nimodipine, combined with chlorpromazine, were chosen on the basis of the results produced by nimodipine combined with amitriptyline.

Drug effects on avoidance responses were evaluated by two-factor analyses of variance (ANOVAs), the factor being treatment (between-subject factor) and daily sessions (within-subject factor).

Trained Animals

To obtain stable high levels of avoidance performance, training sessions were increased to 100 trials each. Mice reaching a criterion of 70% avoidance responses, in the last of five daily training sessions, were selected for drug experiments. Selected mice were subjected to further avoidance sessions on 4 consecutive days. The first of these daily sessions, preceded (30 min) by an injection of saline solution, represented the control session. In the following days mice were subjected to three drug sessions: they received nimodipine (0, 0.5, 1, 2.5, or 5 mg/kg), alone (first and third drug session) or combined with amitriptyline (5 mg/kg; second drug session). Injections of nimodipine were given 30 min before testing and were followed, 15 min later, by the injection of amitriptyline.

Drug effects on avoidance responses were evaluated by a two-factor ANOVA, the factors being treatment (between-subject factor) and daily sessions (within-subject factor).

Locomotor Activity

Mice were subjected to a 30-min activity test. Drug treatment consisted of the administration of nimodipine (0, 0.5, or 1 mg/kg), 30 min before testing, followed by the injection of amitriptyline (0 or 5 mg/kg), 15 min later. Drug effects were evaluated by a one-way ANOVA, followed by Duncan's test for individual between-group comparisons. The doses of nimodipine, combined with amitriptyline, were the doses of the calcium channel blocker found to be the most effective in counteracting the avoidance impairing action of the antidepressant drug.

RESULTS

Avoidance Acquisition

Figure 1 reports the effects nimodipine, administered alone or in combination with amitriptyline, on the avoidance acquisition. Escape responses have not been reported because escape failure seldom occurred. Regarding the intertrial re-

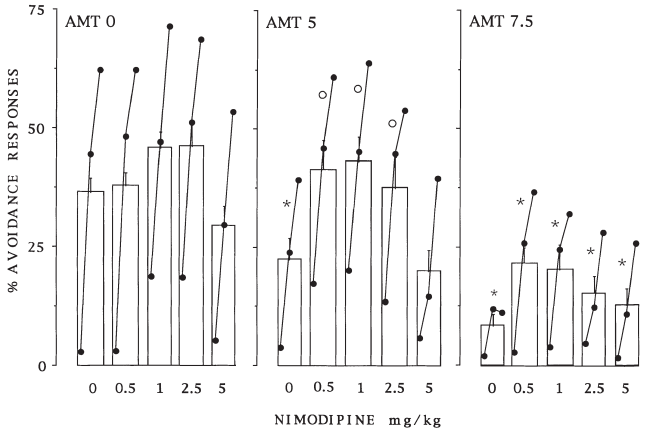

FIG. 1. Effect of nimodipine on amitriptyline-induced impairment of shuttle-box avoidance acquisition. Mean percent avoidance responses in the whole of the three 50-trial daily sessions (columns) and in each session (graphs within columns), in groups of eight mice. Vertical lines indicate SEM. Mice were injected IP with nimodipine, 30 min before each session, and amitriptyline hydrochloride (AMT; 0, 5, or 7.5 mg/kg), 15 min before testing. *$p < 0.05$ vs. nimodipine alone (AMT 0); °$p < 0.05$ vs. amitriptyline alone (dose 0 of nimodipine).

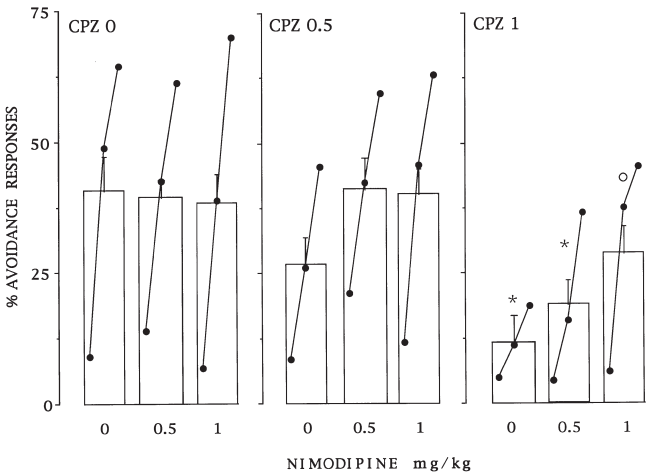

FIG. 2. Effect of nimodipine on chlorpromazine-induced impairment of shuttle-box avoidance acquisition. Mean percent avoidance responses in the whole of the three 50-trial daily sessions (columns) and in each session (graphs within columns), in groups of eigth mice. Vertical lines indicate SEM. Mice received IP nimodipine, 30 min before each session, and chlorpromazine hydrochloride (CPZ; 0, 0.5, or 1 mg/kg), 15 min before testing. *$p < 0.05$ vs. nimodipine alone (CPZ 0); °$p < 0.05$ vs. chlorpromazine alone (dose 0 of nimodipine).

sponses, it should be noted that the number of trials, presenting such responses, were always below the 5% level in the first session. Then, intertrial responses, which were punished by electric shock, gradually disappeared as training proceeded.

A two-factor ANOVA for the avoidance responses revealed significant main effects of treatment, $F(14, 105) = 8.42$, $p < 0.001$, and sessions, $F(2, 210) = 322.05$, $p < 0.001$, and a significant treatment × sessions interaction, $F(28, 219) = 3.51$, $p < 0.001$. A post hoc analysis (Duncan's test), for the three combined sessions, showed a significant dose-dependent reduction of avoidance responses by amitriptyline. Nimodipine had no significant effect alone, but at the dose of 0.5, 1, or 2.5 mg/kg attenuated the avoidance depressant action of 5 mg/kg amitriptyline. At these doses, mice treated with combinations of nimodipine and amitriptyline performed better than mice receiving the antidepressant alone, and the number of avoidance responses did not significantly differ from nimodipine alone (AMT 0). In mice receiving the highest dose of amitriptyline (7.5 mg/kg), nimodipine increased the avoidance responses in the three sessions combined, although not significantly. However, further analysis, by single sessions, revealed a significant avoidance improvement, in the third session, when mice were treated with 0.5 or 1 mg/kg nimodipine.

The results concerning combination of nimodipine and chlorpromazine are reported in Fig. 2. A two-factor ANOVA for the avoidance responses showed significant main effects of treatment, $F(8, 63) = 4.30$, $p < 0.001$, and sessions, $F(2, 126) = 192.17$, $p < 0.001$, and a significant treatment × sessions interaction, $F(16, 126) = 3.51$, $p < 0.001$. Chlorpromazine produced a dose-dependent reduction of avoidance responses, with a significant (Duncan's test) avoidance depression at the dose of 1 mg/kg. Nimodipine attenuated chlorpromazine-induced avoidance impairment. In particular, 1 mg/kg nimodipine significantly reduced the avoidance disrupting action of 1 mg/kg chlorpromazine.

Trained Animals

Figure 3 shows the mean percent avoidance responses exhibited by previously trained mice in the control session and in three drug sessions, in which nimodipine was tested alone or combined with amitriptyline. A two-factor ANOVA revealed no significant main effect of treatment, $F(4, 35) = 2.37$, $p > 0.05$, but a significant effect of sessions, $F(3, 105) = 254.42$, $p < 0.001$, and a significant treatment × sessions interaction, $F(12, 105)$ - 5.17, $p < 0.001$. Pair-wise comparisons (Duncan's test) and analysis of simple effects showed a significant avoidance impairment by 5 mg/kg amitriptyline (second drug session). Nimodipine had no effect alone (first and third drug session) but, at the doses of 0.5 and 1 mg/kg, attenuated the impairing action of amitriptyline. At these doses, performance of mice receiving drug combination was worse than that of the same animals treated with the calcium channel blocker alone, but significantly better than the performance of mice receiving the antidepressant alone.

Locomotor Activity

Figure 4 shows the number of crossings exhibited, in the 30-min activity test, by the experimental groups receiving nimodipine alone (AMT 0) or combined with 5 mg/kg amitriptyline (AMT 5). A one-way ANOVA revealed significant differences among groups. $F(5, 42) = 4.80$, $p < 0.01$. Individual between-group comparisons indicated no effect of nimodipine alone (0.5 or 1 mg/kg), while amitriptyline produced a slight, statistically not significant, locomotor depressant action. However, mice receiving the two drugs combined exhibited lower levels of locomotor activity in comparison with both the control group (dose 0 of both drugs) and the groups treated with nimodipine alone, but not in comparison with the group receiving amitriptyline alone.

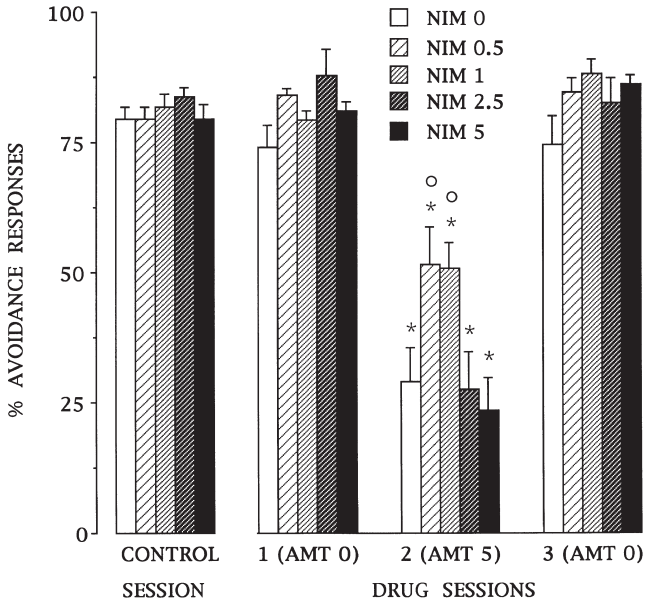

FIG. 3. Effect of nimodipine on amitriptyline-induced avoidance impairment in previously trained mice. Mean percent avoidance responses exhibited by mice in the control session and in three consecutive daily 100-trial drug sessions. Columns represent mean values in groups of eight mice. Vertical lines indicate SEM. Mice received IP nimodipine (NIM), 30 min before each drug session, and amitriptyline hydrochloride (AMT), 15 before testing. Doses in mg/kg IP. $*p < 0.05$ vs. nimodipine alone (AMT 0); $°p < 0.05$ vs. amitriptyline alone (NIM 0).

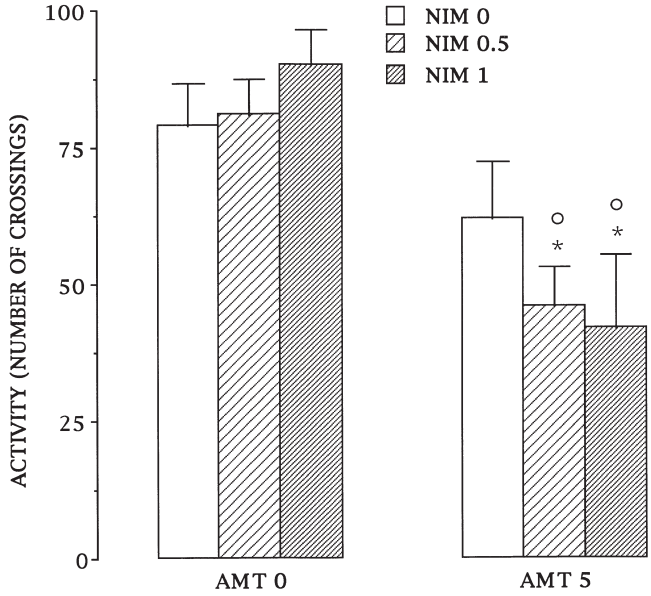

FIG. 4. Effect of nimodipine, given alone or combined with amitriptyline, on spontaneous locomotor activity in mice. Columns represent the mean number of activity crossings for 30 min, in groups of eight mice. Vertical lines indicate SEM. Nimodipine (NIM) was given 30 min before the activity test; amitriptyline hydrochloride (AMT) was injected 15 min before testing. Doses in mg/kg IP. $*p < 0.05$ vs. control group (AMT 0 – NIM 0); $°p < 0.05$ vs. nimodipine alone, at the corresponding dose (AMT 0 – NIM 0.05 or NIM 1).

DISCUSSION

In the present study, the dihydropyridine calcium channel blocker nimodipine, given alone during shuttle-box avoidance training or in previously trained mice, had no significant effect on avoidance performance. However, although ineffective alone, nimodipine attenuated the impairment induced by the antidepressant drug amitriptyline on either avoidance acquisition or on a previously learned avoidance response. The improving action of nimodipine was dose dependent: the lower doses (0.5 and 1 mg/kg) prevented amitriptyline-induced avoidance impairment, while the higher doses (2.5 and 5 mg/kg) had partial or no effect. It is possible that, when higher doses of nimodipine were combined with amitriptyline, the sedative component of the action of the calcium channel blockers (24) may have counteracted avoidance facilitation.

Facilitation by nimodipine of avoidance performance of mice treated with amitriptyline did not seem related to any nonspecific enhancement of locomotor activity, because doses of the calcium antagonist, which prevented amitriptyline-induced avoidance impairment, did not counteract, but actually enhanced the locomotor depressant action of the antidepressant action of the antidepressant drug. Furthermore, the action of nimodipine did not appear specifically related to the avoidance impairment induced by amitriptyline, because the calcium antagonist also reduced the avoidance impairing effect of chlorpromazine. In this respect, the action of nimodipine differed from that exerted by tacrine in similar experimental conditions. Tacrine prevented the avoidance impairment induced by amitriptyline, but enhanced the avoidance disrupting action of chlorpromazine (21).

Failure of nimodipine to improve shuttle-box avoidance learning, when given alone, is in agreement with previous findings showing that nimodipine and nifedipine, another dihydropyridine calcium channel blocker, had slight or no improving effect on avoidance acquisition when tested, in a wide range of doses, in normal mice belonging to three different strains (34,35). The use of an active avoidance test for assessing drug effects on cognitive functions has been questioned because peripheral mechanisms may be involved in avoidance performance (31). However, improving effects of putative cognition enhancers on active avoidance learning have been reported (31) and, in particular, facilitation of shuttle-box avoidance acquisition by nootropic and cholinomimetic agents has been observed (22,28,29,36).

Conversely, in agreement with previous findings [see (21)], in the present study, amitriptyline, given during training as well as in well-trained animals, exerted an avoidance disrupting action. Inhibition by amitriptyline of a previous learned avoidance response indicated that avoidance impairment, even if occurring during training, may be due to interferences of the drug with the performance of the avoidance response rather than with learning processes. This hypothesis was strengthened by experimental evidence indicating that the avoidance impairing action exerted by chlorpromazine (3,23) and amitriptyline (21) may be ascribed to a motor performance deficit, and more exactly to a delayed response initiation, rather than to a deficit in associative learning (3). In a previous study (23), it was observed that, in delaying locomotor initiation, chlorpromazine selectively affects only certain kinds of locomotor acts, and that the speed of locomotion after initiation is not affected by the drug. It seems now that the delayed movement initiation in response to a warning signal,

produced by amitriptyline, is not an effect related to the drug-induced reduction of spontaneous locomotor activity. It must be noted that the NMDA antagonist dizocilpine (MK-801), a drug able to counteract chlorpromazine-induced avoidance impairment (15), was also able to reverse the movement initiation deficits, induced by the neuroleptic haloperidol in a reaction-time task (12). The latter effect was considered indicative of a potential therapeutic utility of NMDA antagonists in the treatment of Parkinson's disease (12). On the basis of these findings, it was proposed that the avoidance impairing action of amitriptyline and chlorpromazine might represent a model of psychomotor deficit, rather than a model of cognitive impairment (21). Therefore, it seems likely that the facilitating effects exerted by nimodipine, in mice treated with amitriptyline (or chlorpromazine), are due to performance improvements, as those previously observed after the administration of tacrine (21).

Prevention of the amitriptyline-induced avoidance impairment by tacrine was ascribed, at least in part, to a cholinergic activation counteracting the anticholinergic component of the action of the antidepressant agent (21). Conversely, suppression of avoidance performance by combined tacrine and chlorpromazine was probably due to simultaneous cholinergic activation and dopaminergic inhibition, causing a general behavioral disruption (21).

Although minaprine (27) and tacrine (21) prevent the avoidance impairing action of antidepressant agents by acting through dopaminergic and cholinergic mechanisms, respectively, it is difficult to ascribe the effects of nimodipine on the avoidance impairment induced by amitriptyline and chlorpromazine to interference by the calcium antagonist with changes specifically induced by the psychotropic drugs in a particular neurotransmitter system. Calcium channel blockers interfere with release and uptake processes of different neurotransmitters (7,24), but the literature data do not at present afford any explanation of the observed behavioral effects. In particular, dihydropyridine calcium channel blockers activate the serotonergic system (11), but such activation cannot account for the attenuation by nimodipine of amitriptyline-induced avoidance impairment, an effect partially imputable to inhibition of serotonin uptake (2). On the other hand, the antidopaminergic properties of calcium antagonists (11, 24) cannot be responsible for the attenuation by nimodipine of the avoidance disrupting action of chlorpromazine, an effect ascribed to selective blockade of central dopamine receptors (17).

It must be recalled that nimodipine, like other calcium antagonists, increases cerebral blood flow by causing a selective vasodilating action on the cerebral circulatory system (24,32), and that a cerebrovasodilatatory action seems to be involved in the protective action of calcium channel blockers against brain injuries and drug-induced behavioral disturbances (9,24,33). The cerebral vasodilating action of nimodipine might have contributed to the improvement of the avoidance performance in mice treated with amitriptyline or chlorpromazine, by exerting a nonspecific neuroprotective action and by influencing the pharmacokinetics of the psychotropic agents, as previously suggested to explain the behavioral effects produced by drug combinations including nifedipine (19,20,34).

In any case, the interaction between calcium channel blockers and central pharmacological agents may be of particular interest, in view of the widespread clinical use of calcium antagonists. It has been reported that calcium channel blockers exert several typical actions of psychotropic drugs and exhibit antidepressant, anxiolytic, and neuroleptic effects (24). With this wide spectrum of nonselective psychotropic properties the question arises whether calcium channel blockers are able to potentiate the therapeutic action and to prevent the adverse effects of typical psychotropic agents (24). The present results suggest that, in case of concomitant administration, the dihydropyridine calcium channel blocker nimodipine might alleviate adverse side effects produced by acute administration of tricyclic antidepressants, i.e., impairment of performance and psychomotor ability. Because effects of the calcium antagonist on memory processes cannot be excluded, further research and other learning tasks could give information indicative of antidepressant-induced cognitive impairment and of possible ameliorating effects of nimodipine.

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